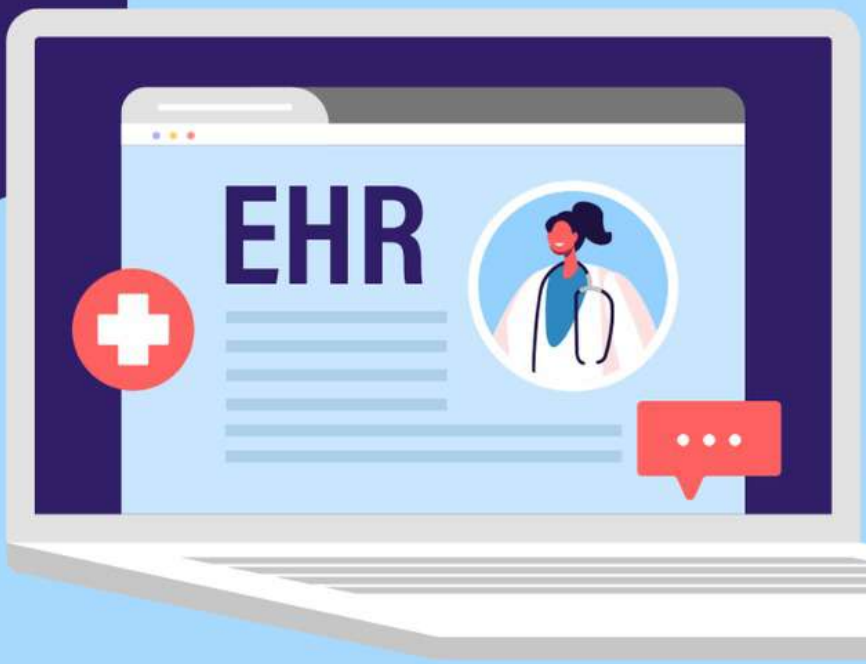
NANOMEDICINE REVOLUTION

BRIDGING NANOTECHNOLOGY & PHARMACEUTICAL SCIENCES



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PREFACE

This book covers the topics which are used in research projects for B. Pharm, M. Pharm & PhD students. A major problem with drugs is the lack of selectivity and specificity of action and pronounced undesirable (side or toxic) effects. Thus in modern day research greatest attention is being paid to 'optimization of drug delivery by maximizing efficacy and minimizing toxicity. We have come a long way in this direction but are still far away from it. The field of Controlled and Novel Drug Delivery is dynamic, more and more advances are being reported through literature and patents and it is the endeavor of this author to disseminate the latest information to the students and teachers.

The contents of this included chapters on nanomedicine, Liposomes, Microencapsulation, Microspheres, Solid lipid nanoparticle, Nanoemulsion, Self Nano Emulsifying Drug Delivery System, Gastroretentive drug delivery system, Parenteral Dosage Form, etc. This book is structured in such a way that basic concepts, methodologies, applications and future prospective give systematic understanding of research projects. This book also covers various advances including applications potential and research exploration possibilities.

We are grateful to Mr. Pavan Dewangan of Evincepub publishers for their enthusiasm in bringing out this book. We express our deep sense of gratitude to our family for their love, support and motivation in academics and research. Your feedback is most welcome to make the future edition of this text book more valuable for students.

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CHAPTER NO 01- INTRODUCTION OF NANO-MEDICINE

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Introduction-

In the early phases of formulation development, Nano particulate drug delivery systems may be evaluated using the factors and methodologies summarized in this article. In order to help readers better comprehend the evolution of Nano pharmacy, the history is briefly reviewed. There are a plethora of nano gadgets designed specifically for use in diagnostics, thanks to nanotechnology. The development of COVID-19 vaccines and the treatment of renal illness, TB, skin disease, Alzheimer's disease, and other cancers are among the many medical applications of nanoparticles. This study covers the many nanoproducts that are based on nanotechnology, such as nanosuspension emulsion. Reportedly, lead, mercury, and tin heavy metal NPs are very stable and hard to degrade, which makes them a potential source of several environmental toxicities. Nanoparticles and nanoparticle systems are the subject of this article, which delves into the fundamentals of drug delivery, pharmacokinetic research, present advances, and future prospects. Nanocarriers such solid nanoparticles, liposomes, dendrimers, polymeric nanoparticles, polymeric micelles, virus-like nanoparticles, carbon nanotubes, and mesoporous silica nanoparticles are detailed in this paper.

Innovations in medication delivery, diagnostics, food, and the creation of biomaterials that may be used in medicine have all been ushered in by nanotechnology, which has also given humans a fresh outlook on old problems. The administration of medicinal compounds and diagnostic processes are two other areas where nanotechnology has found use. Pharmaceutical nanoparticles are structures with tens or hundreds of atoms or molecules in crystalline, amorphous, spherical, or needle-shaped morphology that contain medications or bioactive chemicals. They are sub nano-sized. Preventing medication deterioration is another function of delivery systems based on nanotechnology.

Nanotechnology refers to any generation that operates on the nanoscale and has

applications in the real world, such as the construction of functional structures from single atoms and molecules. The term "nanoscale technology" best describes nanotechnology. One to one hundred nanometres is the nanoscale. It is "the design, characterisation, manufacture, and shape- and size-controlled application of materials at the nanoscale." That is how nanotechnology is defined in the dictionary. To create substances, systems, and devices with fundamentally novel qualities and functionalities, one must "carefully and controlled manipulate, precisely place, model, measure, and produce nanoscale materials" (a different description from the same dictionary). Smaller than one hundred nanometers in diameter are the building blocks of nanotechnology. Such materials may be one, two, or three dimensions thick, depending on their general form. When scientists discovered that a substance's size might impact its physiochemical characteristics, including its optical qualities, the significance of these materials became clear. Twenty nanometer-sized NPs of gold (Au), platinum (Pt), silver (Ag), and palladium (Pd) exhibit reddish-brown, yellowish, black, and dark black hues, correspondingly. The synthesis of Au NPs of varying sizes is shown in as an example of this depiction. These NPs exhibited unique hues and characteristics that may be used in bioimaging applications when their size and shape were varied.

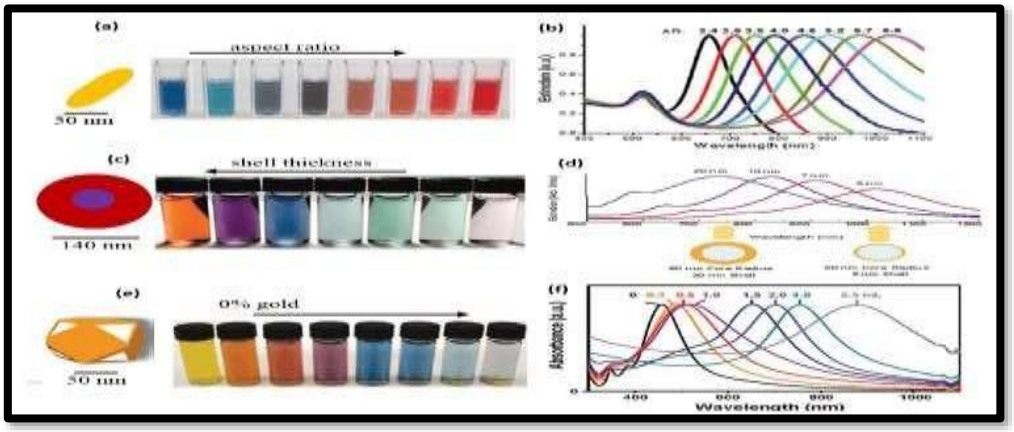

Fig no 01 - Au's optical properties include: (a) colour change in Au nanorods with varying aspect ratios of gold nanoparticles; (b) tenable SPR of gold nanoparticles with varying aspect ratio of gold nanoparticles; (c) colour change observed in Au nano shells with varying shell-thickness (d); and (e) physical appearance of Au nanocages with varying HAuCl4 content in their synthesis; and (f) wavelength tunability (with permission from).

Nanotechnology encompasses a wide range of disciplines and refers to any technology operating at the nanoscale with practical uses. Nowadays, nanoparticles are made via solvent exchange techniques or double emulsion processes. The present technologies for creating nanoparticles have several flaws. Among these significant issues is a lack of capability for size distribution, inadequate medication loading capacity, and low loading efficiency. To address these issues with uniform particle size and efficient loading, nanotechnologies (such as nanostructuring) are useful. Intravenous, subcutaneous, pulmonary, intraperitoneal, and oral administration are the primary entry points for nanomedicines.

There are a few ways in which nanomaterials can enter the body: absorption, which happens when the nanostructures first interact with biological components; distribution to different organs; modification or metabolism; and penetration into the cells of the organ, where they can stay for an unknown amount of time before moving on to other organs or being excreted. Nanomaterials pose a threat at any stage due to their ability to trigger inflammatory responses and pro-oxidant activities, among others. Neurodegenerative disorders (ND) are complex and difficult to comprehend and treat, but nanotechnology-based delivery of diagnostic and therapeutic agents is crucial. The detection and treatment of neurodegenerative disorders (ND) may make use of a variety of manmade nanomaterials. An unique and intriguing strategy to possibly alleviate the difficulties related with ND is the creation of polymeric, lipid, and inorganic nanoparticles.

Medication usually travels into the bloodstream and then reaches the site of injury. These nanotechnology-enhanced medications allow for tailored drug delivery, which increases efficacy while decreasing the likelihood of adverse effects. In order to address medication development issues and provide safer, more cost-effective methods, pharmaceutical corporations are putting a lot of emphasis on nanotechnology. As a result of the increased value of current goods made possible by nanotechnological instruments, new possibilities have emerged across the board in pharmaceutical R&D. Synthetic chemistry relies heavily on catalysts, which increase enantioselectivity and reaction yields at low temperatures. A wide variety of chemical processes may be efficiently catalysed and transported by nanoparticles. The following figure illustrates the ranked arrangement of nanoscale particles often used in medication administration and formulation.

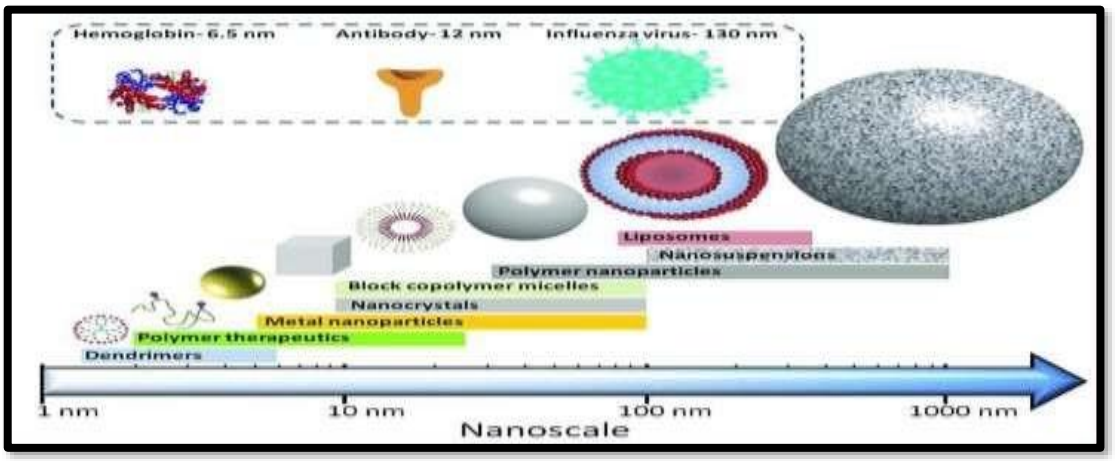

Fig no 02- Different structures of nanomedicines and their approximate sizes

NANO DEFINITIONS -

Nanoscience-

It can be defined as study of phenomenon and manipulation of materials at atomic and molecular scales.

Nanotechnology-

It is related to design characterization, production and applications of structures, devices and systems by controlling shape and size at nanometres scale.

Nano-medicine-

It is defined as submicron size [<1um] modules, used for treatment, diagnosis, monitoring, and control of biological system.

Pharmaceutical nanotechnology

embraces applications of nano science to pharmacy as nano materials, and as devices like drug delivery, diagnostic, imaging and biosensor.

Nano-metrology-

It is the science of measurements at the nano scale. Four commonly used techniques are: transmission electron microscopy (TEM), scanning electron microscopy (SEM), and scanning probe techniques [scanning probe microscopy (SPM)], and optical tweezers (single-beam gradient trap).

Nano-toxicology-

It refers to the study of the interactions of nanostructures with biological systems with an emphasis on the relationship between the physical and chemical properties of nanostructures with induction of toxic biological response.

Bio nanotechnology-

It generally refers to the study of how the goals of nanotechnology can be guided by studying how biological “machines” work and adapting these biological motifs into improving existing nanotechnologies or creating new ones.

HISTORY-

Even though Richard Feynman is often hailed as a trailblazer in the realm of nanotechnology, nobody knows for sure how it all began. The medical field was one of several that made use of nanoparticles even before Feynman. The use of gold nanoparticles in glass was patented in 1449 by John Utynam. Paracelsus, whose real name was Theophrastus von Hohenheim, was a Swiss physician who utilised gold nanoparticles to cure a variety of illnesses in the 1600s. Thus, N&N is not a novel discipline, but its approaches have developed over the years. For his work in measuring the size of particles, such as colloidal gold particles, using a microscope, Richard Zsigmondy was awarded the Nobel Prize in Chemistry in 1925.

He was the first to develop the notion of the nanometres. Though he provided a more in-depth explanation of nanotechnology in his 1959 talk at an international conference, Feynman did not really propose the idea, as previously said. In 1974, Norio Taniguchi coined the word "nanotechnology" to characterise the many methods for processing materials on the nanoscale and the extreme precision of ultrathin materials at the nanoscale. Scanning tunnelling microscopy (STM) and the appearance of clusters in colloid science prompted more research into nanotechnology. The invention of fullerenes and carbon nanotubes followed shortly after this string of triumphs. Thanks to these breakthroughs, scientists and researchers have been able to explore previously uncharted territory ripe with opportunities for the application of nanotechnology.

In 1991 and 2001, the US government launched two campaigns to educate the public about nanotechnology and its potential uses. Along with the aforementioned initiatives, researchers from the International Centre for Technology Assessment tracked nanotechnology advancements in different nations as part of a study. The 1999 conference of the Interagency Working Group on Nanoscience, Engineering and Technology (IWGN) aimed to plan nanotechnology research for the next decade.

In the year 2000, the findings and suggestions put forward by the IWGN were formally sanctioned by the Presidential Council for Science.

According to Joseph and Moore (2008), the market for drug delivery systems that use nanotechnology is projected to see a cumulative growth rate, reaching $20.1 billion by 2012. This represents 11% of the global drug delivery market. The first approach involves homogenising the drug solution under high pressure with an appropriate surfactant (such as Tween 80 or Pluronic F68) to reduce the size of the particles to nanometres. A solvent-free formulation of paclitaxel (Abraxane®) was authorised by the US FDA for the treatment of metastatic breast cancer, marking a milestone in the therapeutic use of albumin nanoparticles.

Table 1: Periodical development in nanotechnology

Year	Development in nanotechnology
1959	R. Feynman initiated thought process
1974	The term nanotechnology was used by Taniguchi for the first time.
1981	IBM Scanning Tunneling Microscope
1985	“Bucky Ball”
1986	First book on nanotechnology Engines of Creation published by K. Eric Drexler, Atomic Force Microscope
1989	IBM logo was made with individual atoms
1991	S. Iijima discovered Carbon Nano tube for the first time.
2002	Feynman Prize in Nanotechnology was awarded for using DNA to enable the self-assembly of new structures and for advancing our ability to model molecular machine systems.
2003	Feynman Prize in Nanotechnology was awarded for modeling the molecular and electronic structures of new materials and for integrating single molecule biological motors with nano-scale silicon devices.
2005-2010	3D Nano systems like robotics, 3D networking and active nano products that change their state during use were prepared.
2011	Era of molecular nano technology started

CLASSIFICATION

Liposomes:

A liposome is a vesicular structure that consists of a lipid bilayer encasing a watery core. The first publication of this information came from Bangham et al. (1965). Liposomes first appeared in the 1970s as a means of medication delivery. Utilising a pair of microfluidic devices allows for the continuous processing of liposome formation, drug loading, and undesirable component removal. Some examples of LBNs include vesicular carriers like micelles and liposomes and particulate carriers like SLNs and NLCs.

In the 1960s, Alec Bangham was the first to describe liposomes, which are nanocarriers made of phospholipids. Due to its biocompatibility and appropriate encapsulating characteristic, Gregory Gregoridas presented liposomes as a delivery technology a few years after its inception. Multilamellar vesicles (MLV), small unilamellar vesicles (20-100 nm), and large unilamellar vesicles (LUV, 100-800 nm) are the three main classifications of liposomes. Here is a simple figure that shows how liposomes are structured. You can see the basic layout of the LUV, SUV, and MLV in the figure

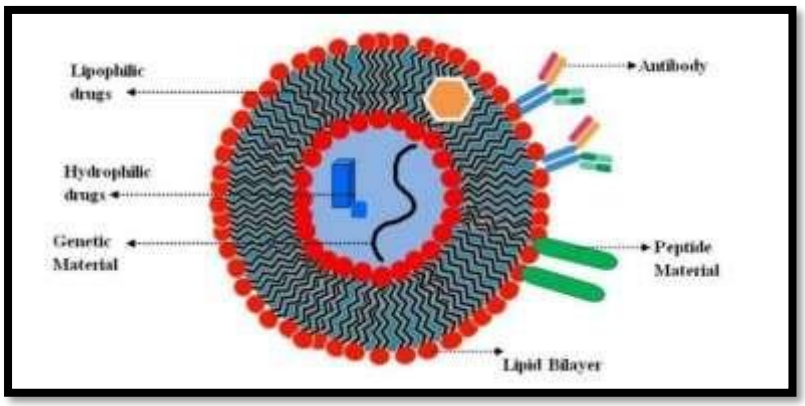

Fig no 03- Structure of liposomes

Micelles-

Micelles are lipid nanostructures that are spherical in shape and lack both a double layer and an interior cavity. In a spherical arrangement, the hydrophobic and hydrophilic ends of the phospholipids face inside and outward, respectively. Micelles, which are smaller than liposomes but nevertheless have medicinal uses, may range in size from 10 to 80 nanometres and have a much shorter half-life in the bloodstream.

An amphiphilic deblock copolymer micelle with a hydrophobic core and a more hydrophilic shell was created in one research via controlled radical polymerisation.

A structure called "polymer micelles" forms when amphiphilic end copolymers orient into a tiny supramolecular core. Micelles made of polymers are less than 100 nm. Micelles made of polymers typically measure less than 100 nanometres in size and are composed of amphiphilic block copolymers that have a supramolecular core-shell arrangement.

Dendrimers-

Sugars, nucleotides, and amino acids come together to form dendrimers, which have many arms that branch out from a central core. Because dendrimers extract bioavailable copper from tumours, they are an efficient cancer treatment. The primary component of dendrimers is the core, which can be an atom or cluster of atoms; the secondary component, dendrimer generations, which are building blocks connected to the core; and the third component, functional groups on the dendrimer's surface, round out the dendrimer. Dendrimers are categorised according to the number of generations, from G1 to G3, and their size grows with each passing generation. Dendrimers may be engineered with a wide variety of chemistry to bind pharmaceuticals covalently and to target ligands, and their surface functional groups can be tailored to specific needs. Their characteristics make them a potential vehicle for transporting bioactive compounds like as genes, metals, vaccinations, and medications to specific locations..

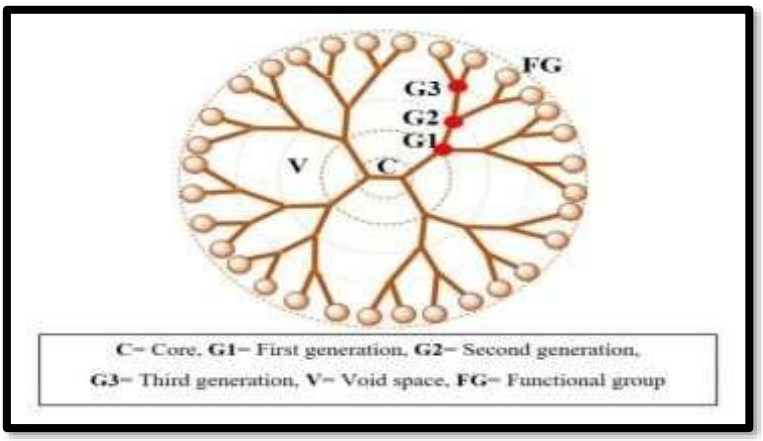

Fig no 04- Dendrimers and generation

Carbon Nanotubes-

effective nucleating agent, which enhances the thermal and chemical properties of PP. The decomposition temperature of pure PP increased from 293°C to 320°C. The

incorporation of carbon nanoparticles as nucleating agents in polypropylene would guarantee enhanced thermal and chemical resistance in aggressive environments.Carbon nanotubes, Iijima contributed to the advancement of nanotechnology in 1991 by introducing carbon nanotubes (CNTs) through the vaporisation of carbon graphite in an arc vaporisation reactor under an inert atmosphere during the synthesis of fullerenes.

In this process, electron macroscopics were generated. Carbon nanotubes (CNTs) are produced by winding grapheme sheets into tube-like structures that are nanoscale in diameter and thousands of times longer than the diameter. CNTs are biocompatible and possess electrical conductivity, in addition to their flexibility. It is capable of being either single-walled or multi-walled, as evidenced by DOX. It exhibits a more robust binding with multi-walled CNTs and facilitates improved drug release from single-walled CNTs.

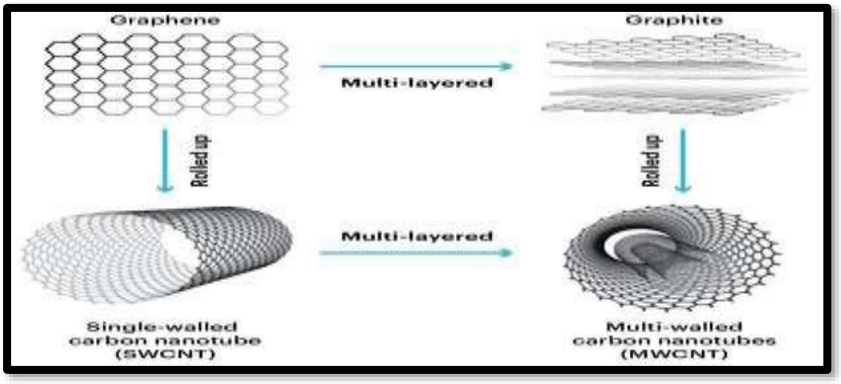

Fig no 05- Structure of Nanotubes

Quantum Dots-

Quantum Dots have a great impact on some important developments in various medical fields such as diagnostic tools (Magnetic Resonance Imaging, MRI), in vitro and in vivo detection and analysis of biomolecules, etc. Quantum Dots consist made of semiconducting material with improved optical properties and a semiconductor core covered by a shell. The size of the quantum dots is between 10 and 100 Åº in radius, which gives them unique physical properties.

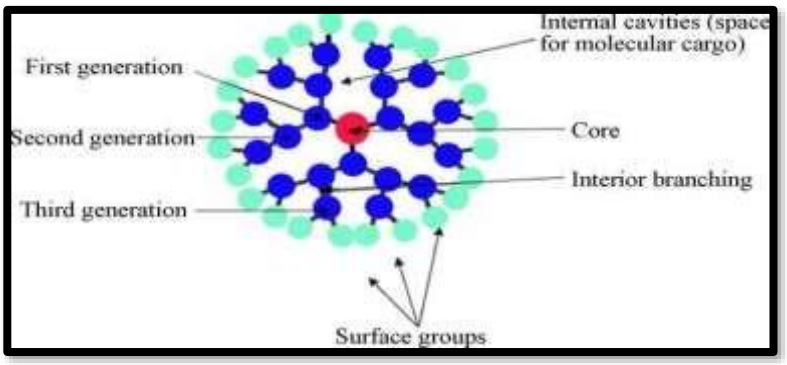

Fig no 06- Structure of Quantum Dots

Nanomaterials-

Nano-crystalline materials-

These are produced to serve as replacements for materials with poor bioavailability, solubility and other properties.

Nanostructured materials-

These are machined forms with specialized shapes and functions, including nano- and micro-electromechanical systems, microfluidics and microarrays

Silica nanoparticles (SiO2 NPs)-

ND is a complex disease; therefore, not all nanoparticles may be used as vehicles for drug delivery, imaging, and diagnosis of neuronal disorders. However, recent application of SiO2 NPs demonstrated upregulation of α-synuclein expression in PD-enhanced autophagy by preventing downregulation of autophagy-PI3K-Akt-mTOR signalling. They have potential therapeutic value, although exposure to SiO2 NPs can cause brain toxicity.

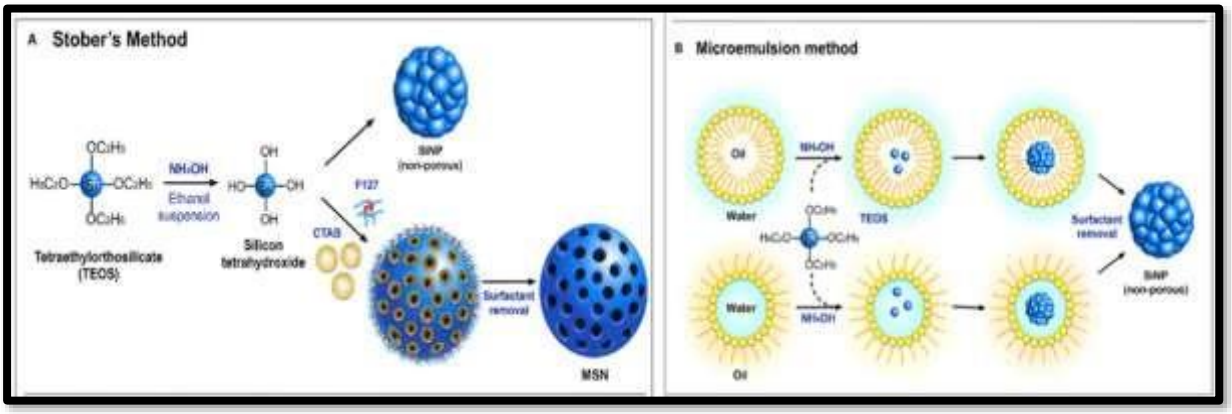

Fig no 06- Silica nanoparticles

Polymeric Nanoparticles-

Polymeric nanoparticles are synthetic nanosized colloidal particles that have a size range of 10nm to 1000nm. Biocompatibility, non-immunogenicity, biodegradability, and non-toxicity are among the numerous advantages of these nanoparticles. Nanocapsules and nanospheres are the two categories of polymer nanoparticles. The active ingredient is situated in the central core of nanocapsules and is encircled by a polymer capsule, while it is dispersed throughout the polymer matrix in concealed nanospheres.

An additional targeted delivery system, a polypeptide fragment of amyloid-β, is modified with a fluorescent probe to facilitate the diagnosis and treatment of brain lesions and maladies. This probe has the ability to specifically bind to apolipoproteins in plasma, thereby facilitating the passage of a molecule across the BBB. The reported an adenosine monophosphate complex and its application in the penetration of the brain and the attack of tumours by crossing brain capillary endothelial cells. Adenosine monophosphate (AMP) is conjugated with imaging agents or antineoplastic medications to achieve this method.

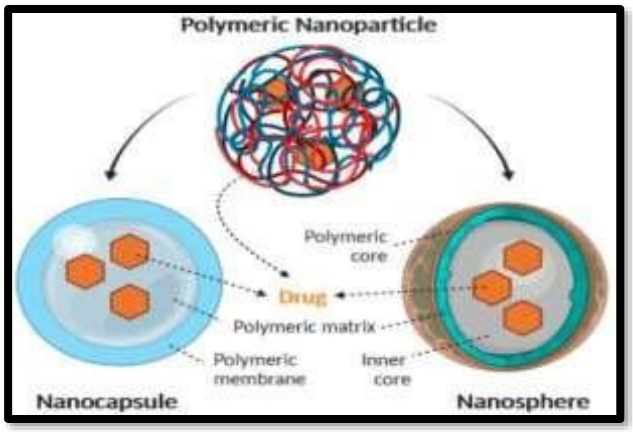

Fig no 07- polymeric nanoparticles

Gold nanoparticles

Researchers are intrigued by gold nanoparticles (AuNPs) because of their minimal cytotoxic effect and predominant optical properties, which are among the numerous nanoparticles. Gold NPs have been employed to treat cognitive deficits and oxidative stress, as well as to image neuronal cells. A promising material for the treatment of Alzheimer's disease, it has the potential to cross the blood-brain barrier by altering its size or engaging a variety of modified ligands.

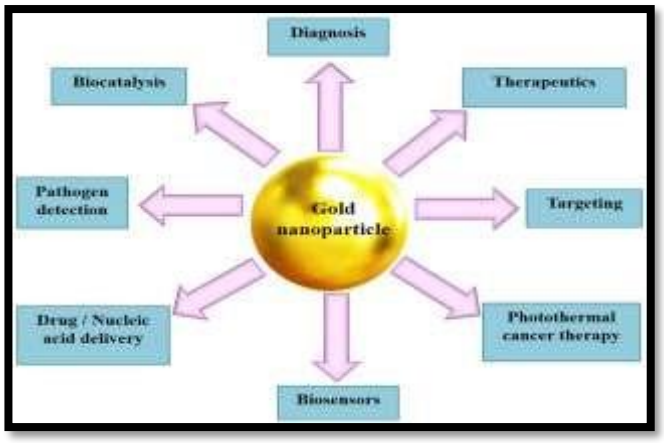

Fig no 08– Properties of gold nanoparticles

Metallic nanoparticles-

Silver and gold are the primary components of metallic nanoparticles; however, other materials may also be employed. The significance of gold and silver nanoparticles is paramount. Metallic nanoparticles are employed as both a biosensor and for drug delivery. Metallic nanoparticles can bind to a variety of biomolecules, including sugars, peptides, proteins, and DNA, and then target them. The surface of metallic nanoparticles is readily accessible for the attachment of biomolecules and ligands. The following is a perspective on metallic nanoparticles.

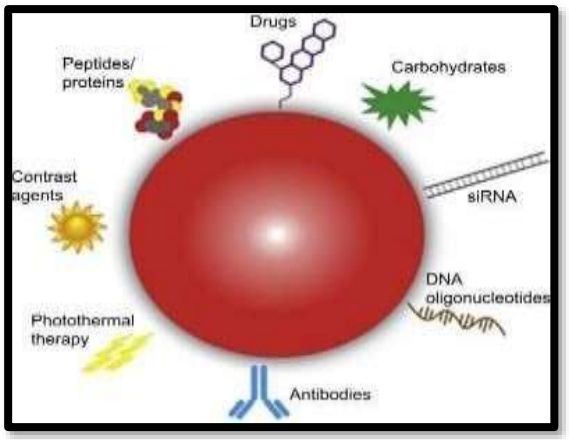

Fig no 09- Metallic nanoparticles

APPLICATION-

Nano-devices for Medicine and Surgery-

This will have a huge impact on medical practice. In addition to laboratory tests, several devices based on nanobiotechnology are used for clinical diagnostics.

Biosensor systems based on nanotechnology could detect emerging diseases in the body at a potentially curable stage. This is extremely important in treating infections and cancer. Some of the body's functions and responses to treatment are monitored without the need for cumbersome laboratory equipment. Some examples include a nanoradio transmitter small enough to be built into a cell and nanoacoustic devices to measure and record the sound of a heart.

ROLE OF NANOTECHNOLOGY IN DRUG –

According to the FDA's definition, drugs are chemicals intended for use in the diagnosis, cure, mitigation, treatment, or prevention of illnesses. Additionally, they include objects, excluding food, designed to influence the structure or function of the human body or other animals. These medications are anticipated to selectively target the cells responsible for the illness, while maintaining a therapeutic concentration that is both accurate and efficacious. Nonetheless, contrary to these anticipations, it is noted that the release rate, stability, and capacity to target particular cells and tissues remain unmanageable and unmonitored.

A medication delivery method is developed to tackle these issues. This system has the ability to control the medication release rate, hence improving the medicine's overall efficacy. Low specificity, insufficient solubility, quick clearance and biodegradation of pharmaceuticals, together with restricted targeting capabilities, are persistent challenges that hinder the effective delivery of medications to the intended tissue or cell. The application of nanomaterials in drug delivery is promising due to their nanoscale dimensions, which enable them to navigate the smallest capillary vessels.

Lipid-based nanoparticles as drug delivery systems

LBN has distinct features essential for use in pharmaceutical nanotechnology. For instance, a high surface area to mass ratio, significant potential for encapsulating poorly water-soluble pharmaceuticals, long-term drug storage stability, sensitivity to change, controlled release, and low toxicity. They may be made by substituting the liquid lipids in an emulsion with solid lipids that remain solid at ambient and physiological temperatures. Drug molecules may be encapsulated at many locations inside LBNs. Lipophilic active compounds are incorporated into the lipid matrix, while

hydrophilic active components are situated on the outside of the lipid matrix According to their size and bilayer quantity, liposomes are categorised into three types: small unilamellar vesicles (SUV) measuring 20–100 nm, large unilamellar vesicles (LUV) ranging from 100–800 nm, and multilamellar vesicles (MLV). Liposomes may be used in numerous medical conditions, including cancer and dermatological disorders, via several routes of administration (parenteral, cutaneous, and pulmonary). The amount of lipid bilayers determines the utilisation of one or more therapeutic compartments inside the liposome structure, whereby hydrophobic substances are integrated into the lipid membrane and hydrophilic medications are encapsulated in the aqueous core.

Polymer-based nanomaterial in drug delivery

The use of polymeric nanoparticles for drug delivery offers significant advantages, such as improved water solubility, reduced likelihood of deactivation, lower antigen activity, and decreased systemic toxicity when compared to conventional free drug delivery approaches.

PNPs are classified into vesicle systems, termed nano capsules, and matrix systems, identified as nanospheres. Recently, researchers have examined the advancements in natural polymers, which also include synthetic polyesters. Natural PNPs have shown advantages over traditional delivery systems due to their improved efficiency and effectiveness. Nonetheless, there are specific limitations, such as challenges with reproducibility, concerns regarding degradation, and the possibility of antigenicity.

The release behaviour of the Teen encapsulated drug is influenced by the manufacturing technique utilised. PNPs demonstrate significant potential as intracellular and site-specific systems. Chitosan is a well-established polysaccharide derivative employed as an efficient hydrophilic drug delivery vehicle. Chitosan has received considerable attention as a carrier in a novel bio adhesive nano system for drug delivery, due to its reactive functionalities, polycationic nature, ease of enzymatic degradation, non-toxic degradation products, and bio adhesive properties. The attributes enhance drug bioavailability and extend the drug residence time at the absorption site.

Nanogel-based drug delivery systems

The formation of nanogels takes place through two primary methods: the preparation of nanogels from polymer precursors and the preparation of Nanogel via heterogeneous polymerisation of monomers. Nanogel typically transport drug molecules through physical inclusions as well as covalent and noncovalent interactions. The impact of size on drug release from the Nanogel drug delivery system is reflected in the diameter of the Nanogel. A Nanogel with a smaller diameter exhibits a greater specific surface area and shortens the diffusion path length of the drug, thereby facilitating an accelerated release of the drug from the Nanogel. Additionally, by preventing the rapid release of the encapsulated drug, Nanogel carriers create a protective shell around themselves that can be disrupted to initiate therapeutic release.

Metal-based nanomaterial as drug delivery systems-

In recent years, there has been a growing interest in the application of metallic nanoparticles across various medical fields, including bioimaging, targeted and sustained drug delivery from biosensors, hyperthermia, and photoablation therapy. Metallic nanoparticles are predominantly composed of silver and gold; however, alternative materials may also be utilised. Gold and silver nanoparticles hold significant importance. Metallic nanoparticles possess a wide range of therapeutic applications, including the delivery of anti-infectives, anti-angiogenic agents, anti-tumor agents, anti-leukemia drugs, and anti-rheumatic drugs. The metallic nanoparticles frequently utilized in drug delivery systems comprise gold (Au), nickel (Ni), silver (Ag), platinum (Pt), ferrous oxide (Fe2O3, Fe3O4, FeO), zinc oxide (ZnO), gadolinium (Gd), silicon dioxide (SiO2), and titanium dioxide (TiO2) particles. The investigation of metal-based nanoparticles as drug delivery systems is driven by factors such as high drug loading, enhanced drug permeability that overcomes first-pass metabolism, electrostatic charge, photo thermal behavioral potential, large surface area, and surface chemistry.

Dendrimer-based drug delivery-

Dendrimers are hyper branched and monodisperse macromolecules characterized by their three-dimensional structures, recognized as one of the most promising polymer

architectures for drug delivery applications. Their spherical shape allows for easy and controlled functionalization of the surface, positioning these structures as highly suitable candidates for drug delivery applications. The specific structure of dendrimers presents several advantages. Drugs may be incorporated into the dendrimer structure through covalent conjugation or electrostatic adsorption methods.

Construction encompasses three fundamental areas: core, branches, and surface. These networks facilitate the targeted delivery of bioactive agents, including drugs, genes, and vaccines, to specific tissues. Their hollow interior creates an opportunity for the absorption of drugs and other bioactive substances that function as vehicles for drug delivery, either through physical means or various interactions. Dendrimers serve as effective gene delivery systems; however, their cytotoxicity limits their application. One approach to address this deficiency is the PEGylation of dendrimers.

ROLE OF NANOTECHNOLOGY IN PRODUCT DEVELOPMENT-

There are many areas of focus where nanotechnology can be applied to enhance drug delivery systems. The domains encompass depot preparations, transdermal drug delivery systems (TDDS) specifically for cancer treatment, enhanced bioavailability through improved dissolution and absorption, along with other related areas. This scholarly article centres on the application of nanotechnology within conventional biphasic liquid dosage forms, specifically suspensions, emulsions, and micelles, aimed at enhancing their performance in drug delivery.

A pharmaceutical nanosuspension is a colloidal dosage form that comprises uniformly dispersed submicron insoluble solid drug particles within an aqueous medium. This formulation is stabilised with surfactants and polymers, and is intended for administration via multiple routes, including oral, parenteral, topical, nasal, ocular, and others. Nano suspension is a technological solution that primarily addresses issues related to drug solubility and bioavailability, while also enhancing drug safety and effectiveness by modifying its pharmaceutical behaviour. This method serves as an alternative strategy for lipid systems when a drug exhibits insolubility in both water-based and organic mediums.

Cancer

Dexa The small size of nanoparticles can be highly beneficial in oncology, especially

in the field of imaging. Nanoparticles, including quantum dots, exhibit quantum confinement properties, such as size-tunable light emission, which can be utilised alongside magnetic resonance imaging to generate exceptional images of tumour sites. In comparison to organic dyes, nanoparticles exhibit significantly greater brightness and require only a single light source for excitation. The application of fluorescent quantum dots has the potential to yield a higher contrast image while being more cost-effective compared to organic dyes utilised as contrast media.

However, quantum dots are typically composed of highly toxic elements. Nanoparticles possess a unique characteristic of a high surface area to volume ratio, enabling the attachment of various functional groups to the nanoparticles, thereby facilitating their binding to specific tumour cells. Additionally, the small size of nanoparticles, ranging from 10 to 100 nm, enables them to preferentially accumulate at tumour sites due to the absence of an effective lymphatic drainage system in tumours.

Nanotechnology in the treatment of neurodegenerative disorders-

One of the most important applications of nanotechnology is in the treatment of neuro degenerative disorders. For the delivery of CNS therapeutics, various nano carriers such as, dendrimers, nano gels, nano emulsions, liposomes, polymeric nano particles, solid lipid nano particles, and nano suspensions have been studied. Transportation of these nano medicines has been effected across various in vitro and in vivo BBB models by endocytosis and/or transcytosis, and early preclinical success for the management of CNS conditions such as, Alzheimer's disease, brain tumors, HIV encephalopathy and acute ischemic stroke has become possible. The nanomedicine can be advanced further by improving their BBB permeability and reducing their neurotoxicity

Parkinson's disease:

This can improve current therapy of Parkinson's disease (PD). Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and affects one in every 100 persons above the age of 65 years, PD is a disease of the central nervous system; neuro inflammatory responses are involved and leads to severe difficulties with body motions. The present day therapies aim to

improve the functional capacity of the patient for as long as possible but cannot modify the progression of the neurodegenerative process. Aim of applied nanotechnology is regeneration and neuro protection of the central nervous system (CNS) and will significantly benefit from basic nanotechnology research conducted in parallel with advances in neurophysiology, neuropathology and cell biology. The efforts are taken to develop novel technologies that directly or indirectly help in providing neuro protection and/or a permissive environment and active signaling cues for guided axon growth. In order to minimize the peripheral side-effects of conventional forms of Parkinson's disease therapy, research is focused on the design, biometric simulation and optimization of an intracranial nano-enabled scaffold device (NESD) for the site-specific delivery of dopamine to the brain, as a strategy. Peptides and peptidic nano particles are newer tools for various CNS diseases. Nanotechnology will play a key role in developing new diagnostic and therapeutic tools.

Antibiotic resistance-

The use of nanoparticles in combination therapy has the potential to reduce antibiotic resistance. Zinc oxide nanoparticles have the potential to reduce antibiotic resistance and improve the antibacterial efficacy of Ciprofloxacin against microorganisms by disrupting various proteins involved in the mechanisms of antibiotic resistance or pharmacological actions of drugs [45].Response of the immune system The nano device bucky balls have been utilised to modify the allergy and immune response. Mast cells are inhibited from releasing histamine into the bloodstream and tissues, as these substances bind to free radicals more effectively than any available antioxidant, including vitamin E.

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CHAPTER NO 02-
NANO PARTICLES: AN OVERVIEW

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BACKGROUND-

Many cosmological, geological, meteorological, and biological phenomena naturally produce nanoparticles. Interplanetary dust, which continues to descend on Earth at a pace of thousands of tonnes per year, contains a large fraction (by number, if not by mass) of nanoparticles, and the same is true of atmospheric dust particles. Many viruses have nanoparticle-sized sizes.

The production and use of nanosized particles were initiated hundreds of years ago in primordial times, however, the past few decades in particular have witnessed notable progress in the interdisciplinary application of this technology Gandhi et al., 2014. In the early 2000s, it was the optimism of scientists in nanotechnology that prompted governmental and funding organizations to undertake strategic reviews of the present significance of nanomedicine (crucial objectives, potential opportunities for improved. health care as well as the risk–benefit analysis of these new technologies) to determine priorities for future funding. The European Science Foundation launched its Forward Look on Nano medicine, which was the first foresight study on medical applications of nano-sciences and nanotechnology. In the same year, the UK government carried out a study to investigate whether nanotechnology could raise new ethical, health, and safety issues. The final report of this investigation was published in 2004 with generally regarded as safe recommendations for a sure, safe, and responsible development of nanotechnology.

HISTORY –

The European Technology Platform Nanomedicine was launched in 2004 from the ingenuity of the European Commission. This group of experts from industry, research centers, and academia convened to prepare the vision regarding future research priorities in nanomedicine. its vision paper and strategic research agenda for

nanomedicine were released, as a first step toward setting up an international platform on nanomedicine, aiming at improving the quality of life and health care of patients. The European Foundation for Clinical Nanomedicine was established in Basel (Switzerland; in 2007) as a non-profit organization which aimed at advancing medicine for the benefit of individuals and society through the application of nanoscience. The Foundation reached its goals through support of clinicians and this led to rapid advancement in the medical applications of nano-sciences. This Foundation created the environment for focused research, interdisciplinary interaction, and information flow between clinicians, researchers, the public, and allied stakeholders

CONCEPT-

A nanoparticle, also known as an ultrafine particle, is a small particle of matter with a dimension of 1 to 100 nanometres (nm). Larger particles (up to 500 nm) or fibres and tubes (less than 100 nm in just two directions) are sometimes referred to as nanoparticles. Metal particles less than 1 nm are commonly referred to as atom clusters instead.

Nanoparticles are distinguished from microparticles (1-1000 m), "fine particles" (sized between 100 and 2500 nm), and "coarse particles" (sized between 2500 and 10,000 nm) by their smaller size, which results in very different physical and chemical properties, such as colloidal properties and optical or electric properties. They normally do not sediment because they are more responsive to brownian motion than colloidal particles, which are typically thought to vary from 1 to 1000 nm.

CLASSIFICATION OF NANO- PARTICLE-

The appearance, size, and chemical properties of nanoparticles are used to classify them into distinct categories. Some of the most well-known classes of nano-particles are listed below, based on physical and chemical features.

Metal Nano-particles-

Metal nanoparticles are nanosized inorganic particles, particularly those of the alkali metals and noble metals, such as copper, silver, and gold, that have unique physical, chemical, and optical properties. They are becoming a more important material in the

development of novel nanodevices for a variety of physical, biological, biomedical, and pharmaceutical applications.

Silver nanoparticles-

In the creation of new pharmaceutical products, the manufacture of homogenous nanosized drug particles with particular size, shape, physical, and chemical properties is of major importance. Silver ions and silver-based compounds are known to be extremely poisonous to microorganisms, with severe biocidal effects on as many as 16 bacteria species, including E. coli. Silver ions have been used in the production of dental resin composites and ion exchange fibres, as well as in the coatings of medical devices, as an antibacterial component.

Nano-silver is deionized water with superfine silver suspended in it that is sold in commercial quantities. In the body, metallic silver nanoparticles with diameters ranging from 5 to 50 nanometers are more effective than silver solution. Nanocrystalline silver products (Acticoat), which use nanotechnology to release nanocrystalline silver crystals, are utilised in wound treatment. They release 30 times fewer silver cations than silver-sulfadiazine cream or a 0.5 percent silver nitrate solution, but they release more of the silver (by Acticoat).

Gold nanoparticles-

Gold nanoparticles with gold cores are a versatile platform with desirable properties for biomedical applications such theragostics, photothermal treatment, and tissue imaging. They're made with core sizes ranging from 1.5 to 10 nanometers, allowing for a broad surface area for effective drug and ligand conjugation. Chemical treatment of hydrogen tetrachloroaurate is a standard way to make gold nanoparticles.

As sophisticated theranostics, gold nanoparticles can be coupled with drugs and targeting ligands to recognise the target receptor precisely for active targeting. Noncovalent contact (for example, electrostatic interaction) or covalent chemical conjugation are both used to achieve therapeutic loading (i.e., organic drug). Diagnostic qualities, tunable core size, monodispersity, low toxicity, large surface to volume ratio, surface plasmon absorption, ability to attach to biomolecules via Au–S bonds, light scattering properties, and simplicity of production are all inherent characteristics of gold nanoparticles.

Iron oxide nanoparticles-

Iron oxide nanoparticles are iron oxide particles having a diameter of one to one hundred nanometers. Magnetite (Fe3O4) and its oxidised counterpart maghemite are the two most common types. They've sparked a lot of curiosity because of their superparamagnetic capabilities and prospective uses in a variety of sectors (although Co and Ni are also highly magnetic materials, they are toxic and easily oxidized). Terabit magnetic storage devices, catalysis, sensors, superparamagnetic relaxometry, high-sensitivity biomolecular magnetic resonance imaging, magnetic particle imaging, magnetic fluid hyperthermia, separation of biomolecules, and targeted drug and gene delivery for medical diagnosis and therapeutics are all examples of iron oxide nanoparticle applications. Long-chain fatty acids, alkyl-substituted amines, and diols are used to coat nanoparticles in these applications. They've been employed in supplement formulations.

Ceramics Nano-particles-

Ceramic nano-particles are non-metallic inorganic solids that are made by heating and cooling. Amorphous, polycrystalline, dense, porous, and hollow shapes are all possible. As a result of their use in applications such as catalysis, photocatalysis, dye photodegradation, and imaging, these nano-particles are attracting a lot of attention from researchers..

Polymeric Nano-particles-

These are mostly organic-based nano-particles, which are referred to as polymer nanoparticles in the literature. They're generally in the shape of nanospheres or nano-capsules. The former are matrix particles with a solid overall mass, whereas the other molecules are adsorbed at the spherical surface's outer edge. The solid mass is totally enclosed within the particle in the latter situation. Because Polymeric nano-particles are easy to functionalize, they have a wide range of applications in the literature.

Nanoshells and magnetic nanoprobes-

Nanoshell particles are thin coverings formed around the core particles of various materials, and they are a specific type of nanocomposite. Nanoshell particles are highly useful materials with customised properties that differ from the core and shell materials. In core shell structures, core particles of various morphologies, including as

rods, wires, tubes, rings, and cubes, can be coated with a thin shell to achieve the desired morphology. Any material, such as semiconductors, metals, or insulators, can be used to make nanoshell materials. Because dielectric materials like silica and polystyrene are very stable, chemically inert, and water-soluble, they are widely employed as cores. Optical absorption in the visible region of the electromagnetic spectrum, luminescence amplification, surface chemical and catalytic characteristics, and magnetic properties are all demonstrated by metal nanoparticles. To make nanoshell particles, a variety of approaches have been devised. A multistep production technique is required to prepare nanoshell particles. To ensure thorough coverage of core particles with the shell material, highly controlled and sensitive synthesis techniques are needed. Precipitation, grafting polymerization, microemulsion, reverse micelle, sol–gel condensation, and layer–bilayer adsorption technique is only a few of the techniques used to make core shell structures.

FORMULATION-

Solvent Evaporation-

The initial approach for making nano particles from a premade polymer was solvent evaporation. The fabrication of an oil-in-water (o/w) emulsion is necessary first in this procedure, which leads to the manufacture of nanospheres. Figure depicts the entire procedure. To begin, an organic phase is made up of a polar organic solvent in which the polymer is dissolved and the active ingredient (e.g., medication) is dispersed or dissolved. Chloroform and dichloromethane have both been commonly employed in the past, though less frequently. They have been superseded by ethyl acetate, which has a superior toxicological profile and so is better suited for biomedical applications, due to their toxicity.

A surfactant-containing aqueous phase is also commonly generated. The organic solution is emulsified with a surfactant in the aqueous phase, then processed with high-speed homogenization or ultrasonication to produce a dispersion of nanodroplets. Evaporation of the polymer solvent, which is allowed to diffuse into the continuous phase of the emulsion, results in the formation of an nanoparticles suspension. The solvent evaporates either by continuous magnetic stirring at room temperature (in the case of more polar solvents) or through a steady reduction in pressure. The hardened nanoparticles can then be cleaned and collected by

Centrifugation, followed by freeze-drying for long-term storage, after the solvent has evaporated. Nanospheres can be made using this technique.

Single emulsion-

The first polymer is dissolved in any organic solvent (e.g., Ethyl Acetate, Acetone, DCM) to generate a single-phase solution, which is then followed by the addition of the medication to produce dispersion. At a suitable temperature, the polymer and drug dispersion is emulsified into an aqueous phase containing surfactants (Pluronic F-68, Nanotechnology-Based Approaches for Targeting and Delivery of Drugs and Genes Polyvinyl alcohol) and stirred. The organic solvent is then allowed to evaporate. In the first example, the emulsion is kept at a low atmospheric pressure while stirring at a constant speed to allow the organic solvent to evaporate. The emulsion is poured into the aqueous phase in the second example to diffuse out the solvent associated with the oil droplet. The PNPs are then rinsed with water to eliminate any excess surfactants.

Double emulsion-

The medication is dissolved in aqueous phase before being added to an organic solvent containing polymer solution and stirred continuously to generate a W/O emulsion in the double emulsion process. The resulting emulsion is mixed continuously at an appropriate stirring speed into an aqueous surfactant solution. The organic solvent is then allowed to evaporate, yielding the required nano particles.

Solvent Diffusion-

An o/w emulsion is formed between a partially water-miscible solvent comprising polymer and medicament and an aqueous solution including a surfactant in this approach. The internal phase of this emulsion is made up of a somewhat hydro-miscible organic solvent, such as benzyl alcohol or ethyl acetate, that has been saturated with water to guarantee that both phases are in thermodynamic equilibrium at room temperature. The production of colloidal particles is caused by solvent diffusion from the dispersed droplets into the exterior phase after dilution with a large volume of water.

This is the most common way for making nanospheres, however nano-capsules can also be made by adding a little amount of oil to the organic phase. This final stage can be eliminated by evaporation or filtration, depending on the boiling point of the organic solvent. Figure illustrates this procedure schematically. Nano particles with dimensions ranging from 80 to 900 nm can be obtained at the end of the process. Despite the need for a large volume of aqueous phase to be removed from the colloidal dispersion and the risk of the hydrophilic drug diffusing into the aqueous phase, this process is often used for polymeric Nano particles synthesis.

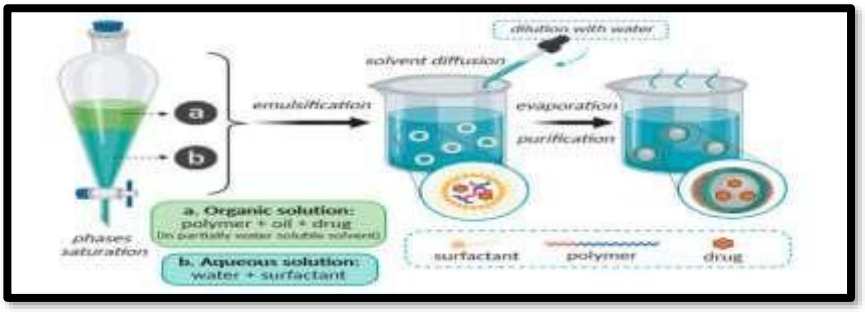

Fig no 01-Schematic representation of the emulsification/solvent diffusion method.

Emulsification/Reverse Salting-Out-

The emulsification/solvent diffusion approach described above can be thought of as a variant of the emulsification/reverse salting-out method. The salting-out method relies on the salting-out effect to separate a hydro-miscible solvent from an aqueous solution, which can result in the creation of nanospheres. The key distinction is the o/w emulsion's composition, which is made up of a gel, a salting-out agent, and a colloidal stabiliser in the aqueous phase, which is made up of a water-miscible polymer solvent such as acetone or ethanol. Examples of suitable salting-out agents include electrolytes, such as magnesium chloride (MgCl2), calcium chloride (CaCl2) or magnesium acetate [Mg (CH3COO)2], as well as non-electrolytes e.g., sucrose. Saturating the aqueous phase reduces the miscibility of acetone and water, allowing the other miscible phases to form an o/w emulsion. At room temperature, the o/w emulsion is made by vigorously swirling it.

The emulsion is then diluted with deionized water or an aqueous solution to allow the organic solvent to diffuse into the exterior phase, the polymer to precipitate, and nanospheres to form. Cross-flow filtration removes the leftover solvent as well as the salting-out agent.It is not necessary for the organic solvent and water to be completely miscible, although it does make the procedure easier. Figure depicts this procedure in diagram form. The nanospheres produced by this process range in size from 170 to 900 nanometers in diameter. By adjusting the internal phase polymer concentration/volume of the exterior phase, the average size can be modified to values between 200 and 500 n

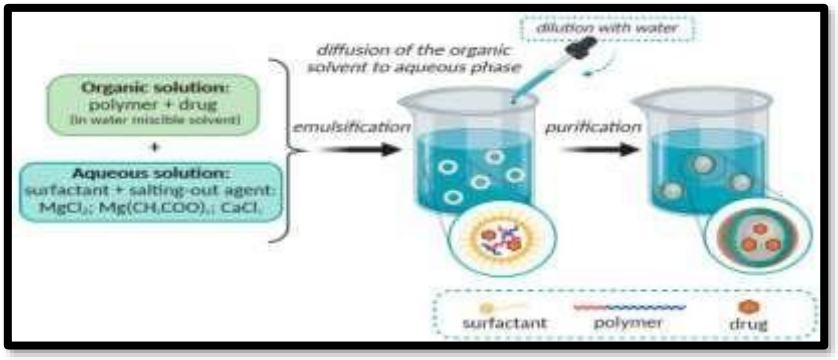

Fig no 02- Schematic representation of the emulsification/reverse salting-out method.

Nanoprecipitation-

Two miscible solvents are needed for this approach, also known as the solvent displacement method. A polymer is dissolved in a miscible organic solvent like acetone or acetonitrile to form the internal phase. They can easily be eliminated by evaporation due to their immiscibility in water. The interfacial deposition of a polymer after the organic solvent has been displaced from a lipophilic solution to the aqueous phase is the basis of this approach. The polymer is dissolved in a water-miscible solvent with an intermediate polarity, and the solution is added to an aqueous solution in a dropwise or regulated manner. The nanoparticles develop instantly in an attempt to escape the water molecules due to the fast spontaneous diffusion of the polymer solution into the aqueous phase. The polymer precipitates in the form of nano-capsules or nanospheres as the solvent diffuses out from the nanodroplets.

The organic component is usually added to the aqueous phase; however, this can be reversed without impacting nanoparticle production. Surfactants are commonly used in the process to ensure the stability of the colloidal suspension, while their presence is not needed for nanoparticle creation. The nanoparticles obtained usually have a well-defined size and a limited size distribution, which are superior to those obtained using the emulsification solvent evaporation technique. Nanoprecipitation is a technique that is commonly used to make polymeric NPs with dimensions of roughly 170 nm, but it can also be used to make nanospheres or nano-capsules. When the active ingredient is dissolved or disseminated in a polymeric solution, nanospheres are formed. The medication is dissolved in an oil, which is then emulsified in an organic polymeric solution before the internal phase of the emulsion is distributed in the external phase.

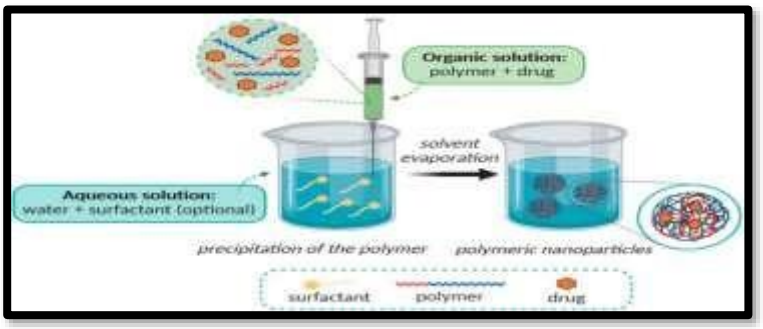

Fig no 03- Schematic illustration of the nanoprecipitation method.

Spray drying-

Aside from emulsification, spray-drying is a rapid, efficient, and low-cost technology with few processing parameters. Spraying a solid-in-oil dispersion or a water-in-oil emulsion in a heated airflow creates the drug-loaded microspheres. The polymer and medication are then dissolved in an organic solvent and thoroughly combined to ensure that all particles are distributed evenly. Spray-dry the suspension system until no more production can be sprayed out and the dried product may be collected.

Phase separation-

The phase separation method entails continuously stirring into the polymer-drug solvent phase, then extracting the preformed mixture, resulting in polymer phase separation by emerging drug-containing droplet. To quench these micro-droplets, the droplet is dipped into a medium that is not soluble in it (both aqueous and organic).

The droplet's coarsening and hardness properties are controlled by the amount of time it spends in the quenching bath. Finally, it is recovered for further use after washing, sieving, filtration, centrifugation, and freeze drying

Supercritical fluid technology-

Traditional procedures are hazardous because they use organic solvents, which are hazardous to both the environment and physiological systems. Because a SCF solvent remains at a temperature above its critical temperature, where fluid exits as a single phase regardless of pressure, it has been investigated as an alternative and safe approach to prepare biodegradable micro and nano particles. Because of its nontoxicity, nonflammability, and low cost, supercritical CO2 is the most often utilised SCF. To dissolve the solute to be micronized, a liquid solvent such as methanol, which is completely miscible with the SCF, is used in the supercritical antisolvent process. Because of the insolubility of the solute non SCF, it precipitates immediately, resulting in the creation of nanoparticles.

CHARACTERIZATION OF NANOPARTICLES-

Morphology-

The shape and size of nano particles have been studied extensively using scanning and transmission electron microscopy (SEM and TEM). To analyse the morphology of nano particles, these are frequently used in conjunction with cryofracture techniques. The transmission electron microscope (TEM) is frequently utilised and can distinguish between nano-capsules and nanospheres, as well as determine the thickness of the nano-capsule wall. Nanospheres have a spherical shape and a solid polymeric structure, whereas nano-capsules have an oily core surrounded by a thin polymeric envelope (approximately 5 nm).

Aspect morphology of nano particles has also been studied using atomic force microscopy (AFM). It can discern surface details at an atomic level and offers information with great resolution in three dimensions and on a nanometric scale. This technique revealed a complex topography on the surface of nanoparticles, as well as the presence of small holes and pores, which were discovered by evaluating sections of samples.

Particle Size Distribution-

nano particles with mean diameters ranging from 100 to 300 nm can be produced using a variety of ways. The size distribution should be unimodal and the polydispersity as low as possible (ideally, practically zero). It is also possible to obtain particles with dimensions of 60 to 70 nm, or even less than 50 nm. The most common techniques for measuring nanoparticle size are dynamic (DLS) and static (SLS) light scattering, but TEM, SEM, and AFM are also frequently utilised. Size measurements differ depending on the method used; for example, electron microscopy provides an image of the particle isolated from its surrounds, whereas DLS allows the hydrodynamic radius of suspended particles to be determined. Furthermore, DLS is a useful supplement to TEM since it can measure bigger sizes, allowing researchers to learn about a nanoparticle's aggregation state in solution by observing variations in particle size distribution.

Chemical Composition and Crystal Structure-

Chemical composition refers to the atomic elements that make up a nanoparticle, as well as native or manufactured functional groups, and can be assessed using either an ensemble or single-particle elemental analysis approach. Atomic absorption spectroscopy is based on the idea of atomic absorption, in which ground state electrons of atoms leap to an excited state by absorbing a specified amount of energy from light at a specific wavelength. The sample mass concentration can be quantified by comparing the signal with calibration standards at known concentrations, because the amount of energy absorbed is related to the type and number of atoms in the light path. Time-of-flight mass spectrometry (TOFMS), which involves ionising small to large organic analytes into the gas phase with minimal fragmentation and then separating/detection using a time-of-flight mass analyser, is one of the techniques used to determine the chemical composition of a single particle.

Surface Area and Chemistry-

Due to its impact on reactivity and surface interactions with ligands, the surface area of nanoparticles is important. Surface area is measured in a variety of ways using various methodologies. Adsorption of an inert gas (such as N2) under different pressure settings forms a monolayer of gas coverage, which is used to quantify the

nanoparticle's surface area directly. The "total surface area" is proportional to the number of gas molecules required to form a monolayer and the adsorbate gas molecule's cross-sectional area.

Because the gas binds to internal holes and fissures, this approach is also used to assess the morphology of porous materials. The elemental or molecular chemistry of a particle surface is referred to as surface chemistry. Because nanoparticles have a larger area/volume ratio, they have a higher fraction of atoms on their surfaces, and these atoms are in direct contact with solvents, influencing their interactions with other molecules. Some nanoparticles, such as nano-capsules, have a core-shell structure in which the atoms on the outer surface differ from those in the inside core. Multiple techniques are available to characterize nanoparticle surface chemistry, for example X-ray photoelectron spectroscopy and secondary ion mass spectroscopy.

Zeta Potential-

The zeta potential represents the particle's surface charge, which is affected by changes in the particle's interface with the dispersing medium, such as dissociation of functional groups on the particle's surface or adsorption of ionic species present in the aqueous dispersion medium, as well as the solvation effect. The zeta potential is estimated from the electrophoretic mobility of particles in a given solvent, which is measured using Doppler techniques. The key components of nano particles include phospholipids, poloxamers, and polymers, all of which can influence the zeta potential when present in formulations. Because substantial repulsive forces tend to prevent aggregation owing to infrequent contacts with nearby nanoparticles, a relatively high zeta potential value, such as | 30 mV|, is required for good physicochemical stability of the colloidal suspension. The zeta potential can be used to figure out how medications interact with nanoparticles.

pH of Suspensions-

Monitoring pH as a function of time provides useful information on the stability of nanoparticulate suspensions. Changing pH, for example, could indicate polymer degradation because it suggests changes in protonation at particle surfaces. Calvo et al. observed a drop in molar mass in suspensions of nano-capsules and nanospheres

after 6 months of storage, as well as a decrease in the pH of these formulationsHowever, depending on the hydrophobicity of the polymer, the decrease in pH values of suspensions over a short period of time can be attributed to both the ionisation of carboxylic groups present in the polymer, releasing protons into the surrounding medium, and the ionisation of carboxylic groups present in the polymer, releasing protons into the surrounding medium. Furthermore, the pH of the medium might affect the zeta potential and electrostatic stability of the formulation, therefore it's important to keep track of it.

Determination of the Drug Association-

Determination of the amount of drug associated with nanoparticles is especially complex due totheir small size, which makes it difficult to separate the free fraction of the drug from the associated fraction. A widely used separation technique is ultra-centrifugation in which the free drug, present in the suspension, is determined in the supernatant after centrifugation. A fraction of the nanoparticles is usually completely dissolved in a suitable solvent to ascertain the total drug concentration. As a result, the difference between the total and free drug concentrations is used to compute the drug concentration associated with nanoparticles. Ultrafiltration-centrifugation, in which a membrane is employed to separate portion of the dispersing aqueous phase from the colloidal suspension, is another approach that has been used. In the ultrafiltration, the free drug concentration is assessed, and the drug fraction associated with nanostructures is estimated by subtracting the total and free drug concentrations.

EVALUATION STUDY-

Organoleptic properties

a) Colour-

It should be unappealing to the eye, and it should be determined using either instrumental or visible procedures that differ from batch to batch. Early batch records and "specs" are extremely useful for later production. If the colour of the body is discovered to be undesired, it might be coated in a variety of colours.

Odor and taste-

Use a less soluble chemical form of an unappealing medicine, or suppress it with

flavours, excipients, coatings, and other means. Drugs that are irritating to the skin should be handled with caution. Stability and bioavailability are affected by the flavours, colours, and excipients utilised. Off-white, cream yellow, tan, and glossy are all possibilities. Pungent, sulphurous, fruity, fragrant, and odourless odours are all possible. Acidic, bitter, bland, strong, sweet, and tasteless flavours are all possible.

Bulk characterization studies-

All solid forms that may exist as a result of the synthetic step, such as the presence of polymorphs, must be identified. During the development phase, bulk parameters such as particle size, bulk density, and surface morphology may be altered to avoid misleading predictions of solubility and stability that are dependent on a specific crystalline form. Bulk characterisation testing entails a variety of procedures.

Crystallinity and polymorphism-

Crystallinity refers to the structure of a solid compound, and these structures vanish in the liquid and vapour stages. Internal structures (cubic, tetragonal, hexagonal, rhombic, etc.) can be classified. Habits that are solid (platy, needle, tabular, prismatic, bladed, and so on), Changing the internal structure affects crystal habits, but changing the chemical form (for example, salt production) affects both the internal structure and crystal habit. Crystallization from various solvents and solidification after melting produce various polymorphs. It's called "hydrates" when the integrated solvent is water. "Anhydrous" refers to a chemical that has no water within its crystal structure.

In three dimensions, atoms in crystalline materials are arranged in regular and recurring patterns. In amorphous substances, for example, atoms or molecules are randomly distributed without a regular atomic order. Polymorphism refers to a compound's ability to crystallise as multiple unique crystalline species, each having a different internal lattice and different crystal shapes (at different free energy states). Melting point, density, vapour pressure, X-ray, colour, crystal structure, hardness, solubility, dissolution rate, and bioavailability are all varied. Identifying the polymorph that is stable at room temperature during preformulation is critical. For examples: There are three types of chloramphenicol: A, B, and C. The B form is the most stable and preferred. Riboflavin comes in three forms: I, II, and III, the latter of which has a 20-fold higher water solubility than the former. Under the melting point of either

polymorph, enantiotropic polymorphs can be interconverted, and the process is reversible at a specific temperature. Sulphur is a good example.

Hygroscopicity-

Many pharmaceuticals have a proclivity for absorbing water. At a given temperature, the amount of moisture adsorbed by a certain weight of anhydrous sample in equilibrium with air moisture. Deliquescent (a substance that absorbs enough moisture from the atmosphere to dissolve itself at a higher level), Efflorescent (a substance that loses water to form a lower hydrate or become anhydrous at a lower level), and Hygroscopic (a substance that exists in a dynamic equilibrium with water) are the three classifications. The relative humidity of the environment influences this process. Karl Fisher, gravimetric, TGA, and gas chromatography procedures are used to characterise it. It is significances as changes in moisture content that affects stability, flow ability, compatibility, etc

Fine particle characterization-

The particle size distribution influences a number of physical and chemical aspects of pharmacological compounds, including drug dissolution rate. bioavailability, consistency of content, taste, and texture colour, and consistency Furthermore, features such as among other things, flow characteristics and sedimentation rates Others are also crucial particle-related factors size. It's critical to figure out as soon as possible how the drug substance's particle size affects formulation and product efficacy. Light microscope with a calibrated grid, sedimentation techniques, stream scanning, Coulter counter, and surface area estimation by BET nitrogen adsorption method are some of the methods for evaluating particle size and distribution.

Bulk density-

The actual and bulk densities of the drug material are extremely helpful in estimating the size of the final dose form. This value is obviously crucial for low-potency medicines, which may make up the majority of the final granulation or table. The bulk density of a product varies significantly depending on the method of crystallisation, milling, or formulation. Once a density problem has been found, it may often be simply remedied through milling slugging or formulation. It has the potential to change the

properties of powder flow. It has an impact on the size of a high-dose capsule productor the homogeneity of a low-dose formulation with considerable densities of medication and excipients.

Powder flow properties-

Powder flow characteristics are crucial for a successful tablet manufacturing process. As a result, during the preformulation evaluation of the drug material, its flow ability feature should be investigated, especially when the drug's predicted dose is high. Powders can be either free-flowing or clumpy (non free flowing). Changes in particle size, density, shape, electrostatic charges, and adsorbed moisture alter flow characteristics. Carr's index and Hausner ratio, Angle of repose, rheology, and thixotropy are some of the characteristics.

Compression properties-

Small quantities of a new drug candidate's compression qualities (elasticity, plasticity, fragment ability, and punch filmmaking tendency) can be determined. This feature is used in the formulation ingredient selection process.

Physical description-

It is feasible to observe based on size, shape, and appearance, and it can be determined either instrumentally or visually.

Solubility analysis-

One of the main goals of the preformulation effort is to develop a method for producing medication solutions. For therapeutic efficacy, a medication must have some aqueous solubility. A drug must first be in solution before it may penetrate the systemic circulation and exhibit a therapeutic effect. Incomplete absorption is common with somewhat insoluble substances. When a solute dissolves, the intermolecular forces of attraction of the material must be overcome by forces of attraction between the solute and solvent molecules. To achieve the solute solvent attraction, the solute solute forces and the solvent-solvent forces must be broken. It focuses on drug solvent interactions that may arise during drug candidate distribution. Orally administered drugs, for example, should be tested for solubility in simulated stomach medium. We must carry out a solubility test. analysis of a novel medicine to serve as a foundation

for future research It is possible that the formulation process will have an impact on the drug's performance.

pKa determination-

The pH partition theory is based on the interactions between the dissociation constant, lipid solubility, and pH at the absorption site, as well as the absorption characteristics of various medications. Potentiometric titration is commonly used to calculate the dissociation constant, or pKa. Weak organic acids or bases make up the majority of medications nowadays. Because their absorption is determined to a significant extent by their specific ionisation or dissociation characteristics, it's crucial to understand them. as they are presented to their degrees of ionisation Barriers in the membrane The degree of ionisation of a drug is determined by the pH of the solution in which it is delivered to the biologic membrane, as well as the drug's pKa, or dissociation constant (whether an acid or base).

Partition coefficient-

The oil/water partition coefficient is a measure of a molecule's lipophilic properties, or whether it prefers the hydrophilic or lipophilic phases. When developing a pharmacological substance into a dosage form, the partition coefficient should be taken into account. If you add a solute to a combination of two immiscible liquids, it will disperse evenly throughout the two phases and attain equilibrium at a steady temperature. The ratio of the unionised drug dispersed between the organic (upper phase) and aqueous (lower) phases at equilibrium can be stated as follows: it is the distribution of the solute (unaggregated & undissociated) between the two immiscible layers.

Dissolution studies-

The dissolving rate is the rate at which a pharmacological substance dissolves in a medium. When dissolution rate data is combined with information on a drug's solubility,

$$\frac{dc}{dt} = \frac{D\,A\,(Cs-C)}{h\,V}$$

D: diffusion coefficient
h: thickness of the diffusion layer at solid liquid interface.
A: the surface area of the drug in contact with the dissolution medium.
V: volume of media.
Cs: saturated solubility of the drug in the dissolution medium at exp. Temp.
C: the concentration of the drug at time t.

dissociation constant, and partition coefficient, it can be used to estimate the drug's absorption potential after delivery. The Noyes Whitney equation describes the dissolving rate of a medication when the surface area remains constant during dissolution. The equation shows that increasing the surface area of a drug (cutting particle size) and increasing the drug's solubility in the diffusion layer can enhance the drug's dissolving rate.

UV Spectrophotometric studies-

The UV Spectroscopic study is performing their role as an addition for identification tools. UV spectrums of drug identification tools. UV spectrums of drug in different solvent were obtained by making the solution of drug in different solvent and analysing this solution using UV – Visible spectrophotometer. The spectrum obtained was compared with the standard (shimadzu UV -Visible spectrophotometer, model UV 1700). Accurately weighed 10 mg of drug was dissolved in 10 ml of volumetric flask and prepared suitable dilution. The spectrum of this solution was analysed in 270 – 300 nm range in UV Visible spectrophotometer and compared with the standard.

Preparation of phosphate buffer PH 6.8 mixed –

Dissolve 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen in sufficient water to produce 1000ml.

Preparation of standard stock solution –

Weighed accurately 10 mg of candidate drug and transferred to 100 ml of volumetric flask. Phosphate buffer PH 6.8 was added to dissolve the drug completely. Make up the volume up to 100 ml by phosphate buffer PH 6.8.

Preparation of standard calibration curve of candidate drug in phosphate buffer PH 6.8 – From above solution various dilution were prepared to get concentration 2,4,6,8,10 µg/ml The graph of concentration v/s absorbance was plotted a data was subjected to linear regression analysis lambda max being 233 nm.

Preparation of phosphate buffer PH 7.4 – Dissolve 2.38 gm of disodium hydrogen phosphate 0.19 gm of potassium di-hydrogen phosphate and 8 gm of sodium chloride

in a 1000 ml volumetric flask and made up the volume up to 1000 ml with distilled water.

Preparation of standard stock solution – Weighed accurately 10 mg of candidate drug and transferred to 100 ml of volumetric flask phosphate buffer PH 7.4 was added to dissolve the drug completely. Make up the volume up to 100 ml by phosphate buffer PH 7.4.

Preparation of standard calibration curve of candidate drug in phosphate buffer PH 7.4 -From above solution various dilution were prepared to get concentration 2,4,6,8,10 µg/ml The graph of concentration v/s absorbance was plotted and data was subjected to linear regression analysis lambda max being 233 nm.

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CHAPTER NO 03- TYPES, CHALLENGES AND APPLICATIONS OF NANO PARTICLES

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Introduction-

Nanoparticles are ultra-small particles, typically ranging in size from 1 to 100 nanometers (nm), that exhibit unique physical, chemical, and biological properties compared to their bulk counterparts due to their small size and high surface area-to-volume ratio. In the context of **nanotechnology**, they serve as fundamental building blocks and are applied across various fields, such as pharmaceutics, medicine, electronics, and materials science.

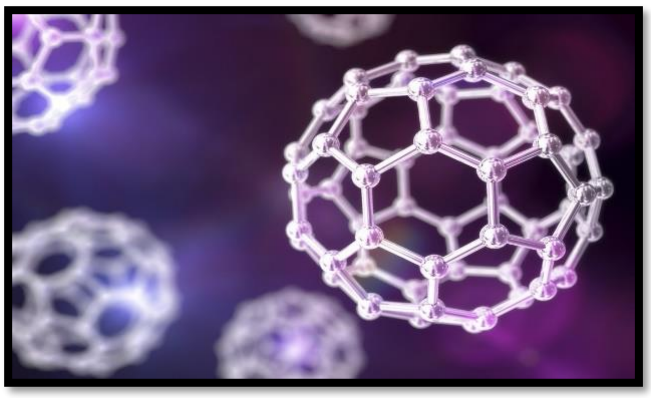

Fig no 01- Nanoparticle

- **Size**: The nanoscale size (1 to 100 nm) allows nanoparticles to exhibit behaviors different from their larger, bulk counterparts. At this scale, quantum effects and increased surface interactions significantly impact their properties.
- **Surface Area**: Nanoparticles have a high surface area relative to their volume, leading to enhanced reactivity, improved solubility, and a greater ability to interact with biological systems.

- **Quantum Effects**: At the nanoscale, quantum mechanics play a more significant role in governing the properties of materials. These effects can alter the optical, electrical, and magnetic behaviors of nanoparticles.
- **Enhanced Permeability and Retention (EPR) Effect**: In drug delivery, nanoparticles can exploit the EPR effect, where they preferentially accumulate in tumor tissues due to the leaky vasculature and poor lymphatic drainage.

Definition of Nanoparticles in Pharmaceutics

Nanoparticles in pharmaceutics refer to tiny particles ranging from 1 to 100 nanometers in size, designed for drug delivery and therapeutic purposes. Due to their small size, nanoparticles can penetrate biological barriers, enhance drug solubility, improve bioavailability, and provide targeted drug delivery, minimizing side effects and improving efficacy.

Types of Nanoparticles in Pharmaceutics-

1. **Lipid-based Nanoparticles**:
   - **Liposomes**: Vesicles with lipid bilayers, used for delivering hydrophilic and hydrophobic drugs.
   - **Solid Lipid Nanoparticles (SLNs)**: Solid lipid core stabilized by surfactants, useful for controlled drug release.
2. **Polymeric Nanoparticles**:
   - Made from biodegradable polymers (e.g., PLGA, chitosan), used for sustained drug release.
   - Can be formulated as nanospheres (solid) or nanocapsules (core-shell structure).
3. **Metallic Nanoparticles**:
   - **Gold, Silver, Iron Oxide Nanoparticles**: Used in imaging, diagnostics, and drug delivery due to their unique optical and magnetic properties.
4. **Dendrimers**:
   - Branched polymers with a tree-like structure, capable of carrying multiple drug molecules or targeting ligands.
5. **Carbon-based Nanoparticles**:
   - **Carbon Nanotubes, Fullerenes**: Used for drug delivery, though concerns about biocompatibility exist.

6. **Protein-based Nanoparticles**:
   - Proteins like albumin used as carriers for anticancer drugs (e.g., albumin-bound paclitaxel).

Lipid-based Nanoparticles

Lipid-based nanoparticles (LNPs) are a type of nanocarrier that uses lipids to encapsulate drugs or therapeutic agents. They are especially useful for delivering hydrophobic (water-insoluble) drugs, improving drug bioavailability, stability, and targeting. These nanoparticles mimic natural lipid structures, making them biocompatible and capable of interacting with biological membranes easily.

Applications in Drug Delivery-

1. **Targeted Drug Delivery**: Nanoparticles can be functionalized with ligands (e.g., antibodies, peptides) to target specific tissues or cancer cells, enhancing precision in treatment.
2. **Controlled and Sustained Release**: Nanoparticles allow for the gradual release of drugs over time, maintaining therapeutic concentrations for extended periods.
3. **Improved Solubility**: Drugs with poor water solubility can be encapsulated in nanoparticles, improving their bioavailability.
4. **Crossing Biological Barriers**: Nanoparticles can cross the blood-brain barrier (BBB) and other tight junctions, enabling the delivery of drugs to the brain or other protected sites.

Challenges and Considerations

1. **Toxicity and Biocompatibility**: Some nanoparticles (e.g., metallic nanoparticles) may accumulate in organs and cause toxicity over time.
2. **Regulatory Hurdles**: The development of nanoparticle-based drugs must meet stringent safety and efficacy standards by regulatory authorities like the FDA.
3. **Scale-up and Manufacturing**: Consistent and scalable manufacturing of nanoparticles can be difficult, impacting cost and quality control.
4. **Environmental Concerns**: Nanoparticles can potentially have unintended effects on the environment when disposed of improperly.

Lipid-based nanoparticles are a highly promising and versatile platform in drug delivery, with applications in cancer therapy, vaccine development, gene therapy, and beyond. Their ability to encapsulate both hydrophilic and hydrophobic drugs, improve drug bioavailability, and reduce toxicity makes them ideal carriers in modern pharmaceutics. However, challenges related to stability, scalability, and long-term safety must be addressed for wider application and commercialization

Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are a type of nanoparticle composed of natural or synthetic polymers. These nanoparticles range from 10 to 1000 nanometers in size and are used in drug delivery, imaging, and therapeutic applications. Polymeric nanoparticles can encapsulate or conjugate drugs, providing controlled release and targeted delivery, making them highly effective for enhancing the bioavailability and therapeutic efficacy of drugs.

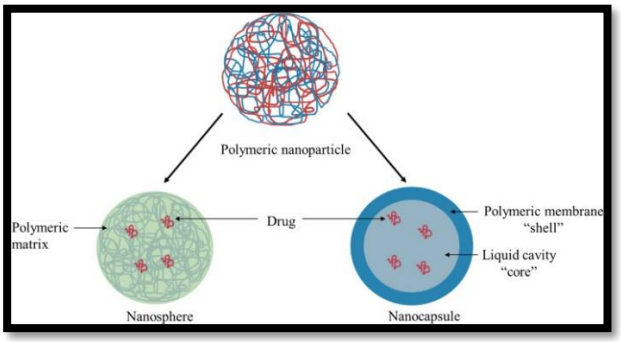

Fig no 03- Polymeric Nanoparticles

Types of Polymeric Nanoparticles

1. **Nanospheres**:
   - **Structure**: Nanospheres are solid matrix-like particles where the drug is dispersed or adsorbed on the surface or within the polymer matrix.
   - **Applications**: They are primarily used for the delivery of anticancer agents, antibiotics, and vaccines.
   - **Advantages**: Nanospheres provide controlled and sustained drug release and protect drugs from degradation.
2. **Nanocapsules**:

- **Structure**: Nanocapsules have a core-shell structure where the drug is confined to an inner cavity surrounded by a polymeric membrane or shell. This core-shell design allows for the encapsulation of both hydrophilic and hydrophobic drugs.
- **Applications**: Nanocapsules are used for targeted drug delivery, especially for hydrophobic drugs.
- **Advantages**: They offer higher drug loading capacity and improved drug release kinetics compared to nanospheres.

Common Polymers Used in Polymeric Nanoparticles

1. **Natural Polymers**:
   - **Chitosan**: A natural polymer derived from chitin (found in crustacean shells), known for its biocompatibility and biodegradability.
   - **Alginate**: A biopolymer derived from algae, commonly used for encapsulating drugs and cells in tissue engineering.
   - **Gelatin**: A protein-based polymer used for encapsulating proteins, peptides, and small-molecule drugs.
2. **Synthetic Polymers**:
   - **Poly (lactic-co-glycolic acid) (PLGA)**: One of the most commonly used synthetic polymers in drug delivery due to its biocompatibility and FDA approval. It degrades into lactic acid and glycolic acid, which are naturally metabolized by the body.
   - **Polylactic acid (PLA)**: A biodegradable polymer used in controlled drug delivery systems.
   - **Polycaprolactone (PCL)**: A biodegradable polymer that provides longer drug release due to its slow degradation rate.

Properties of Polymeric Nanoparticles

1. **Biodegradability**: Polymeric nanoparticles can degrade over time into non-toxic byproducts, making them suitable for sustained drug delivery.
2. **Surface Functionalization**: The surface of polymeric nanoparticles can be modified with ligands, targeting molecules, or polyethylene glycol (PEG) to improve targeting specificity, circulation time, and reduce immunogenicity.

3. **Controlled Release**: The degradation of the polymer matrix and the diffusion of the drug from the nanoparticles allow for controlled and sustained release of the encapsulated drug, ensuring long-term therapeutic effects.
4. **Drug Loading**: Polymeric nanoparticles can encapsulate a wide range of drugs, including hydrophobic and hydrophilic molecules, proteins, peptides, and nucleic acids, enhancing the solubility and stability of the drugs.

Applications of Polymeric Nanoparticles

1. **Drug Delivery**:
   - **Cancer Therapy**: Polymeric nanoparticles are extensively used for the delivery of chemotherapeutic agents. The particles can be engineered to specifically target tumor cells, improving drug efficacy while reducing side effects.
     - Example: **Docetaxel-loaded PLGA nanoparticles** used for targeted cancer treatment.
   - **Oral Drug Delivery**: Polymeric nanoparticles can protect drugs from degradation in the gastrointestinal tract, enabling oral delivery of drugs that would otherwise be destroyed before reaching the bloodstream.
     - Example: Insulin-loaded polymeric nanoparticles for oral administration in diabetes treatment.
   - **Targeted Delivery**: Polymeric nanoparticles can be functionalized with targeting ligands (e.g., antibodies or peptides) that bind to specific receptors on diseased cells, such as cancer cells or inflamed tissues, enhancing drug delivery specificity.
2. **Gene Therapy**:
   - Polymeric nanoparticles are used to deliver genetic material (e.g., DNA, siRNA, or mRNA) to cells for gene therapy applications. These nanoparticles protect genetic material from degradation and can target specific cells for gene delivery.
     - Example: Chitosan-based nanoparticles are used to deliver DNA vaccines.
3. **Vaccines**:
   - Polymeric nanoparticles are used as vaccine carriers, encapsulating antigens and enhancing the immune response. They can improve the stability of antigens and ensure slow release, promoting a stronger and more prolonged immune response.
     - Example: PLGA nanoparticles used in vaccine delivery for enhanced immunization against infectious diseases.

4. **Imaging and Diagnostics**:
   - Polymeric nanoparticles are used in imaging applications (e.g., MRI or fluorescence imaging) by incorporating imaging agents such as dyes or magnetic nanoparticles. They provide enhanced imaging contrast and allow for targeted imaging of specific tissues.
   - Example: Iron oxide-loaded polymeric nanoparticles for MRI imaging of tumors.

Advantages of Polymeric Nanoparticles

- **Biocompatibility and Biodegradability**: Most polymers used in nanoparticles are biocompatible and biodegradable, reducing the risk of toxicity.
- **Controlled Drug Release**: Polymeric nanoparticles can release drugs in a controlled manner, providing sustained therapeutic effects over time.
- **Versatility**: These nanoparticles can encapsulate a wide range of drugs, including hydrophilic, hydrophobic, and sensitive biomolecules like proteins and nucleic acids.
- **Targeted Delivery**: Polymeric nanoparticles can be engineered for targeted drug delivery, reducing side effects and improving treatment outcomes.
- **Protection of Drug**: They protect drugs from premature degradation, especially in harsh environments like the gastrointestinal tract or bloodstream.

Challenges of Polymeric Nanoparticles

1. **Toxicity and Immunogenicity**:
   - Although many polymers are biocompatible, the degradation products of some synthetic polymers can cause toxicity or trigger immune responses, particularly if not properly metabolized.
2. **Manufacturing Complexity**:
   - The production of polymeric nanoparticles requires precise control over size, drug loading, and release properties. Large-scale manufacturing with consistent quality can be challenging.
3. **Drug Loading Limitations**:
   - Polymeric nanoparticles may have limited drug loading capacity, particularly for hydrophobic drugs, and there may be issues with drug leakage during storage or after administration.
4. **Regulatory Hurdles**:

- Ensuring the safety, efficacy, and quality of polymeric nanoparticle-based drugs can be complex, and these systems must meet stringent regulatory requirements before they can be approved for clinical use.

Polymeric nanoparticles hold great promise in the fields of drug delivery, gene therapy, diagnostics, and vaccines. Their versatility, biocompatibility, and ability to provide controlled and targeted drug release make them an important tool in modern medicine. Despite challenges related to manufacturing, drug loading, and regulatory issues, continued advancements in polymer science are expanding the potential of these nanoparticles for treating a variety of diseases.

Metallic nanoparticles-

(MNPs) are tiny particles composed of metals, typically ranging in size from 1 to 100 nanometers (nm). Due to their small size and large surface area-to-volume ratio, metallic nanoparticles exhibit unique physical, chemical, optical, and electronic properties that differ significantly from their bulk counterparts. These nanoparticles are widely used in field such as medicine, electronics, catalysis, and environmental science.

Types of Metallic Nanoparticles-

1. **Gold Nanoparticles (AuNPs)**:
   - **Properties**: Gold nanoparticles exhibit excellent biocompatibility, tunable optical properties, and chemical stability. Their surface plasmon resonance (SPR) allows them to absorb and scatter light, giving them unique optical features.
   - **Applications**: They are used in drug delivery, diagnostics, imaging, and cancer therapy. AuNPs are also used in biosensors and photothermal therapy for cancer.
2. **Silver Nanoparticles (AgNPs)**:
   - **Properties**: Silver nanoparticles possess strong antimicrobial and anti-inflammatory properties. They exhibit plasmonic behavior similar to gold nanoparticles but are less expensive.
   - **Applications**: AgNPs are widely used as antibacterial agents in medical devices, wound dressings, and coatings. They are also employed in biosensing and water purification systems.

3. **Iron Oxide Nanoparticles (Fe_3O_4)**:
   - **Properties**: Iron oxide nanoparticles are magnetic and can be easily manipulated using external magnetic fields. They exhibit superparamagnetic behavior, meaning they become magnetic in the presence of a magnetic field but lose magnetism when the field is removed.
   - **Applications**: They are used in magnetic resonance imaging (MRI), drug delivery, hyperthermia treatment for cancer, and as contrast agents in imaging.
4. **Zinc Oxide Nanoparticles (ZnO NPs)**:
   - **Properties**: Zinc oxide nanoparticles have unique optical, chemical, and antimicrobial properties. They are transparent in thin films and have a wide bandgap, making them useful in electronics and UV-blocking materials.
   - **Applications**: ZnO NPs are used in sunscreens, cosmetics, antimicrobial coatings, and photocatalysis.
5. **Platinum Nanoparticles (PtNPs)**:
   - **Properties**: Platinum nanoparticles have excellent catalytic properties and are chemically stable. Their high surface area enhances their catalytic activity.
   - **Applications**: They are used as catalysts in fuel cells, chemical reactions, and environmental cleanup processes. PtNPs are also explored for use in cancer therapy and biosensing.

Properties of Metallic Nanoparticles

1. **Surface Plasmon Resonance (SPR)**: Metallic nanoparticles, particularly gold and silver, exhibit SPR, which occurs when the conduction electrons on the nanoparticle surface resonate with incident light. This property makes them highly effective in optical applications such as imaging, biosensing, and photothermal therapy.
2. **Catalytic Activity**: Due to their high surface area and the availability of active sites, metallic nanoparticles (like platinum and palladium) are highly efficient catalysts. This property is widely used in industrial chemical reactions, fuel cells, and environmental remediation.
3. **Magnetic Properties**: Magnetic metallic nanoparticles, such as iron oxide, exhibit superparamagnetic behavior, meaning they can be magnetized and

demagnetized quickly. This property is crucial in medical imaging (MRI) and targeted drug delivery applications.

4. **Antimicrobial Activity**: Metallic nanoparticles, particularly silver, are known for their strong antimicrobial effects. Silver nanoparticles can disrupt the cell membranes of bacteria, making them effective in preventing infections in medical devices and coatings.
5. **Optical Properties**: Metallic nanoparticles have unique optical properties, such as tunable light absorption and scattering. These properties are essential for applications in optical sensors, imaging, and photothermal therapy.

Applications of Metallic Nanoparticles

1. **Drug Delivery**:
   - Metallic nanoparticles, especially gold and silver, are used as drug carriers due to their ability to be functionalized with biomolecules. Gold nanoparticles, in particular, can be conjugated with drugs and targeted to specific cells, such as cancer cells.
2. **Cancer Therapy**:
   - **Photothermal Therapy (PTT)**: Gold nanoparticles are used in PTT, where they convert absorbed light into heat, selectively killing cancer cells without damaging surrounding healthy tissue.
   - **Magnetic Hyperthermia**: Magnetic nanoparticles (e.g., iron oxide) are used to generate heat when exposed to an alternating magnetic field, killing cancer cells.
3. **Imaging and Diagnostics**:
   - **MRI Contrast Agents**: Iron oxide nanoparticles are used as contrast agents in MRI, enhancing the visibility of specific tissues, such as tumors.
   - **Biosensors**: Metallic nanoparticles (e.g., gold and silver) are used in biosensors for detecting biomolecules like proteins, DNA, and pathogens due to their unique optical and electrical properties.
4. **Antimicrobial Applications**:
   - Silver nanoparticles are commonly used in medical devices, wound dressings, and coatings to prevent bacterial infections. They release silver ions, which have potent antibacterial effects.
5. **Catalysis**:

- Metallic nanoparticles, especially platinum and palladium, are used as catalysts in various industrial processes due to their enhanced catalytic efficiency.

6. **Environmental Remediation**:
   - Metallic nanoparticles are used in environmental applications, such as removing pollutants from water and air. For example, gold nanoparticles are used in detecting and removing heavy metals from contaminated water.
7. **Electronics and Sensors**:
   - Metallic nanoparticles are used in the fabrication of electronic devices, including conductive inks, sensors, and thin films. Their electrical conductivity and unique optical properties make them suitable for various nanotechnology applications.

Challenges of Metallic Nanoparticles

1. **Toxicity**:
   - Some metallic nanoparticles can exhibit toxicity due to the release of metal ions or accumulation in organs. Silver nanoparticles, for example, can cause cytotoxicity at high concentrations.
2. **Stability**:
   - Metallic nanoparticles can aggregate in solution, which may affect their properties and performance. Stabilization techniques are often needed to maintain their dispersibility and functionality.
3. **Cost**:
   - Some metallic nanoparticles, such as gold and platinum, are expensive to produce, which can limit their widespread application, especially in large-scale industrial processes.

Metallic nanoparticles offer immense potential in various fields, including medicine, catalysis, and environmental science, due to their unique properties like surface plasmon resonance, catalytic efficiency, and antimicrobial action. While there are challenges related to toxicity, stability, and cost, continued research and development are driving innovations that harness the capabilities of metallic nanoparticles for targeted drug delivery, cancer therapy, diagnostics, and more. Their multifunctionality and tunability make them a powerful tool in nanomedicine and beyond.

Dendrimers

Dendrimers are highly branched, tree-like macromolecules with a well-defined, symmetric structure consisting of a central core, interior layers (called generations), and multiple peripheral functional groups. They are typically nanoscale in size, ranging from 1 to 10 nanometers, and their precise, tunable structure allows for a wide range of applications, especially in drug delivery, diagnostics, and nanomedicine.

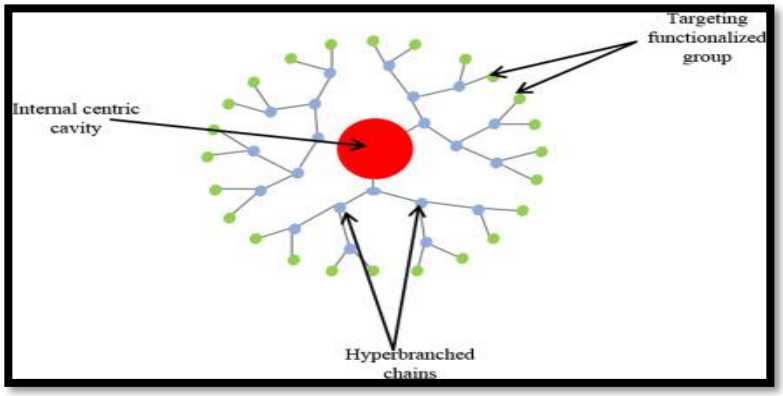

Fig no 02- Dendrimers structure of Dendrimers

Dendrimers are built through a stepwise, branched synthesis process, resulting in a highly controlled and predictable structure. The basic components of a dendrimer are:

1. **Core**: The central atom or molecule that forms the foundation for the dendrimer's branching. Common core molecules include ammonia (NH_3), ethylenediamine, or other small organic compounds.
2. **Branches (Generations)**: Each layer of branching that extends from the core is known as a generation. As the number of generations increases, the dendrimer's size and surface functional groups multiply, giving it a spherical or globular shape.
3. **Surface Functional Groups**: The outermost layer of the dendrimer is made up of terminal functional groups, which can be chemically modified to interact with specific drugs, targeting molecules, or other biological components. These surface groups determine the dendrimer's solubility, biocompatibility, and ability to conjugate with drugs or other molecules.

Types of Dendrimers

1. **Poly(amidoamine) (PAMAM) Dendrimers**:

- **Structure**: One of the most widely studied dendrimers, PAMAM dendrimers have an amide and amine-based structure.
- **Applications**: They are extensively used in drug delivery, gene therapy, and imaging due to their biocompatibility and ability to encapsulate both hydrophobic and hydrophilic drugs.

2. **Polypropylene Imine (PPI) Dendrimers**:
   - **Structure**: These dendrimers have a polypropylene imine backbone and are commonly used in catalysis and material science.
   - **Applications**: They are also being explored for drug delivery and tissue engineering applications.
3. **Polyester Dendrimers**:
   - **Structure**: These dendrimers are made from biodegradable and biocompatible polyesters, which degrade into non-toxic byproducts.
   - **Applications**: They are primarily used in drug delivery, especially for slow-release formulations.
4. **Phosphorus Dendrimers**:
   - **Structure**: These dendrimers have a phosphorus atom at the core and a variety of branching units, making them versatile for various chemical applications.
   - **Applications**: They are used in catalysis, imaging, and as flame retardants, in addition to potential applications in drug delivery.

Properties of Dendrimers

1. **Monodispersity**: Dendrimers have a uniform, highly controlled structure, unlike other polymers that can vary in size and shape. This uniformity allows for predictable behavior in drug delivery and other applications.
2. **Multivalency**: The multiple functional groups on the surface of dendrimers can be chemically modified to carry drugs, targeting molecules, or imaging agents, making dendrimers highly versatile carriers.
3. **High Drug Encapsulation Capacity**: Dendrimers possess internal cavities within their branched structure, which can encapsulate small molecules or drugs. This allows for efficient drug loading and protection of the drug from degradation.

4. **Biocompatibility and Low Immunogenicity**: Many dendrimers, especially those made from biocompatible materials like PAMAM or polyester, exhibit low toxicity and immunogenicity, making them suitable for medical applications.
5. **Enhanced Permeation and Retention (EPR) Effect**: Dendrimers can exploit the EPR effect, where nanoparticles accumulate in tumor tissues due to leaky vasculature, making them ideal for targeted cancer therapies.

Applications of Dendrimers

1. **Drug Delivery**:
   - Dendrimers can carry multiple drug molecules either through encapsulation in their internal cavities or by conjugation to their surface groups. Their controlled size and surface modification capabilities allow for targeted drug delivery to specific cells or tissues.
2. **Gene Therapy**:
   - Dendrimers are used as non-viral vectors for delivering nucleic acids (e.g., DNA, siRNA) to cells. Their multivalency allows for the conjugation of nucleic acids, protecting them from degradation while enhancing cellular uptake.
3. **Diagnostics and Imaging**:
   - Dendrimers can be conjugated with imaging agents such as fluorophores or MRI contrast agents for use in diagnostics. Their multivalency allows them to carry multiple imaging agents, enhancing signal strength.
4. **Antimicrobial Agents**:
   - Dendrimers can be functionalized with antimicrobial agents, enhancing their ability to kill or inhibit the growth of bacteria, fungi, and viruses.
5. **Cancer Therapy**:
   - Dendrimers are used in targeted cancer therapy due to their ability to carry anticancer drugs directly to tumor cells. They can be functionalized with targeting ligands that recognize cancer cell markers, ensuring selective delivery to the tumor site.
6. **Vaccines**:
   - Dendrimers can be used as vaccine carriers, encapsulating antigens and enhancing the immune response. Their multivalency allows them to present multiple antigens or adjuvants simultaneously.

Challenges of Dendrimers

1. **Toxicity**:
   - Some dendrimers, especially those with cationic surface charges, can cause cytotoxicity by disrupting cell membranes. This issue can be mitigated by surface modification with neutral or negatively charged molecules.
2. **Complex Synthesis**:
   - The synthesis of dendrimers is time-consuming and costly, especially for higher generations, which can limit large-scale production.
3. **Drug Release**:
   - Controlling the release of encapsulated drugs from dendrimers can be challenging, especially for drugs that are non-covalently bound. Surface modifications or external stimuli (e.g., pH-sensitive linkers) may be required for controlled release.
4. **Regulatory Hurdles**:
   - Dendrimers, like other nanomaterials, face regulatory challenges due to concerns about long-term safety, toxicity, and biodistribution in the body.

Dendrimers represent a versatile and powerful platform for drug delivery, gene therapy, imaging, and diagnostics due to their highly controlled structure, multivalency, and ability to be functionalized for targeted delivery. While challenges such as toxicity and complex synthesis remain, ongoing research and development are expanding the potential applications of dendrimers in nanomedicine, particularly in cancer therapy and advanced diagnostics. Their precision and multifunctionality make them a promising tool for future therapeutic advancements.

6. Protein-based Nanoparticles

Protein-based nanoparticles are nanoscale particles composed of proteins or protein-derived materials. These nanoparticles have gained significant attention in the field of drug delivery, diagnostics, and vaccine development due to their biocompatibility, biodegradability, and ability to interact with biological systems in a controlled manner. Proteins offer a natural, safe, and versatile platform for creating nanoparticles with specific properties that can be tailored for medical and pharmaceutical applications.

Types of Protein-based Nanoparticles

1. **Albumin Nanoparticles**:
   - **Structure**: Albumin, a natural protein found in blood plasma, is widely used to form nanoparticles. It can encapsulate both hydrophilic and hydrophobic drugs within its structure.
   - **Properties**: Albumin nanoparticles are biocompatible, non-toxic, and biodegradable. They also possess natural affinity for tumor cells, enabling targeted drug delivery in cancer therapies.
   - **Applications**: Albumin nanoparticles are commonly used for the delivery of anticancer drugs, vaccines, and imaging agents.
2. **Gelatin Nanoparticles**:
   - **Structure**: Gelatin, a naturally derived protein from collagen, is used to form biodegradable nanoparticles. Gelatin nanoparticles can be prepared by cross-linking or self-assembly processes.
   - **Properties**: Gelatin nanoparticles are non-toxic, biodegradable, and can be easily modified to carry drugs or biomolecules. They also exhibit good biocompatibility and low immunogenicity.
   - **Applications**: Gelatin nanoparticles are used in drug delivery, tissue engineering, gene therapy, and as carriers for vaccines.
3. **Casein Nanoparticles**:
   - **Structure**: Casein is a milk protein that forms micellar structures in aqueous environments, making it suitable for drug encapsulation and delivery.
   - **Properties**: Casein nanoparticles are biocompatible, biodegradable, and have the ability to encapsulate both hydrophilic and hydrophobic drugs. They also have mucoadhesive properties, which are beneficial for drug delivery to mucosal tissues.
   - **Applications**: Casein nanoparticles are explored for oral and pulmonary drug delivery, as well as for the delivery of nutraceuticals and bioactive compounds.
4. **Silk Fibroin Nanoparticles**:
   - **Structure**: Silk fibroin, a natural protein derived from silk, forms nanoparticles through self-assembly or chemical cross-linking. These nanoparticles can encapsulate a wide variety of drugs.

- **Properties**: Silk fibroin nanoparticles are biocompatible, biodegradable, and mechanically robust. They can be functionalized to achieve sustained drug release and targeted delivery.
- **Applications**: Silk fibroin nanoparticles are used in drug delivery, tissue engineering, and wound healing applications.

5. **Ferritin Nanoparticles**:
   - **Structure**: Ferritin is a naturally occurring iron storage protein that forms cage-like structures, which can be loaded with therapeutic agents or imaging contrast agents.
   - **Properties**: Ferritin nanoparticles are biocompatible, and their structure allows for the encapsulation of various molecules, including drugs, metals, and nucleic acids. Ferritin nanoparticles are also biodegradable and can be engineered to target specific cells or tissues.
   - **Applications**: Ferritin nanoparticles are used for drug delivery, cancer therapy, and diagnostic imaging.

Properties of Protein-based Nanoparticles

1. **Biocompatibility**: Proteins are naturally occurring biomolecules that are generally biocompatible, making protein-based nanoparticles safe for use in medical applications.
2. **Biodegradability**: Protein nanoparticles are biodegradable, breaking down into non-toxic amino acids and peptides that can be easily metabolized or excreted from the body.

Applications of Protein-based Nanoparticles

1. **Cancer Therapy**:
   - Protein nanoparticles can be functionalized to target cancer cells by attaching ligands that recognize tumor-specific markers. This allows for the selective delivery of anticancer drugs, minimizing harm to healthy tissues.
   - **Example**: Ferritin nanoparticles loaded with doxorubicin for targeted drug delivery to tumor cells, enhancing the efficacy of cancer treatment while reducing toxicity.
2. **Vaccine Delivery**:

- Protein-based nanoparticles can act as carriers for antigens, improving the immune response to vaccines. Their biocompatibility and ability to present antigens in a controlled manner make them ideal for vaccine formulations.
- **Example**: Protein-based nanoparticles used as adjuvants or carriers in vaccines for infectious diseases or cancer immunotherapy.

3. **Gene Delivery**:
   - Protein nanoparticles can be used to deliver nucleic acids (e.g., DNA, siRNA) for gene therapy applications. They protect genetic material from degradation and enhance cellular uptake, making gene therapy more effective.
   - **Example**: Gelatin nanoparticles used for delivering siRNA to silence specific genes involved in cancer progression.

Advantages of Protein-based Nanoparticles

- **Natural Biocompatibility**: Protein-based nanoparticles, being composed of naturally occurring biomolecules, are generally well-tolerated by the body and exhibit low toxicity.
- **Biodegradability**: These nanoparticles are biodegradable and break down into harmless byproducts, reducing the risk of long-term accumulation in tissues.
- **Surface Functionalization**: Protein nanoparticles can be easily modified to carry targeting ligands, enabling site-specific delivery of drugs and reducing off-target effects.
- **Controlled Drug Release**: Protein-based nanoparticles can be engineered to provide sustained or controlled release of therapeutic agents, enhancing the effectiveness of treatments.
- **Versatile Drug Loading**: They can encapsulate a wide range of therapeutic agents, including small-molecule drugs, proteins, nucleic acids, and imaging agents, offering flexibility for different medical applications.

Challenges of Protein-based Nanoparticles

1. **Stability**:
   - Proteins are susceptible to denaturation, aggregation, and degradation under certain conditions (e.g., extreme pH, high temperatures), which can affect the stability and efficacy of protein-based nanoparticles.

2. **Production Complexity**:
   - The preparation of protein-based nanoparticles can be complex and may involve multiple steps, such as purification, cross-linking, and surface modification, increasing production costs and time.
3. **Potential Immunogenicity**:
   - Although many proteins are biocompatible, certain protein nanoparticles may elicit immune responses in some individuals, leading to potential safety concerns.
4. **Limited Drug Loading Capacity**:
   - Compared to other nanoparticle systems (e.g., liposomes, polymeric nanoparticles), protein-based nanoparticles may have lower drug loading capacities, which can limit their use in certain applications.

Protein-based nanoparticles offer a promising platform for drug delivery, diagnostics, vaccine development, and tissue engineering due to their natural biocompatibility, biodegradability, and versatility. With their ability to carry a wide range of therapeutic agents and target specific tissues, protein nanoparticles are at the forefront of innovations in nanomedicine. However, challenges such as stability and production complexity need to be addressed to fully realize their potential in clinical applications.

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CHAPTER NO 04- NANO SUSPENSION A PROMISING DRUG DELIVERY SYSTEM

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Introduction-

A submicron colloidal dispersion of distinct nanoparticles is called a nano suspension. Nano suspension is a term used to describe a heterogeneous combination in which solute particles are free to float in the solvent. Submicron colloidal dispersion of nanosized medicine particles stabilized by surfactants results in a biphasic nano suspension, where solid tiny particles are distributed throughout an aqueous medium stabilized by surfactants or polymers. Solubility and bioavailability are the two main components that are fundamental to the creation of novel pharmaceutical drugs.

Analysts are working to develop contemporary methods to improve the solubility and bioavailability of medications in order to address these issues. All medication particles that fall within classes II and IV of the Biopharmaceutical Classification System (BCS) can be combined to create nanoparticle formulations. Drug solubility can be increased by a variety of methods, including liposomes, emulsion, micro emulsion, surfactant dispersion, micro ionization, and precipitation procedures.

These methods, however, are only appropriate for medications that dissolve in organic and aqueous solvents. On the other hand, medications that are insoluble in both organic solvents and water can be employed with the Nano suspension approach. Additionally, Nano suspension technology changes the drug's pharmacokinetic characteristics, improving its profile and efficacy. Nano suspension is easy to make and works with any medicine that isn't soluble in water.

In addition to addressing issues with inadequate solubility and bioavailability, a Nano suspension modifies the drug's pharmacokinetic characteristics, enhancing its safety and effectiveness.The pharmaceutical industry uses Nano suspensions to increase the stability, bioavailability, and solubility of drugs. There are several ways to give them, including pulmonary, ophthalmic, parenteral, topical, and oral.

Fig no 01- Nano suspension range of size is 1-1000 nm

The following significant events have occurred in the history of nanosuspensions:

•1959

Richard Feynman, an American scientist, introduced the idea of nanotechnology.

•1995

Gris-PEG, the first to start using the Nano suspension medication, was put on the market. The griseofulvin Nano suspensions were contained in a sustained-release tablet.

•Currently

A possible dose form for substances that are insoluble in water is Nano suspensions. They have a variety of uses, including as anti-inflammatory, anti-fungal, analgesia, and schizophrenia.

Needs of Nano Suspension:

✓ Because of its poor bioavailability.

✓ The dose-response proportionality is absent.

✓ The overuse of co-solvents and other excipients, as well as the use of extremely basic or acidic conditions to improve solubilization, are examples of harsh excipient use.

✓ Use for medications that are poorly soluble in water or in organic solvents.

Features of Nano suspension

1. Small particle sizes range from 300 nm to 10 microns, while low volume dosages range from 10 to 200 mg/ml.
2. Because co-solvents are eliminated, the dosage is increased, boosting safety.
3. Long-term stability at room temperature or 5°C for up to two years
4. Drugs can be delivered in a regulated and targeted manner via a variety of routes, including oral, respiratory, intramuscular, intramuscular, and ID injections.

Advantages of Nano suspension

1. Enhanced solubility
2. Drugs with low water solubility can be made more soluble by Nano suspensions.
3. An improvement in stability
4. Drugs that are susceptible to deterioration in the body may benefit from the stability that Nano suspensions can provide.
5. Targeted medication administration
6. The effectiveness of treatment may be increased by using Nano suspensions to deliver medications straight to particular tissues or cells.
7. Nano suspension used orally offers enhanced and quick absorption.
8. It is possible to include Nano suspension into hydrogels, tablets and pellets.

Disadvantages of Nano suspension

1. Compaction, sedimentation, and physical stability can all lead to issues.
2. It is large enough to be carried around during handling and transportation.
3. It is impossible to obtain a consistent and precise dosage without suspension.

Techniques for Nano Suspension Formulation

Numerous methods have been developed for making Nano suspensions. Compared to liposomes and other common colloidal drug carriers, Nano suspension arrangements are really more straightforward and economical. These processes are used to produce physically more stable material and for medications that are ineffectively dissolved.

Nano suspensions are primarily prepared using three methods.

1. Bottom-up technology
2. Top-down technology,

3. Combination of these two

In addition to these techniques, there are other methods of arrangement like supercritical fluid technology, emulsification–solvent evaporation, and melt emulsification.

Additionally, these three tactics have been successfully developed in accordance with advanced research.

1. Bottom-up process technology

Bottom-up technology is also called as “Nano precipitation” List and Sucker were the first to use it in 1987. The idea behind this technology is to create particles that are Nano scale in size. This technique, which is an assembly method, creates nanoparticles from molecules by precipitating dissolved molecules and adding insoluble substances. The active ingredient in this approach needs to dissolve in at least one solvent, and appropriate stabilizers must be added to stop particle development following precipitation.

Advantages:

- Its operation and principle are straightforward;
- No additional devices are needed.

Limitations:

- Inadequate reproducibility
- Inconsistent particle size;
- Potential for solvent toxicity;
- Difficulty scaling up

Newly developed bottom-up methods such as:

A. High-pressure homogenization

B. Milling techniques

C. Emulsification-solvent

D. Precipitation

E. Supercritical fluid process

F. Melt emulsification method

G. Lipid emulsion/micro emulsion template

H. Solvent evaporation

A. High-pressure homogenization

This method is often used to plan nano suspensions of many medications that are ineffectively fluid solvents. This method uses a nano-measured gap valve in a high-pressure homogenizer to link the drive to a suspension of a medication and surfactant below weight. The cavitation powers of sedate particles in the fluid stage serve as the foundation for this strategy's rule. To transform the medication's small scale particles into nanoparticles, these cavitation strengths are sufficient.

There are three steps in it.

1. To create a pre-suspension, sedate drug powders are first dispersed throughout a stabilizer solution.

2. The pre-suspension is homogenized in a high-pressure homogenizer at a low pressure for premilling.

3. Finally, it is homogenized at high pressure for 10 to 25 cycles to create nano suspensions of the appropriate size.

Principal

The cavitation concept is the foundation of this tactic. The scattering in a cylinder with a diameter of 3 cm is abruptly transferred through a 25μm small gap. Bernoulli's law states that a closed system's liquid flow volume per cross section is constant. As the diameter decreases from 3 cm to 25μm, dynamic pressure rises and static pressure falls below the ambient temperature boiling point of water. At room temperature, the water then begins to boil and produces gas bubbles, which burst when the suspension exits the gap (a process known as cavitation) and the air pressure returns to normal. The cavitation forces of the particles are significant enough to transform the drug micro particles into nanoparticles.

Homogenization in non-aqueous media

i. **Nano pure:**

Nano pure suspensions, such as PEG 400, PEG 1000, and others, are homogenized in water-free media or water mixes. Because the homogenization is carried out at room temperature (zero degrees Celsius) and below the freezing point (-200 degrees Celsius), it is referred to as "deep freeze" homogenization.

ii. **Nanoedge:**

This technology combines the processes of homogenization and precipitation. The fundamental idea is the same as that of homogenization and precipitation. The Nanoedge technology can be used to solve the main drawbacks of the precipitation

process, including crystal development and long-term stability.

iii. **Nanojet:**

The opposite stream technology, as it is often called, employs a chamber to split a stream of suspension into two or more sections that colloid with one another under high pressure. Because of the tremendous shear forces created during the operation, the particle size is decreased.

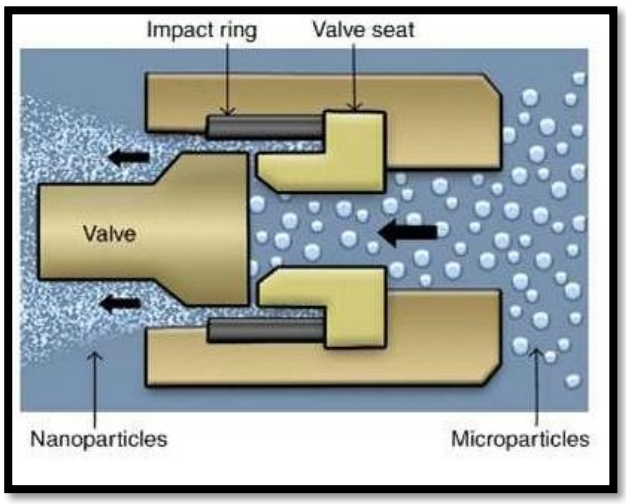

Fig no 02-Schematic representation of the High-Pressure Homogenization Process

B. Milling Methods

i) Media Milling

Another technique used to obtain nano suspensions is media processing. Elan Nano Systems' US 5,145,684 breakthrough, the nano crystal, provides a clear guarantee. In this technique, the medication is processed via media to produce the sedate nanoparticles. The primary vitality input for breaking down the micro particulate drug into Nano measured particles is provided by the high vitality and shear powers generated when the processing media is impacted with the sedate. The milling medium, water or an appropriate buffer, medication, and stabilizer are loaded into the milling chamber during the media processing preparation. The pearls or processing media are then rotated at a very high shear rate.

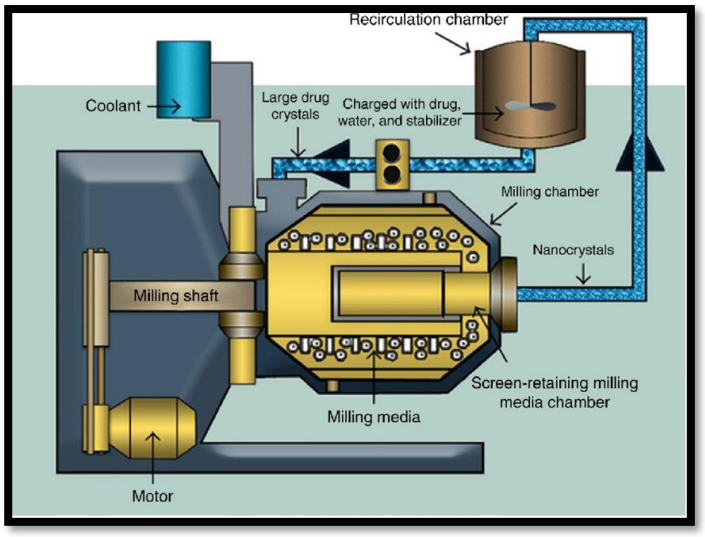

Fig no 03-Schematic representation of the Media Milling Method

ii) Dry co-grinding

Nano suspensions can now be obtained by dry processing techniques. Dry co-grinding is a simple, cost-effective process that doesn't require natural solvents. Particles can be reduced to the submicron level using the co-grinding technique, yielding a consistent, indefinable strength.

C. Emulsification-solvent

Evaporation Method

During this process, a medication arrangement is planned, followed by its emulsification in a different fluid that is not a solvent for the sedate. The medicament precipitates when the dissolvable disappears. A high-speed stirrer can be used to create tall shear strengths, which will control crystal development and particle aggregation.

D. Precipitation

Precipitation technique (solvent-anti-solvent method)

For a very long time, the precipitation approach has been used to plan submicron particles. It is primarily used for medications that are not effectively dissolved.

Process of precipitation technique-

The breakdown of protein in a suitable solvent In the presence of surfactants, this configuration is then combined with a miscible hostile to dissolvable framework. Ultrafine medicate solids are formed when sedate is abruptly super-immersed in the

blended arrangement due to its rapid expansion into the anti-solvent. There are two stages to this approach: crystal formation and nuclei configurations. It is crucial to plan a stable suspension with the fewest molecules, a high nucleation rate, and a slow growth rate. The temperature affects both rates. The medication used in this procedure must be solvent in at least one dissolvable that is miscible with a non-dissolvable.

E. Supercritical fluid process

Medicate arrangements can be used to generate nanoparticles via supercritical liquid innovation. Precipitation with compressed anti-solvent handle (PCA), supercritical anti-solvent handle, and rapid development of supercritical arrangement prepare (RESS) are the several approaches that have been tried. The development of the medication arrangement in supercritical liquid through a nozzle is part of the RESS. This causes the supercritical fluid to lose its dissolvable control, which causes the sedate to precipitate as small particles. Young et al. used this preparation to create cyclosporine nanoparticles with sizes ranging from 400 to 700 nm. As part of the strategy, the medication is atomized inside a compressed CO2 chamber. The arrangement becomes supersaturated when the dissolvable is released, which speeds up the formation of fine precious stones.

A supercritical liquid in which a sedate is ineffectively dissolved and a dissolvable for the sedate that is also miscible with the supercritical liquid are both handled by the supercritical anti-solvent. The medication solution becomes supersaturated after being infused into the supercritical fluid, which is then dissolved in the supercritical liquid. At that stage, the substance accelerates into fine crystals. Griseofulvin nanoparticles, a medication with low solubility, employing this tactic

F. Melt emulsification method

This approach involves dispersing the medication in the stabilizer's aqueous solution, heating it above the drug's dissolving point, and then homogenizing the mixture to create an emulsion. with order to maintain the emulsion's temperature above the drug's softening point, the test holder was wrapped with warming tape that was equipped with a temperature controller. At that stage, the emulsion was either cooled on an ice bath or gradually brought to room temperature.

G. Lipid emulsion/micro emulsion template

Another method for creating Nano suspensions is to use an emulsion that is formed via the standard technique, which uses a somewhat water-miscible dissolvable as the dispersed step. The emulsion is simply diluted to create Nano suspensions. Additionally, Nano suspensions can be created using micro emulsions as templates. An interfacial layer of surfactant and co-surfactant stabilizes the thermodynamically stable and isotropically transparent scatterings of two immiscible fluids, such as water and oil. The medicine can either be piled into the inner stage or intimately mixed with the pre-formed micro emulsion. The sedate Nano suspension is produced by a reasonable weakening of the micro emulsion. The griseofulvin Nano suspension, which is made via the micro emulsion method with water, butyl lactate, lecithin, and the sodium salt of taurodeoxycholate, is an example of this process. The sedate Nano suspension is produced by a reasonable weakening of the micro emulsion.

Lipid emulsions' main advantages as Nano suspension arrangement formats are their ease of creation through emulsion bead control and their ease of scaling up. However, using natural solvents has an adverse effect on the environment and necessitates large amounts of stabilizer or surfactant.

H. Solvent evaporation

The polymer is organized in unstable liquids and emulsions in the dissolvable dissipation process. When the dissolvable polymer is allowed to diffuse through the emulsion's continuous stage, the emulsion transforms into a suspension of nanoparticles. The polymer concentration, stabilizer, and homogenizer speed all had an effect on the molecular measure. Both single emulsions, such as oil-in-water (o/w), and double emulsions, such as (water-in-oil)-in-water (w/o)/w, are arranged using the two main processes used in the conventional approach. These methods call for high-speed homogenization or ultra-sonication, followed by the dissolvable disappearing through continuous, alluring blending at room temperature or under reduced weight. The cemented nanoparticles are collected by ultracentrifugation, rinsed with purified water to remove any other materials, such as surfactants, and then lyophilized. Twofold emulsions or single-emulsions, such as oil-in-water (o/w)

1)Top-down process technology

Large particles, micro particles, and nanoparticles were all decreased by the top-down, disintegration-based technique. The two primary techniques are media milling,

which uses low energy, and high-pressure homogenization, which uses high energy. These techniques are used for items that are already on the market and are more suited for industrial production than bottom-up technologies.

Evaluation of Nano suspension

- **FTIR study**

Mannitol, PVP-K30, and optimized Nano suspension (F4) were analyzed using FTIR spectra (the Agilent Cary 630) [Nano suspensions were lyophilized to transform into solid Nano crystals]. Over experiments were compacted using a motorized pellet press at 10–12 tons of weight after being combined with KBr of IR grade at a 1:100 ratio. At that stage, an FTIR spectrophotometer (8400S Shimadzu, Japan) was used to examine the pellets.

- **DSC study**

Using DSC (Mettler DSC 1 star system, Mettler-Toledo, Switzerland), the thermo grams for mannitol, PVP-K30, and optimized Nano suspension (F4)—Nano suspensions that were lyophilized to transform into solid Nano crystals—were examined. The medication was placed within a perforated aluminum dish and heated steadily at a rate of 10 °C/min between 30 and 350 °C at a nitrogen cleansing rate of 20 ml/min.

- **XRD study**

The Rigaku Analytical XRD in India was used to record the powder X-ray diffraction (PXRD). Using an X-ray diffract meter with Cu as a target and a voltage of 40 kV, the PXRD design of optimal Nano suspension (F4) [Nano suspensions were lyophilized to convert into solid Nano crystals] was carried out. The tests were examined at a scanning rate of 3°/2U/min in the 2θ angle range of 10–50°.

- **Scanning electron microscopy and transmission electron microscopy**

The Jeol model in Tokyo, Japan, was used to record the SEM. The JEM-1400 model was used to record the TEM. The surface geomorphology of the freeze-dried Nano suspension was arranged using SEM and TEM.

- **Particle size, polydispersity index measurement and zeta potential of freeze-dried Nano suspension**

The Zetasizer Nano ZS and a method called dynamic light scattering were used to measure the particle size and dispersion. The total charge that a molecule acquires in a particular medium is known as its zeta potential.

- **Drug content in lyophilized Nano suspension**

Ten milliliters of each preparation were dispersed throughout ten milliliters of isotonic (NaCl) solution and left overnight, while ten milligrams of the medication were melted in ten milliliters of the same solution and left overnight. Filtered dilutions of the medication at a concentration of 1µg/ml were used for all formulations. A UV spectrophotometer set to 272 nm was used to determine the substance uniformity of these dilutions.

- **Viscosity determination**

The Brookfield viscometer was used to test the Nano suspension consistency at 100 rpm using spindle number 60.

- **Saturation solubility studies**

Both the pure medication and different batches of the lyophilized lansoprazole Nano suspension underwent saturation solubility tests. Before being put to a 25 ml stoppard conical flask with 10 ml of distilled water, 10 mg of the pure drug molecule and 10 mg of lyophilized lansoprazole Nano suspension powder were weighed and quantified independently. The same approach was taken with phosphate buffers (1.2, 6.8, and 7.4). The flasks were sealed, allowed to sit at room temperature for twenty-four hours, and then allowed to equilibrate for two days in a rotary shaker. Analysis was done using a UV spectrophotometer calibrated to 272 nm.

- **In vitro release study**

Using USP Type II dissolve equipment, 900 milliliters of buffer with a pH of 7.4, and a rotational speed of 50 rpm, the in vitro drug release was investigated. The temperature was maintained at 37±0.5 °C during the sampling process, and aliquot samples (5 ml) were taken and replaced every 10–120 minutes with the same volume of new medium. A 0.45m limited membrane filter paper supporter was used to filter the 5 ml aliquot sample. The filtrate was then appropriately diluted via the fresh medium and measured

at 272 nm using a UV-Vis spectrophotometer (model UV-2600plus).

- **Stability study of Nano suspension**

The following storage conditions were used for the 30-day Nano suspension stability tests. For stability experiments, the intermediate storage environment has been modified from 30 °C±2 °C to 65%±5% RH. The optimum batch F4 Nano suspension was employed for each condition; the most crucial parameters for activity and physical stability are the drug content, particle size, and in vitro dissolution.

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CHAPTER NO 05 - NANO EMULSION: A REVIEW

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Introduction-

Nanoemulsions have emerged as a promising drug delivery system in the pharmaceutical industry due to their unique properties and advantages over conventional emulsions. This chapter provides a comprehensive overview of nanoemulsions, focusing on their composition, preparation methods, characterization techniques, and pharmaceutical applications. Nanoemulsions are thermodynamically unstable systems consisting of oil, water, and surfactants, with droplet sizes typically ranging from 20 to 500 nm. The main components of nanoemulsions include various oils, emulsifying agents, and aqueous phases. High-energy emulsification methods such as ultrasonic emulsification, high-pressure homogenization, and microfluidization, as well as low-energy techniques like phase inversion temperature and spontaneous emulsification, are employed for nanoemulsion preparation. Factors such as surfactant selection, concentration, and flexibility play a crucial role in the successful formulation of nanoemulsions. Characterization of nanoemulsions involves evaluating parameters such as droplet size, viscosity, drug content, polydispersity, zeta potential, and stability. Nanoemulsions offer several advantages, including improved bioavailability, enhanced absorption, and the ability to solubilize lipophilic drugs, making them attractive for various pharmaceutical applications, such as topical, ocular, intravenous, intranasal, and oral drug delivery. Additionally, nanoemulsions find applications in the food and cosmetic industries and serve as building blocks for advanced materials. Despite their potential, challenges such as high manufacturing costs and the need for a deeper understanding of the fundamental chemistry involved in nanoemulsion production remain to be addressed. In conclusion, nanoemulsions offer a versatile and effective approach for the formulation and delivery of drugs, with their unique properties and advantages making them a valuable tool in the

pharmaceutical industry.

Nano-emulsions are a type of emulsion characterized by droplets approximately 100 nm in size. These systems typically comprise oil, water, and an emulsifier. The emulsifier plays a crucial role in creating small droplets by reducing the interfacial tension between oil and water phases. Additionally, it helps stabilize nano-emulsions through electrostatic repulsion and steric hindrance. While surfactants are commonly used as emulsifiers, proteins and lipids have also proven effective in nanoemulsion preparation.

In recent years, research has focused on developing various methods for nanoemulsion production, broadly categorized as high-energy and low-energy approaches. High-energy techniques, such as high pressure homogenization (HPH) and ultrasonication, require substantial energy input (~108–1010 W kg−1) to generate small droplets. Conversely, low-energy methods exploit specific system properties to create small droplets with minimal energy consumption (~103 W kg−1). Examples of low-energy techniques include phase inversion temperature (PIT) and emulsion inversion point (EIP). Recently, innovative methods like bubble bursting at oil/water interfaces and evaporative ripening have emerged for nanoemulsion production.

Nanoemulsions find applications across various fields. In drug delivery, O/W nanoemulsions are utilized to administer hydrophobic drugs. The food industry employs flavored nanoemulsions with enhanced curcumin/β-carotene content and improved digestibility. Cosmetic applications include skin hydration and ease of product application. Researchers have demonstrated that nanoemulsions can address challenges in pharmaceutical crystallization processes. Furthermore, nanoemulsions serve as building blocks for complex materials like compartmentalized nanoparticles and encapsulated oil droplets. The fourth section of this paper explores key properties of nanoemulsions and their wide-ranging applications.

There exists some confusion in the literature regarding the precise definition of nanoemulsions, which are often mistaken for thermodynamically stable microemulsions that form spontaneously. Figure no 01 summarizes the primary differences between classical emulsions (or macroemulsions), nanoemulsions, and microemulsions in terms of droplet size range and stability characteristics. While both

macroemulsions and nanoemulsions are thermodynamically unstable and eventually undergo phase separation, nanoemulsions (also known as 'miniemulsions') can exhibit long-term kinetic stability due to their small droplet size. It is important to note that nanoemulsion metastability is unrelated to proximity to equilibrium. In contrast, microemulsions, being thermodynamically stable systems in equilibrium, are sensitive to temperature and composition changes. Consequently, nanoemulsions are attractive for the aforementioned applications due to their relative insensitivity to physical and chemical alterations. Two recent studies have elucidated the distinctions between nanoemulsions and microemulsions, providing detailed information on these two classes of liquid-in-liquid dispersions.

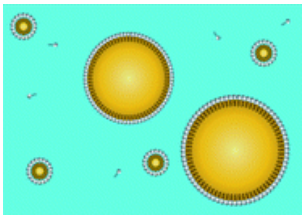
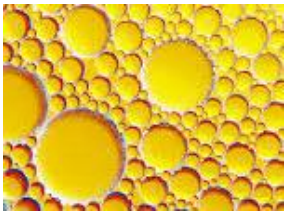
Specification	Type of dosage form		
	Macroemulsion	**Microemulsion**	**Nanoemulsion**
			
Size	1-100 µm	10-100nm	20-500 nm
Shape	spherical	spherical	spherical, lamellar
Stability	thermodynamically unstable, weakly kinetically stable	thermodynamically stable	thermodynamically unstable, kinetically stable
Method of preparation	high and low energy method	low energy method	high and low energy method
Polydispersity	high (>40%)	low (<10%)	low (<10-20%)

Fig no 01- A comparison of macroemulsions, nanoemulsions (also known as miniemulsions), and microemulsions is presented, focusing on their size,

shape, stability, preparation methods, and polydispersity. Due to their smaller size, nanoemulsions and microemulsions possess a greater surface area per unit volume compared to macroemulsions. Furthermore, nanoemulsions exhibit enhanced resistance to physical and chemical alterations owing to their strong kinetic stability.

Nanoemulsion

Nanoemulsions represent an advanced iteration of microemulsions. The early 2000s witnessed the integration of "nano" into technology, impacting colloidal systems. The transition from micro to nano gained momentum due to newly discovered physicochemical properties, applications, and improvements in active molecule delivery. Research on nanoemulsions commenced in the early 21st century. Pharmaceutical scientists were attracted to nanoemulsions because of their reduced toxicity, improved kinetic stability, targeted applications, and visual appeal. Like microemulsions, nanoemulsions are colloidal mixtures primarily composed of oils, surfactants, and aqueous phases.

However, nanoemulsions typically exclude cosurfactants, instead utilizing minimal surfactant quantities. The arrangement of these components results in various colloidal systems, with surfactants and cosurfactants playing a vital role. In pharmaceuticals, most current and investigational medicinal agents are typically hydrophobic, a characteristic crucial for effective delivery to target sites in the human body. As a result, oil-in-water (o/w) nanoemulsions are frequently employed to transport lipophilic active agents in pharmaceuticals. Additional system types include water-in-oil (w/o) and multiple systems. McClements characterizes o/w nanoemulsions as thermodynamically unstable colloidal dispersions of two immiscible liquids, where one liquid is dispersed as minute spherical droplets ($r < 100$ nm) within the other. While nanoemulsion size varies based on manufacturing method, size reports differ. Lovelyn describes nanoemulsions as 100-500 nm, while Koroleva and Yurtov note droplets can be smaller than 100 nm. Anton and Vandamme indicated nanoemulsions generally have sizes under 300 nm. Numerous studies have documented nanoemulsion sizes ranging from 20 to 300 nm, with particle sizes below 200 nm generally considered suitable for nanoemulsion classification.

Classification of nanoemulsion-

Nanoemulsions can be categorized based on their morphology. A 'water-based', or oil-in-water (O/W), emulsion features water as the continuous phase and oil as the dispersed phase, while the reverse scenario yields an 'oil-based' or water-in-oil (W/O) emulsion. The minute droplet size of nanoemulsions enables uniform deposition and penetration of active ingredients through the skin surface. Nanoemulsions demonstrate superior penetration efficacy of ingredients due to their large surface area and low surface tension of the entire emulsion system, thus requiring only 3–10% of surfactants during preparation.

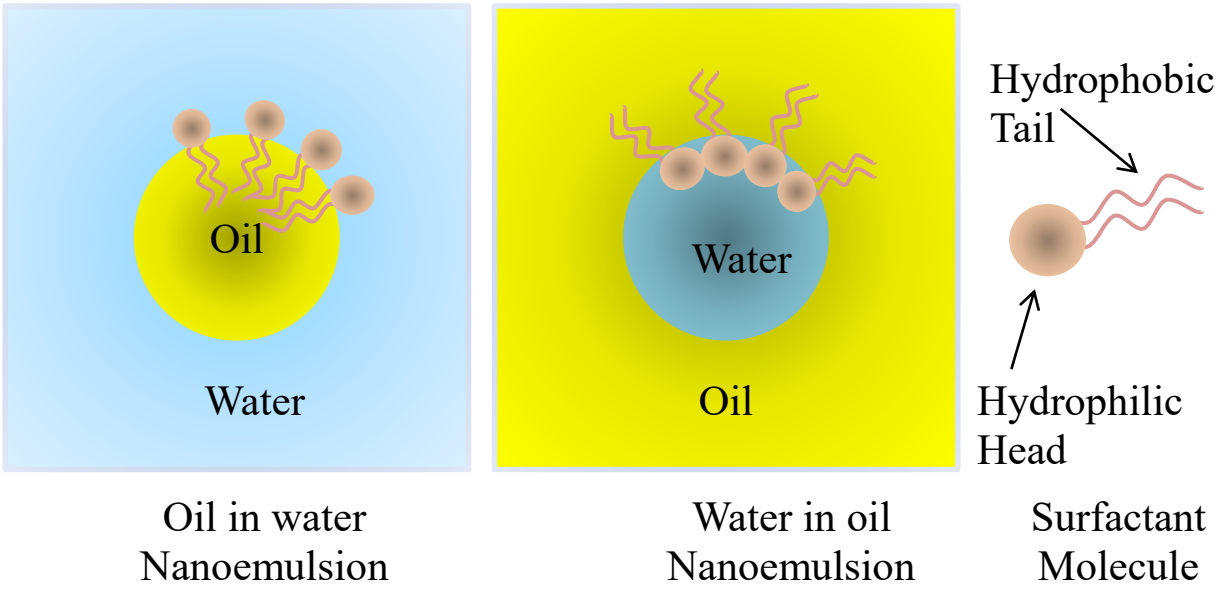


Fig no 02- A schematic illustration of oil-in-water (O/W) and water-in-oil (W/O) nanoemulsions containing surfactant.

Benefits and Drawbacks of Nanoemulsion

Benefits-

Their production requires minimal surfactant, reducing toxicity to biological membranes. The nanoscale size of droplets enhances their resistance to various destabilizing factors. Nanodroplets experience negligible gravitational force, which is counteracted by Brownian motion, preventing sedimentation or creaming. The significantly increased surface area due to their minute size leads to quicker absorption and enhanced bioavailability. Their isotropic, transparent or translucent

nature, moderate viscosity, and mild flavor make them aesthetically pleasing. They are particularly beneficial in cosmetics due to their appealing characteristics (especially easy spreading and wetting). The minuscule size allows for targeted delivery of active agents to specific sites (particularly the brain due to the BBB), minimizing side effects from unintended distribution. They typically employ GRAS-approved excipients, ensuring biocompatibility with all administration routes. They serve as a more stable alternative to liposomes and vesicles in lipid systems. Perfluorocarbon nanoemulsions, in particular, are utilized to deliver solubilized oxygen to ischemic patients

Drawbacks-

High-energy methods for nanoemulsion preparation require expensive and complex equipment like homogenizers and microfluidizers, increasing manufacturing costs. A more comprehensive understanding of droplet generation mechanisms using various methods is necessary for effective market placement. Insufficient knowledge of the fundamental chemistry involved in nanoemulsion production has led to misconceptions among researchers, resulting in reluctance to work on or discontinuation of nanoemulsion research. The cost exceeds that of conventional formulations. As previously mentioned, the stability of nanoemulsions is short-term due to the limited amount of surfactant used

Elements of nanoemulsion-

Nanoemulsions primarily consist of oil, emulsifying agents, and aqueous phases. Various oils can be used, including castor, corn, coconut, evening primrose, linseed, mineral, olive, and peanut oils. While a simple mixture of oil and water may create a temporary emulsion, it will eventually separate due to globule coalescence. Emulgents, or emulsifying agents, are used to stabilize these systems. These agents are categorized as surfactants (e.g., spans and tweens), hydrophilic colloids (e.g., acacia), and finely divided solids (e.g., bentonite and veegum). An ideal emulgent should be non-toxic, chemically stable, and compatible with the product in terms of taste and odor. Desirable properties of emulgents include:

Ability to reduce surface tension below 10 dynes/cm,

Rapid adsorption around dispersed phase globules to prevent coalescence,

Creation of adequate zeta potential and viscosity for optimal stability, and

Eeffectiveness at low concentrations. Emulgents form different types of films around dispersed globules: monomolecular, multimolecular, or particulate.

Monomolecular films-

Surfactant-type emulgents stabilize nanoemulsions by creating a monolayer of adsorbed molecules or ions at the interface, which reduces interfacial tension. Modern practice favors using a combination of emulgents over a single agent. This combination typically includes a predominantly hydrophilic emulgent in the aqueous phase and a hydrophobic agent in the oily phase, forming a complex film at the interface.

Multimolecular films-

Hydrated lyophilic colloids create multimolecular films around dispersed oil globules. These colloids do not significantly lower surface tension but form strong, coherent multimolecular films. Their ability to increase the continuous phase's viscosity enhances emulsion stability.

Solid particulate films-

Emulgents that form particulate films are small solid particles partially wetted by both aqueous and non-aqueous liquid phases. These particles concentrate at the interface, creating a film around dispersed globules that prevents coalescence.

Nanoemulsion preparation techniques-

The creation of nanoemulsions involves active ingredients, additives, and emulsifiers. Two primary approaches are used: high-energy and low-energy emulsification. High-energy methods encompass vigorous stirring, ultrasonic emulsification, high-pressure homogenization, microfluidization, and membrane emulsification. Low-energy techniques include phase inversion temperature, emulsion inversion point, and spontaneous emulsification. A combination of these methods can produce reverse nanoemulsions in highly viscous systems.

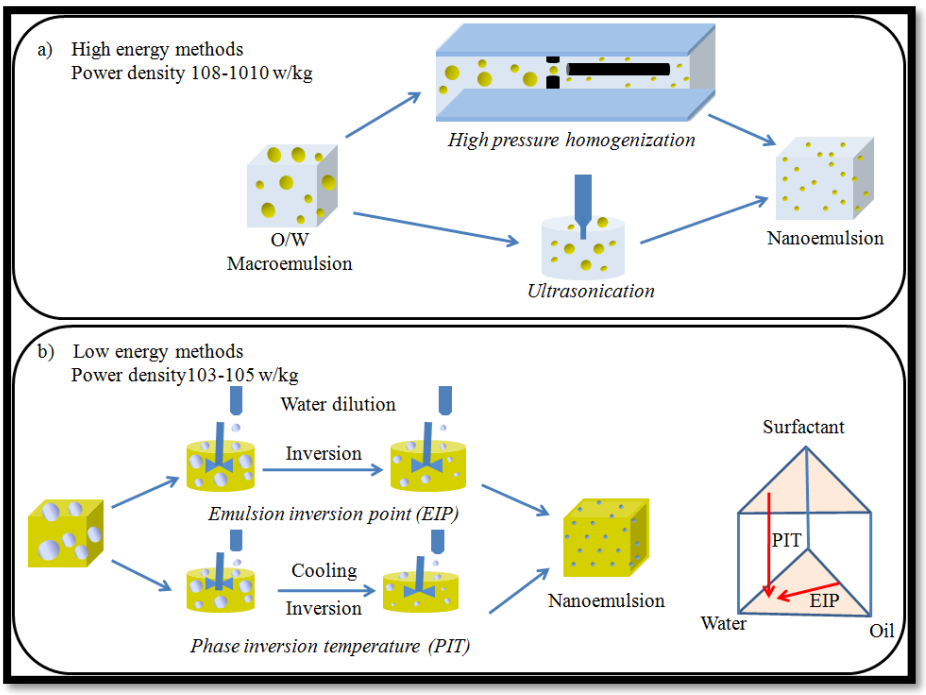


Fig no 03- Illustration of high and low energy techniques for O/W nanoemulsion production. (a) High energy processes like high pressure homogenization (HPH) and ultrasonication reduce macroemulsion droplets to smaller sizes. (b) Low energy methods begin with W/O macroemulsions and create smaller droplets as they transition through a low interfacial tension state during phase inversion. The emulsion inversion point (EIP) method triggers phase inversion through water dilution, while the Phase Inversion Temperature (PIT) approach induces inversion by cooling the mixture.

Ultrasonic emulsification-

This method effectively reduces droplet size using sonotrodes, or sonicator probes. These devices contain piezoelectric quartz crystals that expand and contract in response to alternating electric voltage. When the sonicator tip contacts the liquid, it generates mechanical vibrations, causing cavitation - the formation and collapse of vapor cavities. This technique can produce emulsion droplets as small as 0.2 micrometers in laboratory settings.

High-pressure homogenization-

This technique employs high-pressure homogenizers or piston homogenizers to create nanoemulsions with extremely small particle sizes, down to 1 nm.

Microfluidization-

This patented mixing technology uses a device called a microfluidizer. It applies high pressure to force the drug product through an interaction chamber, resulting in very fine submicron particles. The process is repeated to achieve the desired particle size for a uniform nanoemulsion.

Phase inversion temperature-

This method involves altering the phase of a microemulsion by applying elevated temperatures

Spontaneous emulsification-

This process consists of three steps: (a) creating a homogeneous organic solution of oil and lipophilic surfactant in a water-miscible solvent and hydrophilic surfactant, (b) injecting the organic phase into the aqueous phase under continuous magnetic stirring to form an o/w emulsion, and (c) removing the aqueous phase through evaporation under reduced pressure.

Key considerations in nanoemulsion preparation-

The selection of surfactants is crucial to achieve ultralow interfacial tension, a primary requirement for nanoemulsion production. Surfactant concentration must be sufficient to stabilize micro droplets. The surfactant should also be flexible or fluid enough to facilitate nanoemulsion formation.

Nanoemulsion characteristics-

A nanoemulsion is considered stable when it lacks an internal phase, shows no creaming, resists microbial degradation, and maintains its aesthetic qualities in terms of appearance, color, scent, and texture. The instability of emulsions can be categorized as follows:

Flocculation and creaming-

Flocculation occurs when globules combine to form larger clusters or floccules, which move more rapidly within the emulsion than individual globules. Creaming refers to

the upward or downward movement of dispersed globules, resulting in a concentrated layer. Flocculation often leads to creaming.

Cracking-

Emulsion cracking involves the separation of the dispersed phase into a distinct layer. Unlike creaming, which can be reversed by agitation, cracking is irreversible and signifies permanent instability. Cracking may result from: introducing an emulsifier with opposite properties, emulsifier breakdown or precipitation, adding a solvent that dissolves both oil and water phases, extreme temperatures, microbial activity, creaming.

Other instability factors-

Emulsions may degrade when exposed to very high or low temperatures or light. To prevent this, they are typically stored in airtight, colored containers at moderate temperatures.

Phase inversion-

This physical process involves changing the emulsion type from oil-in-water (o/w) to water-in-oil (w/o) or vice versa. Phase inversion can be triggered by altering the phase volume ratio, adding electrolytes, or changing temperature.

Nanoemulsion evaluation parameters-

Droplet size analysis-

Nanoemulsion droplet size is measured using light-scattering techniques with a particle size-analyzer counter, LS 230. It can also be assessed through correlation spectroscopy, which examines light scattering fluctuations caused by Brownian motion. Additionally, transmission electron microscopy (TEM) can be used for droplet size analysis.

Viscosity determination-

Nanoemulsion viscosity is measured using a Brookfield-type rotary viscometer at various shear rates and temperatures.

Dilution test-

This test helps identify the emulsion type by diluting it with either oil or water. The principle is that an emulsion can be diluted with more of its continuous phase without compromising stability. Thus, o/w nanoemulsions can be diluted with water, while w/o nanoemulsions can be diluted with oil.

Drug content-

To determine drug content, a pre-weighed nanoemulsion sample is extracted using an appropriate solvent. The extract is then analyzed using a spectrophotometer or HPLC, comparing it to a standard drug solution.

Polydispersity-

Polydispersity indicates the uniformity of droplet size in a nanoemulsion. A higher polydispersity value suggests less uniform droplet sizes. It is defined as the ratio of standard deviation to mean droplet size and is measured using a spectrophotometer.

Dye test-

In an oil-in-water (o/w) nanoemulsion, a water-soluble dye distributes evenly throughout the mixture. However, in a water-in-oil (w/o) nanoemulsion, the dye only colors the dispersed phase, resulting in an uneven appearance. This difference can be observed immediately through microscopic examination.

Refractive index-

An Abbes refractometer is utilized to determine the refractive index of nanoemulsions.

pH-

A pH meter is employed to measure the pH of nanoemulsions.

Zeta potential-

The Zeta PALS instrument is used to assess the zeta potential, which indicates the surface charge of droplets in nanoemulsions.

Fluorescence test-

Many oils exhibit fluorescence under UV light. When exposed to fluorescent light under a microscope, w/o nanoemulsions display uniform fluorescence across the entire field. In contrast, o/w nanoemulsions show spotty fluorescence.

Percentage transmittance-

A UV-visible spectrophotometer is used to measure the percentage transmittance of nanoemulsions.

Conductance measurement-

A conductometer is employed to measure nanoemulsion conductance. This test involves immersing electrodes connected to a lamp and power source into the emulsion. In o/w emulsions, water conducts electricity, illuminating the lamp. Conversely, in w/o emulsions, the external oil phase prevents current flow, leaving the lamp unlit.

Filter paper test-

This method exploits the fact that o/w nanoemulsions spread rapidly on filter paper, while w/o nanoemulsions migrate slowly. However, this test is not suitable for highly viscous creams.

Properties and applications-

Nanoemulsions possess unique characteristics, including small droplet size, exceptional stability, transparency, and adjustable rheology. These features make them attractive for use in food, cosmetic, and pharmaceutical industries, as well as in drug delivery system. Additionally, they can serve as building blocks for advanced materials with distinctive properties. This section reviews literature on nanoemulsion properties and applications.

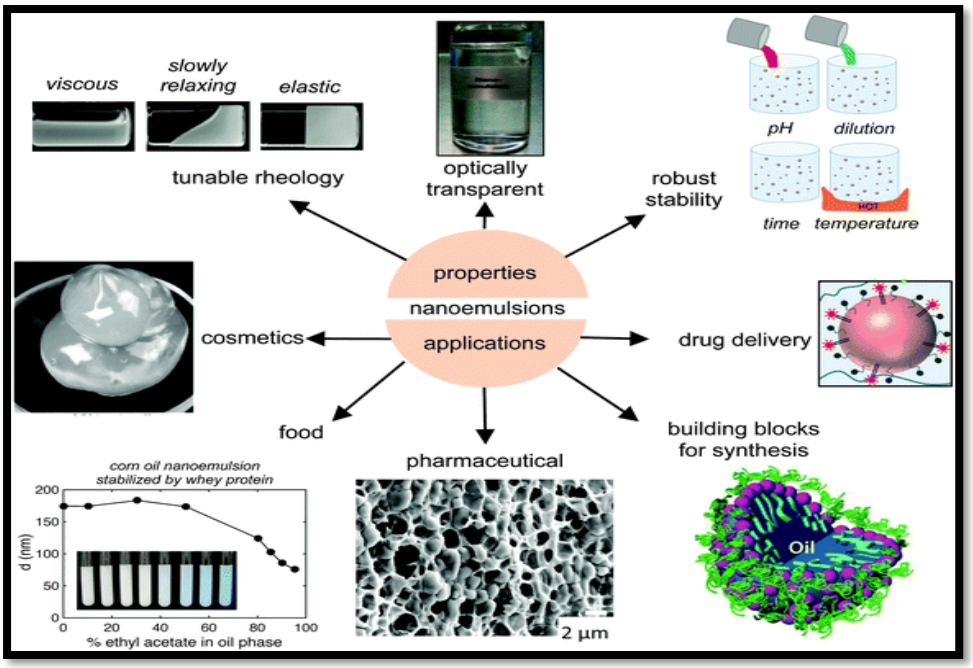


Fig no 04: Schematic illustrating various properties and applications of nanoemulsions. These include small size, low polydispersity, kinetic stability, and tunable rheology. Nanoemulsions find use in cosmetics, food and pharmaceutical industries, drug delivery, and as components for material synthesis.

Droplet size and stability-

Nanoemulsions contain droplets with diameters around 100 nm. Due to their size being significantly smaller than visible light wavelengths, nanoemulsions often appear transparent (Figure 4). However, by manipulating droplet size, the appearance of nanoemulsions can be adjusted from transparent to milky white .

Adjustable rheology-

Nanoemulsions offer versatile rheological characteristics that can be modified by adjusting the volume fraction of the dispersed phase, altering droplet size, and incorporating salt or depletion agents. These emulsions are particularly noteworthy in terms of rheology, as they can display substantially higher elasticity compared to macroemulsions, with elasticity approximating the Laplace pressure of an undeformed droplet. In the cosmetics industry, the manipulation of emulsion rheology often influences consumer perception of products.

Research by Wilking et al. demonstrated that nanoemulsion flow behavior can be adjusted from a fluid state to a slow-relaxing fluid or gel-like system by varying the number of passes through a high-pressure homogenizer (HPH) (Figure 4). This irreversible flow-induced elastification occurs due to excessive droplet rupture, resulting in a jammed nanoemulsion structure. Additionally, rheological responses can be modified by introducing salt or depletion agents, leading to droplet gelling. Another approach involves adding polymers capable of physical association with each other or with nanoemulsion droplets.

Nanoemulsions in drug delivery-

Nanoemulsions have found applications in various drug delivery methods, including topical, ocular, intravenous, intranasal, and oral routes. These formulations exploit the lipophilic properties of nanoemulsions to dissolve water-insoluble drugs, while their adjustable charge and rheology allow for the creation of easily administrable aqueous solutions. Although skin serves as a protective barrier, it also impedes drug absorption through topical application. Nanoemulsion-based topical medications offer distinct advantages, as the oil phase in O/W nanoemulsions enhances lipophilic drug solubility, while the aqueous phase provides a gentle, skin-compatible environment capable of dissolving biopolymers like alginate to modify formulation properties. Numerous studies have investigated nanoemulsions for topical drug deliver, with some incorporating permeation tests to assess delivery efficacy. Certain research suggests that nanoemulsion formulations, due to their small size and low ζ-potential, deliver hydrophobic drugs more effectively than conventional suspensions. Mou et al. developed hydrogel-thickened nanoemulsions with superior permeation rates compared to traditional hydrogels. Researchers have also explored nanoemulsions for ocular, intravenous, intranasal, and oral drug delivery. In these investigations, pharmaceutical compounds are dissolved in the dispersed phase, and formulations undergo testing for bioavailability and delivery efficiency in simulated real-world conditions. For example, oral drugs were evaluated for absorption in an environment mimicking small intestine walls.

Nanoemulsions in food industry-

The food industry can utilize nanoemulsions to create innovative products

incorporating ingredients that are typically challenging to include due to low water solubility, such as β-carotene, a pigment responsible for the color of vegetables like carrots and possessing significant health benefits. Yuan et al. examined the size and stability of β-carotene nanoemulsions in response to temperature, pH, and surfactant type. Qian et al. formulated β-carotene nanoemulsions stabilized with β-lactoglobulin, a biocompatible emulsifier. They also reported on the bioaccessibility of these nanoemulsions by simulating oral, gastric, and small intestine environments. β-Carotene nanoemulsions have been prepared using various methods (such as high pressure homogenization, microfluidization, and evaporative ripening) and different emulsifiers.

Nanoemulsions as structural components-

Nanoemulsions serve as fundamental elements in creating more intricate materials by leveraging their diminutive size and extensive surface area. These properties facilitate the attachment of functional entities, such as custom-designed macromolecules, to the liquid-liquid interface. A prime illustration in polymer synthesis is emulsion polymerization, where hydrophobic monomers within droplets undergo polymerization to form polymeric particles. Nanoemulsions, also referred to as miniemulsions, have been extensively employed in polymer production.

Nanoemulsions in crystallization and pharmaceutical applications-

Eral et al. introduced a method for generating size-controlled crystals of pharmaceuticals with poor water solubility, encased in a polymer matrix through a continuous process inspired by soft matter physics. This technique eliminates the need for high-energy grinding methods and avoids unwanted polymorphic transitions, a significant drawback of conventional approaches. The researchers dissolved the active pharmaceutical ingredient (API) in nano-sized anisole droplets suspended in an aqueous solution containing alginate (a biopolymer) and F68 (a biocompatible polymeric surfactant). They then cross-linked the continuous phase, resulting in droplets trapped within a hydrogel. The final product is a composite hydrogel.

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CHAPTER NO 06 - NANO EMULSION AN EMERGING NOVEL TECHNOLOGY

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INTRODUCTION.

Nano-formulation-

Nano-formulation is the formulation of drug having nano particle size. Nano-formulation can increases the effectiveness of the drug by enhancing the properties of the drug. nano-formulations are specific to the targeted delivery site. Using nanosuspension we can prepare various nano-formulations like, Nanogel, Nanoemulsion, Nanoemulgel, Nanofilm, liposomes, dendrimers etc. In that the Nanoemulgel is the most effective formulation, because of their stability. Stability of the nanoemulgel is higher than other formulation. Stability enhanced by the distribution of oil droplet into gel to form nanoemulgel. Nanoemulgel is the combination of nanoemulsion and hydrogel. Nanoemulgel is prepared by addition of nanoemulsion into hydrogel matrix which enhances solubility as well as skin penetration of the drug.

Nano-Emulsion:-

Definition:- Nanoemulsion is the thermodynamically stable transparent (translucent) dispersions of oil and water, stabilized by an interfacial film of surfactant and co-surfactant molecules having a droplet size of less than 100nm.

In general Emulsion is the mixer of two or more immiscible liquids, but nanoemulsion is the dispersion of oil and water which is stabilized by using surfactant and co-surfactant having droplet size less than 100nm.

One liquid creates the dispersed phase and another liquid forms the dispersing medium in a nanoemulsion. Nano emulsions comprise droplets with diameters ranging from 10 to 200 nm and each droplet has a protective coating of emulsifier molecules. The delivery of vaccines, DNA-encoded medications, antibiotics, cosmetics, and topical preparations are just a few of the many uses for nanoemulsions that are

common today. They can be administered through a variety of channels, including oral, pulmonary, ophthalmic, and transdermal. Typically, an emulsifier, water and oil make up a Nanoemulsion.

For the production of tiny droplets, an emulsifier is essential because it reduces the interfacial tension, or surface energy, between the oil and water phases of the emulsion The emulsifier also plays a role in stabilizing Nano emulsions through repulsive electrostatic interactions and steric hindrance Nanoemulsion of two immiscible liquids (usually an oil phase and an aqueous phase), in which one liquid functions as a continuous media and another as a way for droplets to disperse inside the other liquid. Nanoemulsions for Solubilization of poorly water-soluble drugs usually consist of oil phase dispersed in an aqueous medium, where the lipophilic drug is in oil phase.

The active substances in the form of nanoparticles are better suited for a variety of purposes and have a high surface-to-volume ratio, which encourages dispersibility in the emulsion. This emulsion method avoids early destabilization due to decreased gravity force and Brownian motion, which is why there is no sedimentation during storage.

The tiny size of nanoemulsion also prevents flocculation, another destabilizing agent, extending the shelf life of products.

COMPOSION OF NANOEMULSION:-

The main components of the nanoemulsion are Oil, Surfactant and Co-surfactant.

- **OIL-**

The selection of oil it play important role in the nanoemulsion formulation it determines the the amount of drug that can solubilize in the system. The main function of oil phase in nanoemulsion is to solubilize the hydrophilic or lipophilic drug moiety in order to improve bioavailability and therapeutic effects of the drug. The oil phase represents both the long chain triglycerides and medium chain triglycerides with different concentrations for nanoemulsion formulations. The most widely used components of the oil phase are saturated fatty acids, fatty acid esters, and soybean oils.

- **SURFACTANT–**

The non-ionic surfactants are widely used with relatively high HLB. It is preferred over

ionic surfactants because of their lower toxicity. Surfactants have less self-emulsification capacity. Generally, the concentration of surfactant is range between 30% to 60% w/w to form stable nanoemulsion. The selection of surfactant mainly depends on the solubility of the drug and also factors like rapidity, efficiency, type of emulsion formulation, cloud point of surfactant. Based on HLB value of the surfactant it may form o/w,w/o or bicontinuous microemulsion. The surfactant having high HLB and hydrophilicity in immediate formulation of o/w droplets and quick formulation dispersion in the watery medium. The dispersion of surfactant in water, oil, and oil mixture, depending on the intermolecular forces

- **CO-SRFACTANT-**

In the formulation of nanoemulsion, high concentrations of surfactants are required to reduce the interfacial tension,
The co-surfactant can used to reduce the concentration of surfactant. Co-surfactants play an important role in The stability of the nanoemulsion. These are also helpful to improving penetration of the nanoemulsion There are various co-surfactants, that are used in nanoemulsions such as short to medium Length a in alcohols. Selection of Co-surfactant is also mainly depends on the solubility of the drug.

The effect of the order in which the various compounds are mixed during formulation is a crucial factor to consider while creating nanoemulsions. It is crucial to stress that surfactants must be combined with the oily phase in order to prepare nanoemulsions. As a result, conditions that are particularly favorable for the creation of nanoemulsions are realized. On the other hand, combining surfactants with water during the first steps of preparation might encourage the formation of "macroscopic" emulsions.
Nanoemulsions are nanoscale emulsions that range in size from a few tens to several hundred nanometers. In order to reduce surface tension and prevent emulsion coalescence—which is caused by the system's attempt to achieve a state of minimal Gibbs free energy—surfactants function at the interface between the two immiscible phases. Because they can easily solubilize hydrophobic pharmaceuticals, less effects, and have been easily transformed into next- generations of mar nanomaterials, nanoemulsions hold enormous promise as powerful nanomedicines. An overview of bioinspired nanoemulsions for drug delivery is given in this article, which also covers preparation and stability, introduces various emulsion systems, lists

various surfactant types and factors to consider when selecting one, and then goes on to discuss emulsion nanomedicine and clinical applications.

HISTORY:-

The different kinds or morphologies of the nanoparticles generated, can be broken down into polymeric nanospheres, solid lipid nanoparticles (SLNs), or polymeric. The links between Nano emulsion formulation processes and nanoparticle morphology are neither obvious nor systematic and should be tackled with particular detachment

Following oral intake, the aggregate total of the droplets' overall interaction(IE) can be used to characterize When nanoemulsions are taken orally, they enter the gastrointestinal system (GItract) and are exposed to a range of environmental factors. According to Persson et al., in these situations, the postprandial response is at least partially activated. Stimulation of 'lipid sensing' mechanism in GI tract leads to secretion of gastric lipases which start fractional digestion of LCT or MCT making up the nanoemulsion, to yield simpler di-glycerides, mono-glycerides and free fatty acids. Intravenous nanoemulsions Intravenous nanoemulsion applications for nanoemulsions are diverse. They are employed to provide medications with limited therapeutic indices and/or poor bioavailability. A lipophilic anticancer drug called chlorambucil has been used parenterally to treat breast and ovarian cancer. It was created utilizing the high-pressure homogenization processand ultrasonication. To improve tamoxifen's efficacy in treating breast cancer, Tagine et al. created a water-soluble nanoemulsion of the medication.

OBJECTIVES:-

- Quicken the rate of absorption.
- Eliminates absorption fluctuation.
- Aids in the drug's solubilization.
- Increases bioavailability.
- The medication can be delivered by a number of different methods, including topical, oral, and intravenous.
- Beneficial for disguising tastes.
- The drug moiety penetrates quickly and effectively
- Patient compliance is increased by liquid dose forms

TYPES OF NANOEMULSION:-

Types are Depending on constituents and relative distribution of the internal dispersed phase, Nanoemulsions are mainly has three types-

- O/W (Oil in Water) Nanoemulsion
- W/O (water in oil) Nanoemulsion:
- Bicontinuous Nanoemulsion: (O/W/O, W/O/W)

- **O/W (Oil in Water) Nanoemulsion:**

In this Nanoemulsion Oil droplets are dispersed in water (continuous Aqueous phase) of Formulation.

- **W/O (water in oil) Nanoemulsion:**

In this Nanoemulsion water droplets are dispersed in continuous Oily phase of Formulation.

- **Bicontinuous Nanoemulsion: (O/W/O, W/O/W):**

Droplets of Oil and water are interdispersed within formulation.

Phase volume ratio (Φ):

It measures comparative volumes of internal and external phases comprising a Nanoemulsion and determines its droplet number and overall stability. The exterior phase is typically the one with a larger volume. To predict the type of Nanoemulsion formed under Oil/lipids Nano emulsions generally contain 5–20% oil/lipid droplets in the case of O/W emulsions, though it may sometimes be significantly larger (up to up to 70%). Lipids/oils to be used in Nano emulsions are generally propositioned on the solubility of drug.

Effect of Fick's first law:

Drug release from a nanoemulsion droplet can be triggered by a range of stimuli, such as pH, temperature changes, enzyme activity, and the ionic strength of the surrounding fluid. Release of drug from nanoemulsion in passive cases is dictated by Fick's first law and is given by the following equation,

t1/2=0.0585r2KOWD

Where,

t1/2 is the time required for half of drug to diffuse out of oil,

r is droplet radii,

D is the diffusion coefficient of drug(an intrinsic property) and

KOW is oil water partition In-vitro characterization of Nano emulsion

Effect of Particle size:

When creating nanoemulsions, it is necessary to adhere to a precise droplet size, and size estimation must be done after formulation. Numerous attributes are influenced by droplet size. Smaller or deformed droplets tend to cling together, but larger, more spherical droplets will usually flow more easily. The polydispersity index measures the uniformity of droplet size distribution; if the index is less than 0.2, nanoemulsions are typically referred to be "monodisperse".

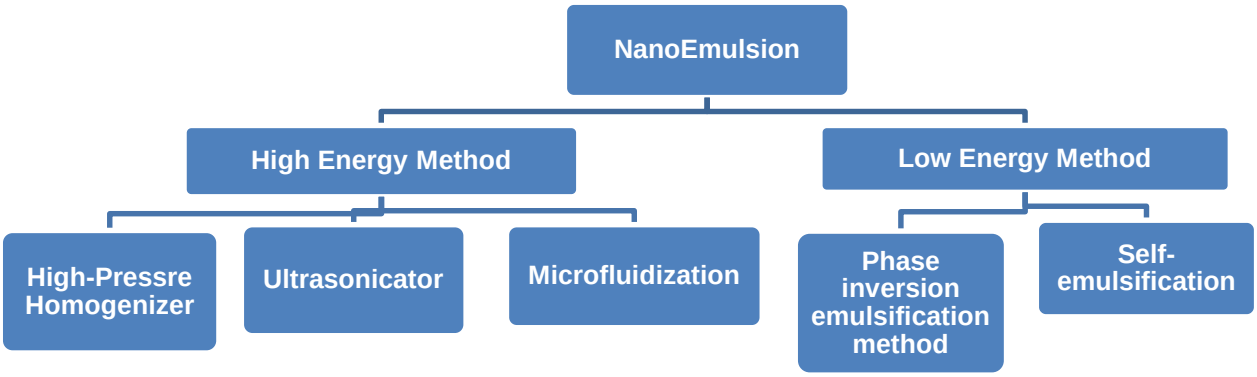
Particle size Droplet aggregation Instability affecting Nano emulsion is usually mediated by droplet aggregation which causes growth of droplet size, implying that all special characteristics imparted due to Nano scale are lost. Increased aggregation may eventually lead to phase separation, which damages the system permanently. An empirical approach to the energetics underlying the aggregation process has been developed using classical Newtonian mechanics.

MECHANISM:-

The entropy was changed in a way that favours dispersion more than the energy needed to increase the surface of dispersion; as a result, the free energy in conventional emulsion is a direct function of the energy needed to create new surfaces between the oil and water phases and the addition of an emulsifying agent to lower interfacial tension, which led to the stabilisation of the emulsion.

FORMULATION TECHNIQUES OF NANOEMULSION :-

We Classified Different Method of Preparation of Nanoemulsion -



1. **High Energy Methods:**

   High energy methods are normally used to formulate nanoemulsion. High mechanical energy is used that provide strong disruptive forces, which break up large droplets to nanosized droplets and produce nanoemulsions with high kinetic energy.

- **High Pressure Homogenizer:**

  The preparation of nanoemulsions requires high- pressure homogenization. In This technique we use high-pressure homogenizer to prepare nanoemulsions having low particle size (up to 1 nm). In this process, some forces, such as hydraulic shear, intense turbulence and cavitation, act together to form nanoemulsions with extremely small droplet size. The resultant product can be resubjected to high-pressure homogenization until nanoemulsion with desired droplet size and polydispersity index is obtained.

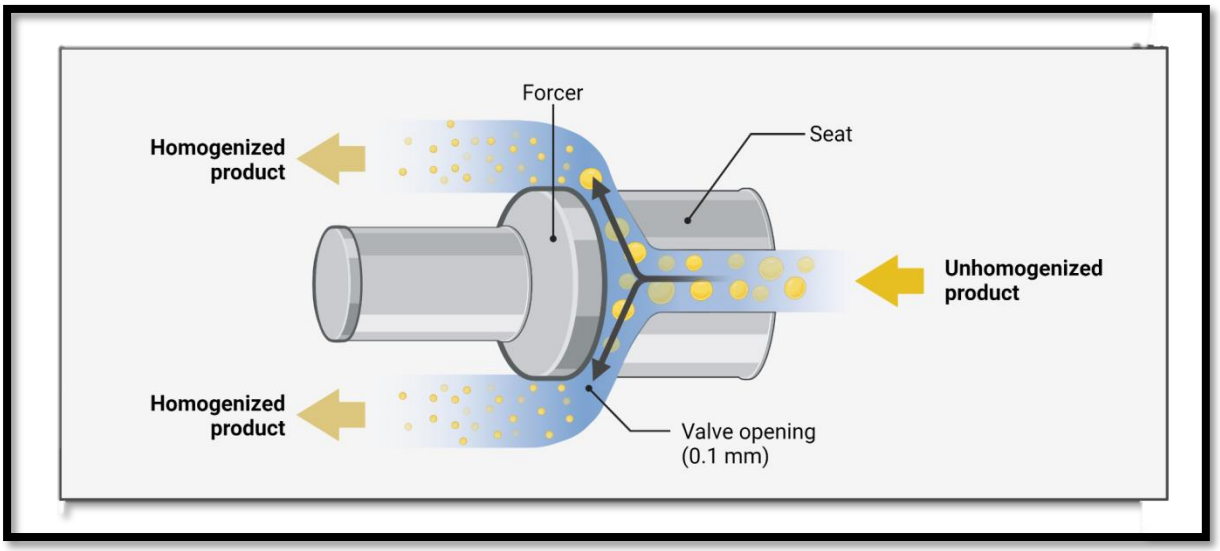


Fig no 01. Mechanism of High Pressure Homogenizer

Microfluidization-

Microfluidization is a technology which is patended to use of a device called microfluidizer. This device uses a high-pressure positive displacement pump (500 - 20,000 psi), which forces the product through the interaction chamber, consisting of small channels called “microchannels”.

The product flows through the micro- channels on to an impact area resulting in very fine particles of submicron range. The two solutions (aqueous phase and oily phase) are combined and processed in homogenizer to form a coarse emulsion. The coarse emulsion is transferred into a microfluidizer where it is further processed to obtain a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber of the microfluidizer frequently until the desired particle size is obtained.

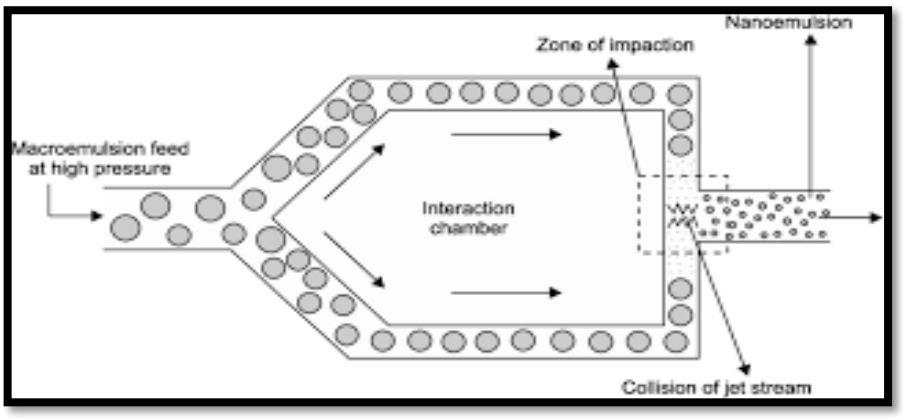


Fig no 02-Mechanism of Micro-fluidizer

Ultrasonication-

Ultrasonic emulsification is very efficient in reducing size of Droplets. In ultrasonic emulsification, the energy is provided through sonotrodes called as sonicator probe. It contains piezoelectric quartz crystal which can enlarge and contract in response to change electric voltage. As the tip of sonicator contacts the liquid, it produces mechanical vibration and cavitation occurs. Cavitation is the forming and collapsing of vapour cavities in liquid.

Thus, ultrasound can be directly used to produce emulsion; it is mainly used in laboratories where emulsion droplet size as low as 0.2 micro meter can be obtained.

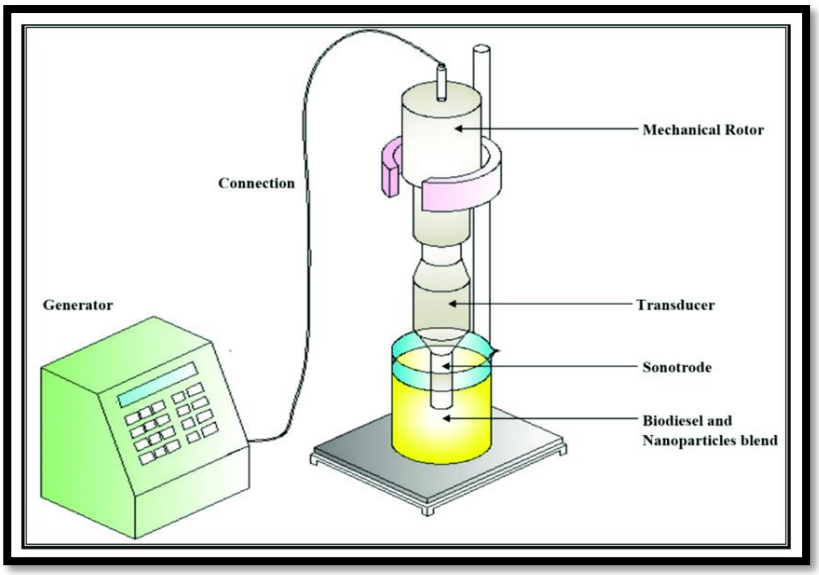


Fig no 03- Ultrasonicator

Low Energy Methods-

These methods require low energy for production of nanoemulsion systems. Low-energy emulsification methods are more effective as these methods utilize internal chemical energy of the systems, and require only gentle stirring to formulate nanoemulsions. Low-energy emulsification method involves two method, phase inversion emulsification and self-emulsification.

Phase inversion emulsification-

Studies on nanoemulsion formulation by the phase inversion temperature method have shown a relationship between minimum droplet size and complete Solubilization of the oil in a microemulsion by continuous phase independently of whether the initial phase equilibrium is single or multiphase Nanoemulsion preparation by persuasion method doesn't require any external force, but instead it involves formation of fine dispersions when phase transitions occur by changing the temperature or composition while keeping the parameter constant.

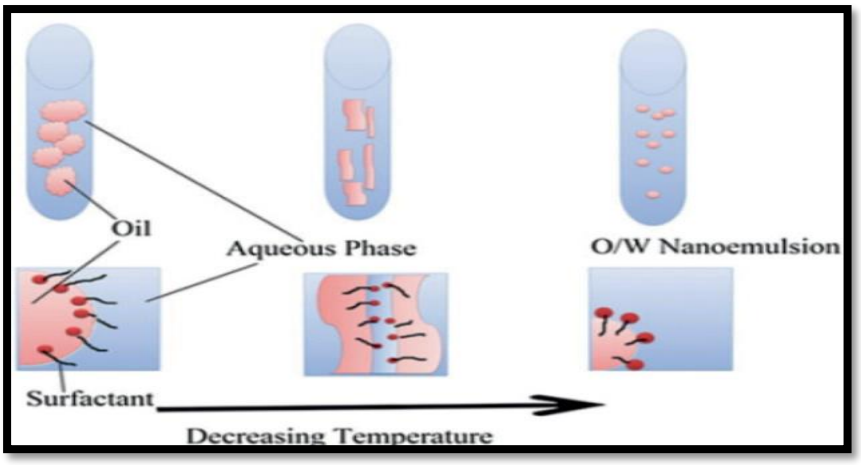


Fig no 04- Phase inversion of Nanoemulsion by decreasing temperature

Persuasion method can be broadly categorized as,

(i) phase transition from near- optimum state by changing single variable, which includes one variable of formulation such as temperature. Hydrophilic-lipophilic deviation (HLD) for optimal value is close to centre level for a system, for example, employing higher temperature to microemulsion.

(ii) Phase transition from near optimal state via altering multiple variables, meaning by changing more than one variable of formulation. For example, using higher temperature and adding salt in a microemulsion.

(iii) Catastrophic inversion, in this inversion of low internal phase emulsion occurs to convert internal phase to external phase.

(iv) In this stabilization of Phase is occur by liquid crystal formation,in which nanodroplets stabilized from a state close to HLD-0 by liquid crystal formation.

Self-emulsification:

In this method we generate nanoemulsions at room temperature without use of any organic solvent and heat. Kinetically stable nanoemulsions with small droplet size (~50 nm) can be formulate by adding water into solution of surfactant in oil, with gentle stir-ring and at constant temperature. Hydrogel formulation is very similar the solvent evaporation . The only difference from the solvent evaporation method is that the drug solution in this case is miscible with the drug anti-solvent.

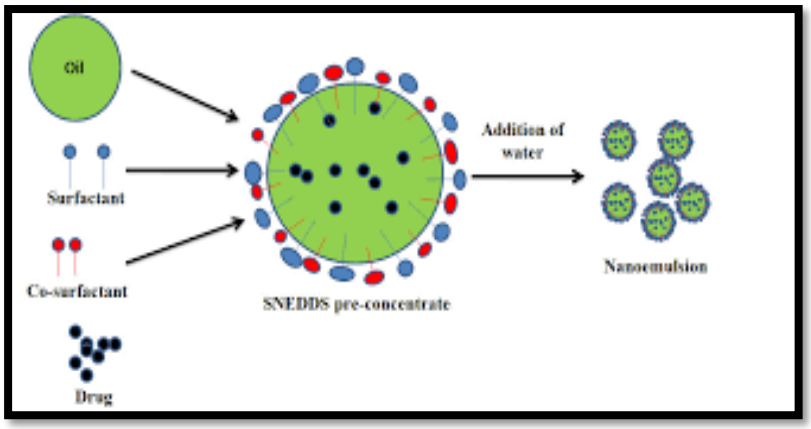


Fig no 05-Self-emulsification of nano-emulsion

FORMULATION OF NANOEMULSION-

i) Nanoemulsion formulations were prepared using selected oil, surfactant, cosurfactant along with aqueous phase by water titration method.

ii) Required quantity of Drug was added to sufficient amount of oil in a beaker having a small magnetic bead and was mixed completely by magnetic stirrer.

iii) Then surfactant and cosurfactant at definite ratio of Smix (Surfactant Co-surfactant ratio) were added into mixture and was mixed by gentle stirring.

iv) The above mixture was finally allowed to titrate by distilled water under constant stirring on a magnetic stirrer.

v) Store the Prepared nanoemulsion in sealed container at room temperature till further use.

EVALUATION OF NANOEMULSION-

1. **Viscosity-**

   The viscosity was measured to determine rheological properties of formulations. To determine the viscosity, Brookfield viscometer at 30˚C with a CPE 61 spindle at 30 rpm was use. For accuracy, Results are taken in triplicate and the average was taken in to consideration.

2. **pH-**

   Another important parameter of nanoemulsion is pH. The pH of the final preparation and route of administration is decided by excipient which is used in formulation. The change in the pH may affect the zeta potential of the formulation which in turn can

affect the stability of preparation. Digital pH meter is used to measure the pH of the formulations. For accuracy, Results are taken in triplicate and the average was taken in to consideration

3. **Drug content**-

The drug content of Drug nanoemulsion formulation was measured using UV visible spectroscopic method. The 2 µg/ml of aliquot was prepared using nanoemulsion formulation using diluting solvent. The samples were measured as 278.2 nm using UVVIS spectroscopic method. For accuracy, Results are taken in triplicate and the average was taken in to consideration

4. **Centrifugation-**

This was characterized to check the physical stability. The nanoemulsion formulation was centrifuged at 5000 rpm for 10 minutes to determine whether it shows signs of creaming or phase separation. The system was observed visually for appearance.

5. **Conductivity**-

Electrical conductivity of formulated samples was measured using a digital conductometer at ambient temperature. For accuracy, Results are taken in triplicate and the average was taken in to consideration

6. **Dilution test-**

In formulation continuous phase is added, nanoemulsion shall not crack or separate into phases. Maximum amount of oil and water were added to w/o and o/w formulations respectively and then examine visually for clarity and phase separation. Here 50- and 60-times dilution of the formulation was visually checked for phase separation and clarity For accuracy, Results are taken in triplicate and the average was taken in to consideration.

7. **Globule size and Zeta potential analysis**-

The Malvern zetasizer was used to calculate globule size and PDI. Nanoemulsion formulation was diluted 50 times and 100 tomes with distilled water before analysis to reduce the multiple scattering effect. Light scattering was measured at a 90-degree angle at room temperature. The zeta potential, surface charge, of the nanoemulsion

was measured at 25˚ in triplicate using Zetasizer.

ADVANTAGES OF NANOEMULSION-

Advantages of Nano emulsion over Other Dosage Forms-

- Increase the rate of absorption.
- Helpful in taste masking.
- Helps in solubilizing lipophilic drug.
- Provides aqueous dosage form for water insoluble drugs.
- Less amount of energy requirement.
- The use of Nano emulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.
- They are non-toxic and non-irritant then they be easily applied to skin and mucous membranes.
- They do not show the problems of integral creaming, flocculation, coalescence, and sedimentation.
- They can be taken by enteric route because they are formulated with surfactants, which are approved for human consumption (GRAS)

DISADVANTAGES OF NANOEMULSION-

- Use of a large concentration of surfactant as well as cosurfactant necessary for stabilizing the nanodroplets.
- Nano emulsion stability is influenced by environmental parameters like temperature and PH. These parameters changes upon Nano emulsion delivery to patients.
- Nanoemulsions have limitations like stability, temperature, and pH. They affect the melting point of compound because of their poor solubility.
- The large concentration of surfactant as well as co-surfactant necessary for stabilizing the Nano droplets.
- NE stability is influenced by environmental parameters such as temperature and pH.
- The surfactant should be nontoxic for using pharmaceutical applications
- The formulation of nano emulsions is an expensive process due to size reduction of droplets is very difficult as it required a special kind of instruments and process methods

LIMITATION OF NANOEMULSION–

Rheological properties of the formulations play important role in delivering drug effectively through skin. Small particle size is important in the topical formulation but, viscosity and pH and spreadability is also important to deliver drug through skin. The nanoemulsion , is not promising formulation to used topically due to low viscosity and spreadability.

APPLICATION OF NANOEMULSION-

- Nanoemulsion has become a very attractive formulation for the delivery of pharmaceuticals.
- Nanoemulsion are also shows a good advantage in the field of cosmetics.

The attraction of Nano emulsion formulation in pharmaceuticals and cosmetics is due to following reasons

- Nanoemulsion never shows the creaming and sedimentation kind of problems due to its very small droplet size. These problems are very common with conventional emulsion and even microemulsion. Basically, both problems are associated with the gravitational force over the droplet of emulsion. But in case of Nanoemulsion the droplet size is very small which minimized the working of gravitational force over the droplets and possess creaming and sedimentation of emulsion.
- Dispersibility of Nanoemulsion is very high as contrasted to microemulsion because small droplet size prevents the flocculation of droplets and this process makes the system dispersed without separation.
- Nanoemulsion has a transparent and fluidy property which improves the formulation patient compliance and safe for administration due to the absence of any thickening agent and colloidal particles.
- Nanoemulsion formulation may become the stable alternate for the liposomes and vesicle type of delivery systems.
- Use of Nanoemulsion in cosmetics.
- Nanoemulsion in the treatment of various other disease condition.
- Nanoemulsion as a vehicle for a ocular delivery.

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CHAPTER NO 07 - NANOEMULGEL

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Introduction

Targeted medication administration, a lower chance of systemic toxicity, better patient adherence, more effective treatment, and greater drug absorption are some advantages of topical application. A topical gel with a nanoemulsion distributed throughout a gel matrix is called a nanoemul gel.

Nanoemulsions are heterogeneous isotropic systems made up of nanoscale droplets of one liquid distributed throughout another. Usually, the droplet diameters are between 20 and 500 nm. Typically, high shear mixing techniques are used to prepare the nanoemulsion, which is composed of droplets of an oil phase dispersed in an aqueous phase stabilised by surfactants or stabilisers.These systems have a longer shelf life than basic emulsions, micelles, suspensions, etc. because of their great thermodynamic stability. Despite its many benefits, nano-emulsions are constrained by their low viscosity, which results in poor spreadability and retention duration.

The skin's ability to absorb things can be improved by creating a nanoemulgel, which is a gel matrix loaded with nanoemulsions. A formulation-related intervention to enhance the systemic transport and therapeutic profile of lipophilic properties are the nanoemulgel drug delivery system. The recently created therapeutic compounds' lipophilic characteristics cause problems such inconsistent oral bioavailability, absorption, pK differences across and within subjects, and a lack of dose proportionality. By transforming the nano-emulsion into a nano-emulgel with the use of an appropriate gelling agent, a continuous development procedure can reduce these issues and concentrate on the solubility enhancement method.

The nano-emulgel, which is a combination of gel and emulsion, functions as a colloidal system. Like other nano-carriers, the emulsion component enhances penetration and shields the medication from hydrolysis and enzymatic destruction. Maintaining the drug's therapeutic concentrations for an adequate amount of time is just as crucial as improving the drug's penetration through the skin. The gel component decreases

surface and interfacial tension, increasing thermodynamic stability, and increases viscosity and spreadability, which prolongs retention duration.

The disadvantages of any gelling system are eliminated when nano-emulsion is incorporated into it. The combined nano-emulgel has the refined qualities of a nano-emulsion mixed with the properties of a gel. Because of its particle size and thermodynamic stability, nano-emulgel has advantages over conventional emulgel. Improved skin penetration, higher active ingredient loading, decreased irritation, and improved spreadability are just a few advantages that nano-emulgels provide.

Nano-emulsions in drug delivery systems-

Nano-emulsions are isotropic biphasic mixtures of water and oil in which the water phase is distributed as nanoparticles in the oil phase. The application of a surfactant interfacial layer stabilises the system. Nano-emulsions differ from conventional emulsions in that they are less likely to experience phase separation.

Numerous in-vivo investigations have been conducted to show the viability and uses of topical micro and nanoemulsions. The application of these topical lipidic compositions has also been validated by in vitro studies. The appearance of these nano-emulsion systems is translucent or transparent. Compared to other lipid carriers, nano-emulsions have higher thermodynamic stability. The solubilisation capability of nano-emulsions is higher than that of ordinary micelle solutions. Due to the enhanced surface area caused by the oil droplets' nanosize, these formulations are able to absorb and solubilise significant amounts of active medicinal compounds. The common problems with an emulsion are the phenomena of creaming or sedimentation.

Nano-Emulgel in drug delivery systems :
Emulgel-

Emulgel is a gel and emulsion combination, with the emulsion utilised as a vehicle to deliver a specific medicine to the skin being either type W/O or O/W. A traditional emulsion can be transformed into emulgel by adding the gelling ingredient to the water phase. Emulgel's many advantageous qualities for dermatological use include its ease of spreading, greaselessness, thixotropic nature, water solubility, ease of removal, extended shelf life, non-staining, and bio-friendliness.

Nano-Emulgel in topical delivery-

The thermodynamic instability of emulsion is decreased by forming nano-emulgel by integrating the nano-emulsion into a hydrogel matrix. Because the exterior medium is more consistent, the non-aqueous phase's mobility is reduced, which results in enhanced thermodynamic stability. The formulation's longer retention time and thermodynamic stability allow the drug to be released gradually, which benefits medications with a short half-life by making nano-emulgel a controlled release dosage form for topical administration. When added to a gelling system, nano-emulsion improves skin penetration, increases active moiety loading, reduces irritation, and increases spreadability.

The optimised nanoemulgel improved the analgesic efficacy by reducing inflammation and increasing percentage reaction time in the pharmacodynamic study. The developed nanoemulgel fared better than other conventional topical formulations in terms of medication penetration and long-term stability.

Background-

Numerous medication molecules are now available to address various health care system difficulties as a result of massive efforts made in recent decades for various drug discovery methods. Unfortunately, because of their poor clinical utility, over half of these medications are either classified as class II or IV in the biopharmaceutical categorisation system (BCS) or are removed from the development pipeline altogether.

It has been determined that a nanoemulsion-based gel, or nanoemulgel, made from various nanolipoidal formulations, is an appropriate strategy for effective topical drug administration. Many synthetic and herbal active pharmaceutical ingredients (APIs) have been patented as nanoscale emulsified gels for a range of therapeutic uses in recent years.

Nanoemulgel is a drug delivery systems to increase the therapeutic action of lipophilic drugs. By adding nano-emulsion to gel, a unique system is created that enhances stability and allows for both immediate and controlled release of the medicine. Because of its safety profile, ease of application, lack of gastrointestinal degradation or first pass metabolism, and capacity for targeted delivery, nano-emulgel has also drawn more attention.

The development of a transdermal dosage form has thus become necessary in order to reduce the adverse effects of oral medication and to maintain comparatively constant drug levels over extended periods of time. The stratum corneum's barrier

qualities, which make it one of the human body's most impermeable epithelia to foreign chemicals, are the main issue with transdermal drug administration. Chemical permeation enhancers can be used to reduce these permeability issues. However, because many of these chemical enhancers are typically irritants, their use may be hazardous, particularly in long-term applications.

Therefore, the development of a new transdermal vehicle system that does not require the use of chemical enhancers to promote medication penetration through the skin is desirable.

Nanoemulsion is a promising methods for improving drug transdermal penetration. Since nanoemulsions have a higher potential for skin penetration, they have been used as a carrier system for transdermal delivery of a variety of medications. Additionally, it is anticipated that the nanoemulsion system's constituents will function as permeation enhancers on their own, eliminating the need for irritating chemical penetration enhancers.

Importance to study-

Being an isotropic, transparent (or translucent) heterogeneous mixture of two media (oil and aqueous), nanoemulsion holds great promise since one phase is disseminated in the other and stabilised by an interfacial layer of surfactant molecules. According to studies, nano-emulsions can solubilise drugs more effectively than simple micellar solutions. Additionally, their thermodynamic stability gives them an advantage over unstable dispersions like emulsions and suspensions because they can be produced with less energy (heat or mixing) and last longer. Nowadays, nearly 40% of the medications on the market and 90% of those in the development pipeline are lipophilic nature. The medications' lipophilic nature causes issues such low solubility, erratic absorption, and pharmacokinetic heterogeneity between and within subjects.

In topical administration, the skin, which serves as the body's primary barrier, views the APIs as external substances and prevents them from entering the body.

Many approaches to improve drug penetration have been investigated. A mechanism that can be accomplished by the use of chemical penetration enhancers, ultrasound, iontophoresis, sonophoresis, electroporation, and microneedles is the disturbance of the structure of the skin layer.

It was found that using nanocarriers was a useful method for getting beyond the SC

barrier without aggravating skin injury and achieving effective medication penetration. Through the use of intracellular and intercellular transport pathways, they help transfer drugs through the skin. They interact with skin constituents to mediate transport or to establish drug depots for sustained or stimuli-induced release. Nano/micro emulsions, micelles, dendrimers, liposomes, solid lipid nanoparticles, and nano-structured lipid carriers are a few examples of these innovative topical delivery systems.

Nano-emulsions are a promising drug delivery technology due to their high drug-loading and solubilising capacities, stability, ease of manufacturing, and regulated release patterns. More lipophilic molecules can pass through topical membranes in these nano-emulsions than in liposomes because of their lipophilic core.

Preparation of Nanoemulgels

Nanoemulgels are organized by means of manner of two steps, at the beginning of first step nanoemulsion will be frammed and nanoemulsion can be blanketed inside the gelling agent within the direction of the second step. Nanoemulsions are spontaneously manufacyuring thru blending the compositions with the aid of the usage of reducing the interfacial tension amongst oil/water interfaces or can be designed with the resource of application of out of doors power into the heterogenous mixture. so that a thermodynamically solid nanoemulsion can be prepared with the aid of adopting excessive power and espresso energy emulsification methods.

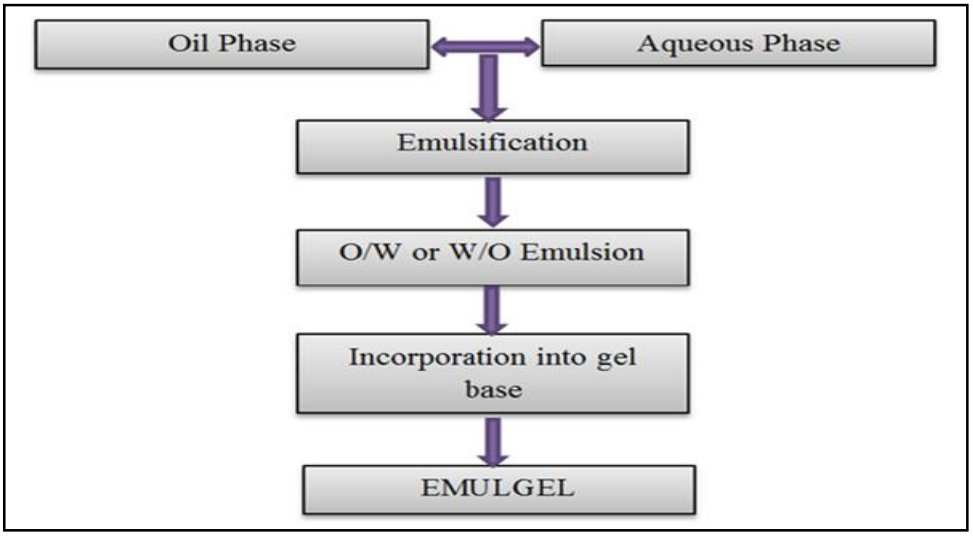

Fig no 01- Preparation of Emulgel

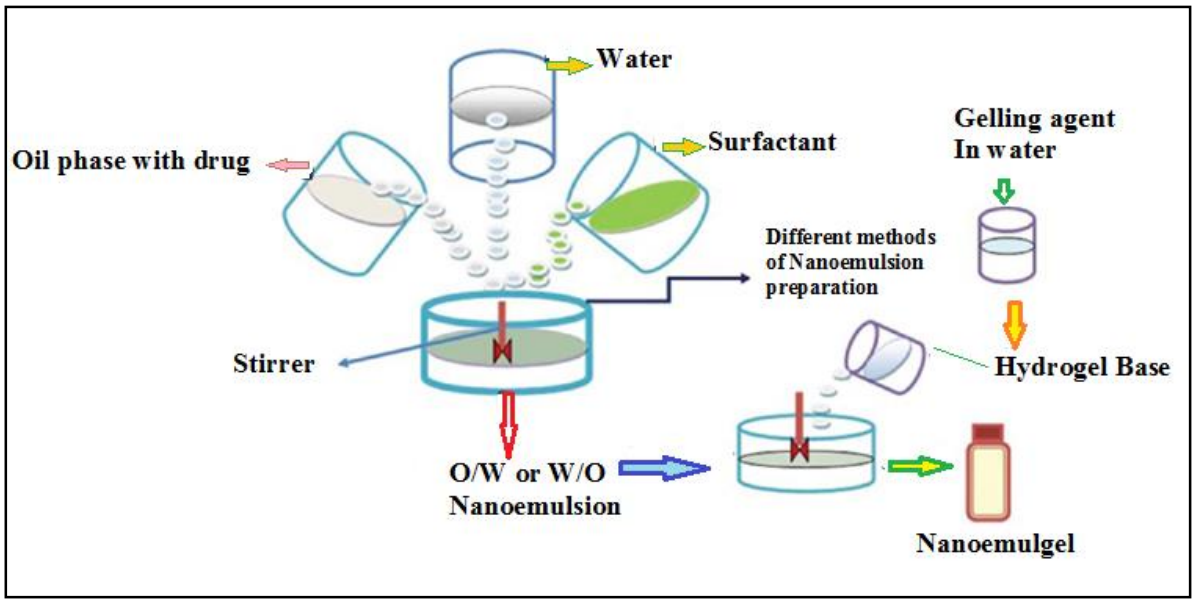

Fig no 02- Formulation of Nanoemulgel

Step1

Excessive strength emulsification technique excessive shear pressure produced through ultrasonicators, excessive stress homogenizers, microfluidizers, and so on are used to rupture the oil phase to shape nanosized droplets in the aqueous section through manner of optimizing required time, temperature, and problem properties to reduce the dimensions of the dispersed to the nano-range. Therefore, this method of education of nanoemulsion requires enter from outdoor electricity which makes the advanced formulations thermodynamically risky due to the presence of free electricity into it. Furthermore, this approach is first-rate to acquire the dimensions of the dispersed phase as little as 1 nm through element converting, while it's miles inapplicable for thermo labile components.

Low energy emulsification technique, low strength technique for coaching of nanoemulsions consists of spontaneous approach and phase inversion approach, that are positioned to be excessive nice over high energy emulsification technique in terms of thermodynamic balance of the final system due to incorporation of excessive electricity throughout production process. Blending of oil, water, and surfactant in a tremendous ratio need to formulate the nanoemulsion spontaneously, instead by way of addition of aqueous phase inside the oil segment where in the surfactant may be combined with everybody medium, should generate preferred nano-dependent

droplets dispersed within the non-prevent phase. The order of addition of the number one additives, pH of the medium and residences of protected surfactant and cosurfactant, influences the emulsification procedure.

In particular, temperature-established change in HLB for certain nonionic surfactants, in standard poly-ethoxylated surfactants (e.g., Tween 80, Tween 60, Tween 20, Cremophor EL, Labrasol, and so forth.), is utilized in this method. Spontaneous method is most appropriate for the thermolabile additives to be covered into the nanoemulsion. Alternatively, temperature-based spontaneous twist of non-ionic surfactants is used for segment transition throughout segment inversion technique. The emulsion formed at segment inversion temperature can be reversed on cooling with stirring. This method is also restricted to include thermolabile components, despite the fact that this trouble can be reverted by means of coming near decreased phase inversion temperature by using truly deciding on the surfactant(s).

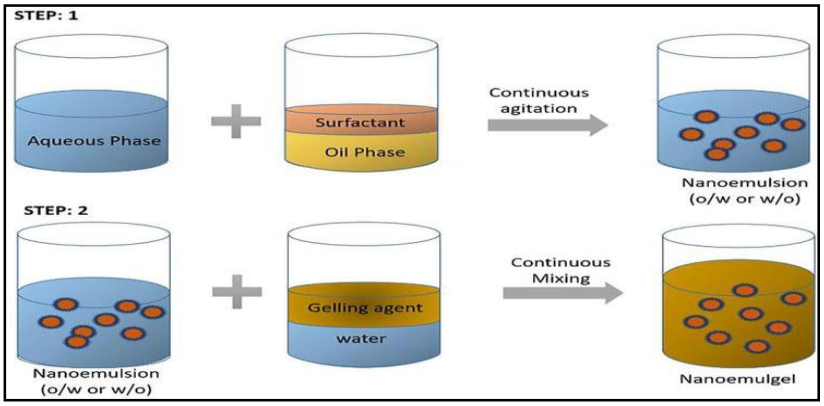

Fig no 03- Different steps of Nanoemulgel preparation

Step 2

Nanoemulsion organized with the aid of adopting any of the above strategies can be converted to nanoemulgel the use of gelling dealers. Reason of use of jelling agent inside the nanoemulsion method is to exchange its physical state , from liquid to gel. Addition of gelling agent to an o/w nanoemulsion tool thickens the system thru forming gel-like shape. That is due to the thixotropic nature of the agent which lets in within the gel solution transition throughout utility of shear strain to the system without converting its extent. Furthermore, on standing, there may be an automatic reversal of the state from choice to gel.

A few typically used gelling sellers are used in the schooling of nanoemulsion gel, which incorporates Carbomer 940, chitosan, Carbopol 934, Carbopol 940, Carbopol 980, Poloxamer 407, methyl cellulose, Carbopol 971, and so on. Incorporation of

gelling agent inside the nanoemulsion had been proven to affect the pharmacokinetic houses of the drug blanketed into this nanocarrier system. Gelling medium is prepared through dissolving gelling retailers into an aqueous media with non-stop stirring at a consistent charge at specific conditions for particular time to reap complete swelling. In the long run, the emulsion can be delivered into the organized gel at a selected ratio with continuous blending for homogeneity. Impact of nanoemulgel improvement inside the pharmacokinetic and pharmacodynamic houses of the drug has been summarized inside the following section of the item.

Evaluation parameters:

Measurement of pH :

The pH of different topical preparations, as determined by a pH meter, 5-6 ranges. 1gm gel is dissolved in 10ml of water for pH testing. Each formulation's PH is performed in triplicate to prevent errors.

Droplet size and Poly Dispersity Index (PDI) -

A NEG's hydrodynamic diameter, or droplet size, is equal to the diameter of a hard sphere that is homologous to the drug molecule and diffuses at a similar pace. The ratio of the droplet size standard deviation to the mean droplet size is known as the PDI, and it is used to ascertain the size distribution of the nanoemulsion droplet. The formulation's ex vivo and in vivo performance are impacted by the droplet size and PDI in addition to drug release and formulation stability. Additionally, it is crucial to evaluate batch-to-batch uniformity. The solution is clear and transparent if the nanoemulsion is 50–200 nm in size, and it looks milky or hazy if it is 500 nm or larger. Specifically, the globule size is measured using the dynamic light scattering (DLS) approach, however the zeta sizer or master sizer can be used to assess both the size and PDI.

Zeta potential-

The presence of several types of surfactants in their formulation gives nanoemulsions their electrical charge. The stability of the formulation is improved when the repulsion's magnitude rises with zeta potential. For example, the strong zeta potential of emulsion globules prevents them from aggregating. A surface charge modulator can change the surface charge. For example, using a positively charged modifier causes the zeta potential to become positive, and vice versa. Therefore, cationic or anionic surfactants are essential for the stability of emulsions.

Drug content determination :

100 mg of the produced nanoemulgel were dissolved in 10 mL of distilled water to determine the amount of medication contained in the gel. Using distilled water as a blank, this mixture was examined using a UV spectrophotometer set to 260 nm.
The drug content was quantified by :

$$\%\text{Drug content} = [\text{Absorbance of test}/\text{Absorbance of standard dilution}] \times 100$$

Rheological properties-

Rheological investigations are in charge of examining how materials flow and deform in reaction to external forces or stresses. The flow behaviour of the formulation is influenced by the concentrations of several excipients, including oils, surface-active agents, and gelling agents, as shown by a rheological examination of the materials. Changes in the formulation's viscosity and flowability could have an impact on the drug's stability, spreadability, and other in vivo characteristics. A formulation's shear-thinning qualities, for example, provide a thin layer on the skin's surface, increasing permeability, whereas a viscous formulation decreases permeation. This makes the rheological characteristics a crucial factor in the creation of NEGs, and they can be evaluated with a range of viscometers, including the Brookfield viscometer, or rheometers. [43]
The viscosity of the nanoemulgel formulations was determined at different velocities using spindle number 4 (Brookfield viscometer). The flow index were calculated from equation:

$$\tau = Kr^n$$

where τ is shear stress,
r is shear rate,
K is consistency index, and
n is flow index.
Taking log on both sides,

$$\log \tau = \log K + n \log r$$

Thus from the plot of log of shear stress versus log of shear rate, slope of the plot was

taken as flow index and antilog of Y-intercept gave the flow index.

Spreadability test :

The spreading width of the nanoemulgel between the two glassplates was measured one minute after preparation to assess the spreadability of the generated nanoemulgels 48 hours later. On a glass plate, a second glass plate was placed over a circle with a diameter of 1 cm that contained 500 mg of nanoemulgel. It was observed that the increase in diameter caused by the addition of weights caused the gel to spread.

The spreadability test can be calculated by using the formula :

$$S = m \cdot l/t ,$$

where S is spreadability,

m is weight placed on upper slide,

l is length of upper slide, and

t is the time taken.

In-vitro drug release study-

A formulation's therapeutic bioavailability, potency, and safety are all related to how well it releases and dissolves drugs in vitro. The drug release from nanoemulgels is evaluated by the in vitro dissolution test in a regulated setting that simulates the body in a time-dependent way, including membrane type, temperature, dissolving media volume and pH, and agitation rate. The combined effects of several physicochemical characteristics, such as globule size, viscosity, etc., may be shown by the in vitro release test (IVRT).

Thermodynamic stability test-

Thermodynamically stable, nanoemulsions without phase separation, creaming, or cracking are created at specific concentrations of oil, water, and a blend of surfactant and cosurfactant. The resultant nanoemulgel formulation's thermodynamic stability was evaluated using centrifugation stability.

The interfacial film's strength is reflected in its stability under centrifugation. For 30 minutes, the nanoemulgel formulation was centrifuged at 3500 rpm. When using freeze/thaw cycles, test tubes containing the nanoemulgel were hermetically sealed

and kept vertically in a freezer at -21°C for 16 hours, followed by 8 hours at ambient temperature (25°C). For any changes, the nanoemulgel was monitored. Three repetitions of this cycle were made.

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CHAPTER NO 08- SELF NANO-EMULSIFYING DRUG DELIVERY SYSTEM

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INTRODUCTION

Definition

Self-Nano emulsifying drug delivery systems (SNEDDS) are nano-emulsion pre-concentrates or anhydrous nano-emulsion forms. They forms fine oil-in-water (O/W) nano-emulsions in aqueous media by utilizing one or more hydrophilic solvents and co-surfactants under stirring. When distributed in water, the size range of globules in SNEDDS is less than 100 nm. Recently, SNEDDS is used to improve water solubility of BCS Class II and Class IV drugs, which are weakly soluble in water. Medium-chain triglyceride oils are combined with a non-ionic surfactant, essential for oral absorption. This treatment enhances dissolution rate and drug absorption, making SNEDDS crucial for improving drug absorption rates and ensuring reproducibility of plasma drug concentration profiles.

Following factors which affects self-nano emulsification:

- Physicochemical nature and concentration of the oil, surfactant, and co-emulsifier or co-surfactant play critical roles in preparation of SNEDDS.
- Ratio of components, particularly the oil-to-surfactant ratio, is also essential. Additionally, temperature and pH of aqueous phase during nano-emulsification are important considerations.
- The physicochemical attributes of drug, i.e. hydrophobicity/ lipophilicity, pKa, and polarity must be carefully evaluated.
- These factors require attention when formulating SNEDDS.
- Furthermore, acceptability of components for desired route of administration is also very important during formulating SNEDDS.

Compared with ready-to-use Nano emulsions, SNEDDS can offer advantages such as:

- SNEDDS enhance the pharmacokinetics of the delivered drug, leading to a reduction in dosage frequency.
- They have a larger drug payload and are highly stable formulations with simple manufacturing procedures.
- SNEDDS improve drug partitioning between water and oil by increasing the surface interfacial area.
- They also accelerate and increase the extent of drug absorption.
- Due to the reduced globule size, the medication penetrates more easily and more quickly.

Disadvantages

- Increased production costs.
- The formulation contains greater surfactant concentrations (30-60%).

Components used in SNEDDS

Oils

Oil phase is essential in formulation of SNEDDS because the physicochemical characteristics of the oil (like molecular volume, viscosity and polarity) have a major impact on the solubility of drug, droplet size of nanoemulsion, the spontaneous nature of nano-emulsification process. Maximum drug loading in the SNEDDS is often achieved by selecting the oily phase that has the highest potential for solubilization of the intended medication candidate. Additionally, the chosen oil needs to be able to produce nanoemulsions with tiny droplets. The selection of the oily phase so frequently includes a compromise between the oily phase's solubility of the medicine and its ability to promote the creation of a nanoemulsion with the required properties. Oils having lengthy hydrocarbon chains, such long-chain triglycerides or fixed oils like soybean oil, are known to be challenging to nano-emulsify. While long-chain triglycerides are more tough to nano-emulsify, medium-chain triglycerides and oils with short chains (or low molecular volume), such medium-chain monoglycerides and fatty acid esters (like ethyl oleate), are simpler. The oil lipophilicity and the oily phase

concentration in SNEDDS are directly correlated with nanoemulsion size. Lately, SNEDDS have also been made from oil mixes, like those that contain lacidipine, a calcium-channel blocker with poor oral bioavailability. Because it may dissolve medications like paclitaxel, itraconazole, and saquinavir that are hard to dissolve with traditional oily components, vitamin E (d-a-tocopherol) has attracted a lot of attention as an oily phase. Despite lack of reports on vitamin E-based SNEDDS at this time, there is a great deal of promise for their development.

Table no 01- Oils used for SNEDDS

Medium chain triglycerides (C8-C10)	Long chain triglycerides (C14-C22)	Mixed mono, di and triglycerides
Caprylic/capric acid triglycerides, palm seed oil, and fractionated coconut oil. Some examples of available proprietary names include Captex 355, Miglyol 812, 810, and Capmul MC.	Vegetable oils are glyceride esters of unsaturated long chain fatty acids, often known as triglycerides, such as olive oil, soybean oil, sesame oil, and maize oil.	Propylene glycol esters and a caprylic/capric acid combination of mono and diglycerides. Examples are Imwitor 988, Maisene 351, Imwitor 308, and so on.

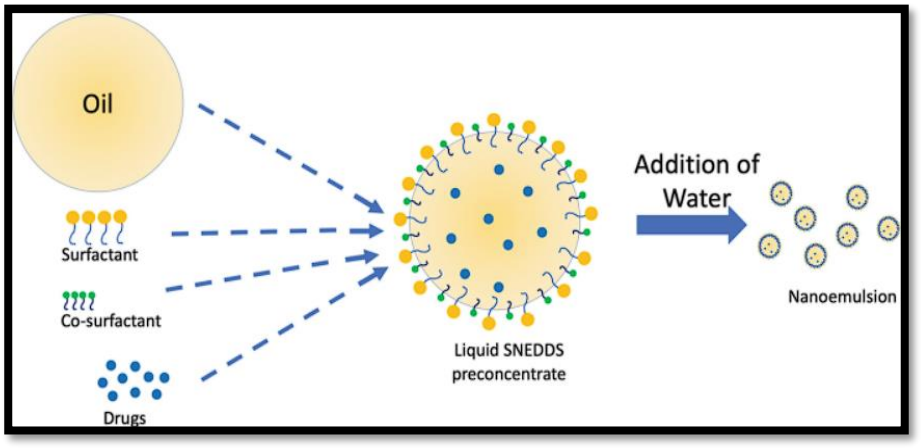

Fig no 01- Self Nano-Emulsifying Drug Delivery System

Surfactants and Co-solvents

When creating SNEDDS, choice of surfactant is crucial. Properties including cloud point, viscosity, and affinity for the oily phase, and HLB (in oil) have a big impact on

nano-emulsification procedure, self-nano-emulsification region, and the Nano emulsion's droplet size. Another important factor influencing droplet size of the nano emulsion is surfactant concentration in SNEDDS. When choosing a surfactant, consideration must also be given to the surfactant's regulatory status (such as generally regarded as safe [GRAS] status) and acceptability for the intended route of administration.

The fact that surfactants are not harmless should not be overlooked; their chemical makeup and concentration can have both positive and negative biological impacts. Cremophor EL (polyethylene glycol [PEG]-35-castor oil) is one of several non-ionic surfactants that improve the permeability and absorption of medications that are vulnerable to P-glycoprotein-mediated efflux. Structure, concentration, and mode of administration of these surfactants can all affect their potential negative consequences. For instance, Cremophor EL is usually well tolerated when taken orally, but is capable of causing anaphylactic shock and histamine release when given parenterally.

Certain surfactants may irritate GI mucosa and skin at higher concentration. Notably, the unfavourable characteristics of surfactants may reduce after associating with the oily phase; for instance, the haemolytic capability of surfactants significantly reduces when they associate with the oily phase in submicron emulsions.

Therefore, surfactant (hydrophilic or lipophilic) and/or amphiphilic solubilizes with pharmaceutical acceptability are utilized in this context. Incorporating co-emulsifiers or solubilizers into SNEDDS can expand the self-nano-emulsification region in phase diagrams. Amphiphilic solubilizes, such as propylene glycol, PEG, and glycol ethers (e.g., diethylene glycol monomethyl ether or Transcutol P), are frequently included in SNEDDS to decrease the time needed for self-nano-emulsification and enhance drug loading. In some cases, short-chain alcohols like ethanol are also employed by researchers. However, while these solubilizes can enhance drug loading into SNEDDS, their effects must be carefully considered.

Table no 2- Surfactants and Co-solvents used for SNEDDS

Nonionic Surfactants	Water Soluble Nonionic Surfactants	Cosolvent
In the SNEDDS, oleate esters such as polyoxyethylene glyceryl trioleate, polyoxyethylene sorbitan trioleate, and PEG 6 Sorbitan oleate are extensively employed. Polysorbate 85 and Tween 85 are commercially available.	Castor oil derivatives with saturated alkyl chains produced by hydrogenation of vegetable oil-derived compounds. Phospholipids are another type of derivative. Polysorbate 80 is a proprietary term for ether ethoxylates, and brands of water-soluble oils available include Cremophor RH40, Cremophor EL, poloxamer 407, different Labrasols, Labrafac Labrafils, and Gelucires, among others.	Propylene glycol, polyethylene glycol, ethanol, and glycerol are all examples of co-solvents. Others include diethylene glycol monoethyl ether, alcohol, polyethylene glycol, propylene carbonate, tetrahydrofurfuryl, and tetrahydrofurfuryl. Products marketed include PG, PEG 300, PEG 400, 600, Transcutol, and Glycofurol, among others.

Aqueous Phase-

Aqueous phase into which SNEDDS are introduced affects stability of nano emulsion and the size of its droplets. When developing SNEDDS, the aqueous phase pH and ionic concentration are therefore very important factors. A wide range of pH values can be found in the physiological environment, from 1.2 in the stomach to 7.4 & higher in the blood and intestine. Furthermore, different ions present in the physiological environment can have a substantial impact on the characteristics of nano-emulsions made from SNEDDS. The capacity of electrolytes to affect nanoemulsion properties including droplet size and physical stability is widely recognized.

Drug-

It is crucial to understand that therapeutic agent has a substantial influence on a number of SNEDDS characteristics, including phase behaviour and nanoemulsion droplet size. Effectiveness of SNEDDS is significantly influenced by a number of drug physicochemical characteristics like log P, pKa, molecular weight and structure, and presence of ionisable groups. For example, we find that when aqueous phase is water,

adding the medication cefpodoxime proxetil to SNEDDS decreases the nano-emulsification region. However, cefpodoxime proxetil pH-dependent solubility causes the nano-emulsification zone to expand when the aqueous phase's pH reaches 1.2. Additionally, we discover that when a drug is added to SNEDDS, the size of the nanoemulsion droplets may increase in comparison to SNEDDS without the drug. The amount of medicine added to the SNEDDS affects its characteristics as well because larger the drug amount, larger the droplet size of the nanoemulsion. High-stability nanoemulsions are produced when molecules' flexibility helps to generate a stable, closed-packed interfacial layer. In conclusion, the drug's characteristics and dosage have a big impact on a lot of different parts of SNEDDS, like phase behavior and final droplet size.

Background of the study

The administration of controlled ocular drugs is one of several innovative strategies being researched to get around the drawbacks of conventional ophthalmic preparations. The majority of ophthalmic formulations on the market nearly 90%—are administered in conventional dosage forms as ointments, suspensions, and solutions. These forms have the advantages of low production costs, straightforward preparation, and simple patient administration. And yet, only five minutes after applying an eye drop, a large portion of the drug is removed from the eye because of tear turnover. The cornea allows fewer than 5% of administered medications to reach intraocular tissues due to poor bioavailability and a shorter residence time caused by other variables such nasolacrimal drainage and conjunctiva absorption.

The absorption of topical drugs is complicated by the eye's particular design and physiology.

Many medications have a slower rate of absorption due to the ocular barrier. The human cul-de-sac has a capacity of 30 µL, yet the majority of eye drop dispensers emit about 50 µL. Even when the volume of tears returns to normal, about 7 µL is still in the cul-de-sac, resulting in significant drug waste. In order to maximize therapeutic effects and reduce the disadvantages of conventional dose forms, researchers concentrate on sustaining drug concentration in the eye for extended periods of time. Novel research and development methodologies are therefore emphasized in contemporary research.

Solid lipid nanoparticles (SLN), liposomes, niosomes, micro- and nanoparticles, and

micro- and nanoemulsions are examples of colloidal dosage forms that act as drug reservoirs and can extend the precorneal duration of treatment. Over the past 35 years, opportunistic fungal infections have also become much more common and severe, which has raised mortality rates. Fungal keratitis, which is characterized by inflammation of the corneal stroma and abnormalities in the corneal epithelium, is a dangerous condition that can cause corneal scarring and blindness if treatment is not received.

Importance to study

More drug retention and optimal bioavailability, however, require a number of techniques to enhance solubility and bioavailability of weakly aqueous-soluble drugs. There are situations when incorporating the medicine into a unique drug delivery system is important to prevent issues with traditional oral formulations, such as low bioavailability, nasolacrimal drainage, tear turnover, and conjunctival absorption. Lipid emulsions for ophthalmic usage are intended to improve transcorneal/ transconjunctival penetration or extend delivery to the eye in order to maximize medication bioavailability from a medical perspective. Depending on the level of lipophilicity of the medications present in o/w-type lipid emulsions, the penetration route through the cornea or conjunctiva/sclera may be chosen.

Formulation Techniques

Optimization studies play a crucial role in developing Self Nano-emulsifying Drug Delivery Systems (SNEDDSs) after initial selection of potential components. These studies aim to determine the optimal quantities of three key elements:

1. Oily phase
2. Surfactants
3. Co-solvents

The primary objective of these optimization studies is to identify the precise combination and proportions of these components that will result in the spontaneous formation of nano-emulsions. This process typically involves:

1. Systematic variation of component ratios
2. Evaluation of emulsification efficiency
3. Assessment of droplet size and size distribution
4. Stability testing of the resulting Nano-emulsions

Common optimization techniques include:

1. Response surface methodology (RSM)
2. Design of experiments (DoE)
3. Simplex lattice design
4. Ternary phase diagrams

These methods help researchers explore the formulation space efficiently and identify the optimal composition that yields stable, spontaneous nano-emulsions with desired characteristics. The optimized SNEDDS formulation should demonstrate:

1. Rapid and consistent self-emulsification
2. Small droplet size (typically <100 nm)
3. Narrow size distribution
4. Stability under various conditions

SNEDDS with increased drug solubilization capacity, improved bioavailability, and consistent performance can be created by researchers by carefully adjusting the proportions of oily phase, surfactants, and co-solvents. Following the selection of possible SNEDDS constituents, optimization research is conducted to determine the ideal concentrations of oily phase, surfactants, and co-solvents that may result in spontaneous nano-emulsion.

Preparation and observation of Self-Emulsifying Region by Water Dilution method -

In an aqueous solution, SNES produces a fine o/w emulsion with a small amount of agitation. Interfacial tension is decreased and the globules are kept from coalescing by the mechanical barrier that the surfactant and co-surfactant/co-solvent create. This prevents coalescence by promoting adsorption at the contact. At order to create the Self-Nano Emulsion, initial experimental batches are created utilizing oils, surfactants, and co-surfactants at quantities chosen according to their solubility; these concentrations range from 10 to 90% (v/v), 5 to 45% (v/v), and 5 to 45% (v/v), respectively. It is possible to examine the effects of different surfactant and oil concentrations on emulsification since the sum of the surfactant, co-solvent, and oil concentrations for each mixture is always 100%. Every trial batch of Self-Nano Emulsion is examined for visual appearance and classified as either milky, transparent, or turbid. Oil, surfactant, and co-surfactant quantities are listed in Table

No. 3. A magnetic stirrer is used to completely mix the ternary mixture until it is homogenous. After adding this mixture, drop by drop, while gently agitation, to predetermined volume of water, appearance is noted.

Preparation of batches of SNEDDS using suitable factorial design-

To make SNEDDS, a 0.1% w/v (1 mg/ml) medication is added to combinations of oil, surfactant, and co-surfactant in different component proportions that always add up to 100%. At 25°C, the drug dissolves with continuous stirring until a transparent mixture is reached (REMI Equipment's Pvt. Ltd, Mumbai). Using a suitable, different batches of SNEDDS are made, and optimization is done with regard to polydispersity index, zeta potential, particle size, and clarity.

Preparation and observation of Self-Emulsifying Region by Ternary phase diagrams-

For some components, ternary phase diagrams are frequently used to determine emulsification area. In these figures, the concentrations of the other two components are constant, while the ratio of one component changes. The region of emulsification can be visually observed or particle size of the emulsion or nano-emulsion that results from aqueous dispersion can be measured. Emulsification area SNEDDS compositions all produce globule-containing spontaneous nano-emulsions diameters smaller than 200 nm following water dispersion.

A variety of statistical experimental designs, including Box–Behnken, central composite, simplex lattice, full-factorial, and D-optimal designs, can be used to optimize SNEDDS in addition to ternary phase diagrams. A response surface design that effectively represents the quadratic behavior of components, the Box–Behnken design is built on three levels (−1, 0, +1). The formula for determining number of runs (N) required for Box–Behnken design is $N = 2k (k-1) + C0$, where k is number of independent variables and C_0 is number of central points. Utilizing the Box–Behnken design, SNEDDSs of polypeptide-k are optimized (Figure 2b).

While size grows at increasing amounts of oil (oleoyl polyoxyl-6 glycerides, X1) and cosolvent (diethylene glycol monoethyl ether, X3), study finds that size decreases (Y1) with higher levels of surfactant (Tween 80, X2). Figure 4b illustrates how drug loading (Y3) rises with increasing ratios of X1, X2, and X3. More negative zeta potential values (Y4) are also observed when oil concentration (oleoyl polyoxyl-6 glycerides, X1)

increases. By improving droplet size (Y1), drug loading (Y3), and zeta potential (Y4), the optimized SNEDDS increases polypeptide-k oral bioavailability in rats.

Response surface designs that are most frequently utilised are central composite designs. They consist of factorial or fractional factorial designs with central points and a set of axial points, which allow curvature to be estimated. For a polynomial with quadratic terms to have coefficients, experimental design must have a minimum of 3 levels for each factor. For a central composite design, 2k + 2k + nc experiments are needed, where nc is number of central points and k is number of variables.

Main composite designs for SNEDDSs are PEG 600 (cosolvent, X3), MCM (oil, X2), and Capmul and Labrasol (surfactants, X1). SNEDDSs are further screened and optimized via central composite design after preliminary Taguchi design investigations show that oil and surfactant are important components. Particle size (Y1) is shown to grow only when the amount of oil decreases at medium to high surfactant concentrations. Particle size (Y1) increases with a decline in surfactant amount. For emulsification time (Y2), an increase in surfactant amount reduces Y2, while an increase in oil amount increases Y2.

Regarding the percentage drug release in 15 minutes (Y3), it is observed that at low oil levels, Y3 is high only when surfactant amount is high. Y3 decreases as the surfactant amount declines (Figure 2c).

The simplex lattice design constitutes a triangular grid of experiments (runs) and is described as a space-filling design. In this design, the factor space is represented by the fractions of excipients in each composition that must add up to unity. A lattice arrangement is utilised to evaluate the mixture points, and the dependent variables—which show how the components influence the response are represented by a simplified polynomial function. Particularly for combinations with four or more components, this design is a useful tool for examining the characteristics of blends over broad composition ranges parts.

Evaluations with specifications

Particle Size and Polydispersity Index-

Using dynamic light scattering on a HORIBA Nano Partica SZ-100 (Japan) particle size at 25°C, the mean particle size is calculated. Light scattering techniques are used in triplicate for this measurement. Prior to measurement, distilled water is used to dilute the samples. The findings are displayed as a plot of the Z-average mean, or

average diameter of the suspension's particle size, against the sample volume %. Furthermore, Polydispersity Index (PDI) is computed to evaluate consistency of suspension's size distribution. Triplicate samples are taken for every determination, and the mean and standard deviation (SD) are the final values.

Zeta Potential

Using a Zetasizer (HORIBA, NanoPartica ZP-100, Japan), the charge on the particles is measured at 25°C. At 3.3 V, light scattering is quantified by combining phase analysis and laser Doppler velocimetry. For every formulation, three samples are used to calculate the average zeta potential.

Assessment of self-emulsification time

By measuring prepared SNES emulsification time, its self-emulsification property is assessed. Using a magnetic stirrer, 200 mL of simulated tear fluid at pH 7.4 and 37°C are combined with 1 mL of each produced SNES (10 mg drug/mL). In addition to recording the amount of time needed to completely emulsify the SNES, visual observations of the self-emulsification behavior are made.

Drug content (%) assay

1 mL of SNEDDS (equal to 1 mg of drug) is dissolved in 2 mL of methanol & 8 mL of distilled water in a 10 mL volumetric flask to assess microemulsions percent drug content (%). A further 10 mL is made in a different flask by removing 0.1 mL of the prepared stock solution and diluting it with distilled water. Using the blank emulsion as a reference at a wavelength of 262 nm, the absorbance is measured by use of a double beam UV/Visible spectrophotometer (Shimadzu, Japan) following the proper dilutions with distilled water & methanol.

Viscosity

A Brookfield viscometer (Brookfield Engineering Labs, Middleboro, MA, USA) is used to measure the viscosity of the created SNEDDS formulations at 25 ± 0.5. Spindle CC3-14 is used for the measurement, and it is sheared at a rate of 100 rpm.

pH

All micro emulsion samples are subjected to a pH meter (Digital Systronic, Mumbai,

India) calibrated with pH 4 and pH 7 which is standard buffer solutions at 25°C 0.5°C. Every measurement is carried out in triplicate.

Dilution Study

The effect of dilution on emulsion characteristics is examined in order to model the behavior of dilution in vivo. Using distilled water and artificial tear fluid at pH 7.2, 1 mL of each formula is diluted 10, 100, and 1000 times in this test. The diluted systems are mixed using magnetic stirrers at 37°C and 100 rpm to completely homogenize and replicate body temperature. The systems are then visually inspected for indications of phase separation after being kept at room temperature for a full day.

The in-vitro performance of the formulations is visually evaluated using the grading system below:

Grade A: Emulsion forms quickly and appears transparent or blue (within one minute).

Grade B: Emulsion forms quickly, is slightly less clear, and has a bluish-white appearance.

Grade C: Fine milky emulsion forms within two minutes.

Grade D: Emulsion is dull, greyish-white, and slow to emulsify (more than two minutes), with a slightly oily appearance.

Grade E: Formula contains significant oil globules on the surface with minimal or poor emulsification.

In-Vitro Diffusion study

The drug release is studied in vitro using a Franz diffusion cell. 3 mL of the SNEDDS formulation and 13 ml of simulated tear fluid (STF) pH 7.4 ± 0.2 are injected into the acceptor compartment as part of this assay. The cellophane membrane of the Franz diffusion cell is placed between the two compartments and inflates under STF. Using a magnetic stirrer, STF temperature is kept at 37 ± 0.5 °C with 50 rpm. Samples of 1 mL are collected for this test at intervals of 0.5, 1, 2, 4, 6, and 10 hours. Volume extracted from each sample is replaced with an equivalent volume of original sample solution, and each sample is taken in triplicate. Each sample, at its specific time interval, is analysed using a UV-Vis spectrophotometer at wavelength of 262 nm, with aid of a blank solution. The drug content is determined through regression on the calibration curve.

Drug release kinetics modelling

The release kinetics method is used to evaluate kinetics of drug release from micro emulsion by applying a number of kinetic equations, including the Higuchi model, zero-order release kinetics, and first-order release kinetics. Several criteria are used to produce the release data. The Korsmeyer-Peppas equation is used to derive parameters "n," time component "k," the release rate constant, and regression coefficient "R" in order to comprehend release mechanism.

Various kinetic models are as follows:

A) Zero Order

$$\% R = kt$$

In this model, the drug concentration is plotted against time. Zero-order rate constant (K_0) and regression line (R^2)) values are obtained from graph, representing an ideal release for achieving prolonged pharmacological action. This approach applies to delivery techniques such as transdermal, coated, osmotic, and matrix tablets containing poorly soluble drugs.

B) First Order

For First order release kinetics, the release data was fitted into the following equation,

$$\text{Log (fraction unreleased)} = kt / 2.303$$

Cumulative percentage of drug remaining was plotted against time in this log. The value of the regression line (R2) and the first order rate constant K1 were obtained from the graph. This model can be used to investigate release profiles of pharmacological dosage forms,like those that introduce water-soluble medications in porous matrix, and to analyze hydrolysis kinetics.

C) Higuchi Kinetics (Matrix)

Plotting the Hixson-Crowell release mechanism against time in minutes involved taking the Cube Root of initial drug amount minus the Cube Root of the medication released at time (t). After that, the graph's regression line value (R2) and rate constant of release (KHC) were taken out..

$$\%R = kt^{0.5}$$

Systems with a drug distributed in a homogeneous swellable polymer matrix, such as matrix tablets containing a water-soluble drug, may utilize this model.

D) Korsemeyer - Peppas Equation

For Korsemeyer-Peppas release mechanism, log cumulative % drug release is plotted against log time. Then rate constant of release and regression line value (R^2) are

obtained from graph.

$$\%R - kt^{n}$$

$$\text{Log } \%R = \log k + n \log t$$

When more than one type of release phenomenon may be present or when release mechanism is well-known, this model is frequently used. Different release mechanisms could be described by the "n" values, where a value of "n" < 0.45 indicates Fickian diffusion and 0.45 < n < 0.89 indicates non-Fickian diffusion.

whereas if 'n' value is 0.89 corresponds to case II transport and higher than 0.89 indicates super case-II transport depicted in table.

Table no 03- Diffusion exponent and release mechanism

Diffusion exponent (n)	Overall diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

E) Hixson- Crowell Equation

$$(\text{Fraction unreleased})^{1/3} = 1 - kt$$

Pharmaceutical dosage forms i.e tablets can be dissolved in planes parallel to drug surface using above equation if the dimensions of tablets decrease proportionately while maintaining a consistent starting geometric form. When this model is applied, it is assumed that drug particle dissolving rate, rather than potential diffusion through polymer matrix, controls the release rate.

Several kinetic models, including zero order, first order, Higuchi, Hixson Crowell, and Korsemeyer-Peppas, were fitted to dissolution data that was acquired. This was done in order to identify the medication release mechanism. In kinetic investigations, the best suited model is chosen by comparing the regression (R2) values that are obtained.

Fourier Transform Infrared spectroscopy (FT-IR) analysis

The drug's compatibility with the oil, surfactant, and co-surfactant that make up SNEDDS is ascertained by the FTIR analysis. Using the potassium bromide dispersion method, an infrared spectrophotometer (IRAffinity1, Shimadzu, Japan) with Fourier transform is employed. Using dried potassium bromide for baseline correction,

the transmittance percentage is examined in the 4000–400 cm^{-1} spectral range with 40 scans and a resolution of 4 cm^{-1}.

X-ray diffraction (XRD)

Primary Evaluation of material properties such crystal texture, crystal flaws, crystallinity, and molecular stresses is done using this technique. At particular angles, lattice planes scatter an X-ray beam. As the X-ray beam travels through the object, the atoms in its path disperse or diffract it. Using Bragg's law and a properly positioned detector, the interference resulting from X-ray scattering is studied in order to determine crystalline structural characteristics of material.

Transmission electron microscopy (TEM)

The medication SNEDDS's unique morphology is examined using transmission electron microscopy (TEM) (Joel JEM 1230, Tokyo, Japan). To prepare the sample, put a drop of suitably diluted SNEDDS onto a copper grid coated with carbon. Let it sit for two minutes, then use filter paper to remove any surplus liquid. Following room temperature air drying of the carbon grid, the sample is placed into the TEM system for observation and negatively stained with a drop of 2% phosphotungistic acid solution.

Stability studies

The increased SNEDDS formulation's stability tests are carried out at a regulated room temperature (25°C ± 2°C, 60% ± 5% RH) in compliance with ICH recommendations. Over the course of three months, the SNEDDS formulation's zeta potential, polydispersity index, and particle size are examined.

Morphology

Using Transmission electron microscopy (TEM) and Scanning Electron Microscopy (SEM), morphology of nano-emulsion droplets is ascertained. SEM provides information regarding droplet morphology by using back-scattered electrons. Electrons are sent through the dispersion in a TEM to create the droplets' shape and distinguish distinct chemical compounds according to their densities. Cryo-SEM and cryo-TEM have recently been created to investigate actual morphological data of Nano formulation.

Ex-Vivo Permeation Studies

It is known that intestinal absorption has a significant impact on the plasma levels of substances placed into SNEDDSs. The gastrointestinal (GI) absorptive capacity of medicine and the mechanisms underlying this process are ascertained using a number of separated systems, which helps to minimize the use of live animals in experiments. Single-pass intestinal perfusion (SPIP) and intestinal recirculating perfusion (IRP) are commonly utilized devices that offer conditions more similar to those experienced following oral consumption.

Based on the idea that drug permeation causes amount of drug in the perfusion nano-emulsion to decrease with time, SPIP makes it possible to determine the pace and degree of permeation via intestinal segments (such as the duodenum and jejunum) after cannulating both ends. Compounds that are quickly absorbed benefit from SPIP. Alternatively, IRP uses the same perforate and repeats the operation several times. For medications that are absorbed slowly, this method is used to enhance concentration changes by lengthening the retention period in the intestine, which greatly enhances the likelihood of drug absorption.

In-Vivo Pharmacokinetics study

Animal pharmacokinetic studies are crucial in predicting oral bioavailability in humans during drug development, in addition to basic in vitro research. The medicine loaded in SNEDDS is usually given to animals orally (either pre-concentrated or dispersed in water). A variety of analytical methods are frequently employed to examine the medication absorbed in plasma, including Liquid chromatography-UV and liquid chromatography-mass spectrometry. AUC0-t, Cmax, Tmax, and t1/2 are pharmacokinetic parameters that are extrapolated from animals to people in order to determine an appropriate dose for human first trials.

In contrast to dogs, rabbits, or pigs, rats are a cost-effective, practical, and somewhat high-throughput animal model. Rats are also useful because they may be used to block enzymes, transporters, and efflux pumps, which makes it possible to assess how these elements affect medication absorption. It is crucial to remember, nevertheless, that a fundamental problem in extrapolating bioavailability from animals to humans is considerable variation in anatomy and physiology among species, which results in variations in how well medication doses are absorbed orally. Numerous

published papers detail SNEDDS pharmacokinetic investigations in animals, including rabbits, dogs, and rats. Various SNEDDS formulations have outperformed native medications both in vitro and in vivo.

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CHAPTER NO 09- NANO-STRUCTURED LIPID CARRIER SYSTEM

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INTRODUCTION

The first generation of lipid nanocarriers was improved to enable medication delivery via diverse routes of administration for the treatment of physiological problems. NLCs are made by replacing a portion of the solid lipids with liquid lipids, resulting in a drug-incorporated matrix. They attempt to increase the oral bioavailability of weakly water-soluble medicines, and NLCs are now found in a variety of cosmetic items and dermal creams on the market. The use of NLCs for drug targeting in a variety of illnesses is being investigated extensively.

NLCs have been studied for targeted medication delivery to systems such as the lungs, brain, anterior and posterior ocular tissues, and malignant tissues in a variety of diseases. Their applications include increasing bioavailability, specificity, and even reversing multidrug resistance. NLCs can be used for oral and topical treatments, brain and cancer targeting, and gene delivery. In order to get over the challenges caused by SLNs, this second-generation lipid nanoparticle evolved in 1999. NLCs provide the benefits of prior lipid nanoparticles, including improved drug loading capacity and greater stability than SLNs. NLCs entered the cosmetics industry in 2005, and there are already about 40 cosmetic items available. Despite their high encapsulation capability, NLCs have not yet been widely used as a drug delivery mechanism.

A fully ordered crystalline structure in SLNs frequently emerges during homogenisation and storage, allowing the medication to escape into the dispersion medium due to restricted drug-loading space. NLCs avoid this problem thanks to their unique matrix, which blends liquid and solid lipids. This mixture generates an incomplete core with a possibly amorphous structure, allowing for increased drug loading while limiting drug escape. The NLC core's amorphous structure prevents the medication from being expelled into the aqueous phase. When a medicine is extremely soluble in liquid lipid, an oil-in-solid fat-in-water (O/F/W) system can be

generated, in which microscopic oil globules are spread throughout the solid lipid core, allowing drug to be released gradually from droplets of oil.

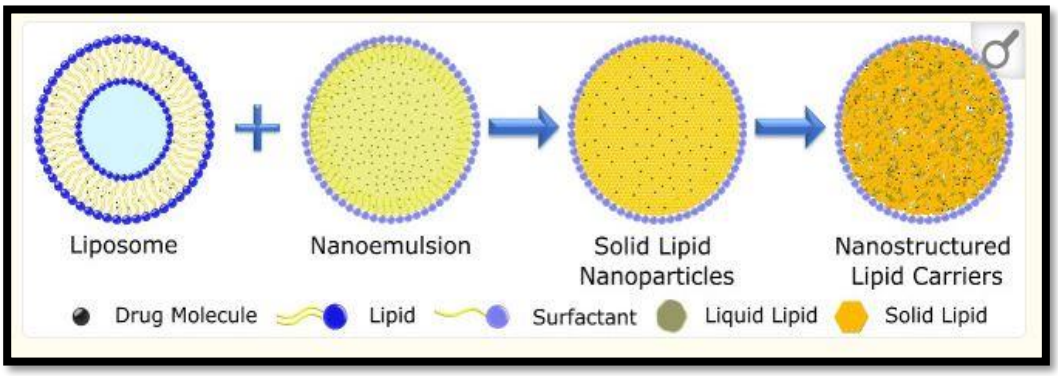

Fig no 01- Evolution of Nano-structured lipid carrier

Lipid Nanocarriers –

First form of lipid nanocarriers are solid lipid nanoparticles (SLNs), created by integrating medicines into solid lipids using either cold or hot homogenization procedures, depending on the drug's thermal stability. However, SLNs have limitations, like drug leakage from the matrix during storage and decreased drug loading efficiency. To solve these challenges, nanostructured lipid carriers (NLCs) were created, based on the idea of integrating pharmaceuticals into a matrix made up of both solid and liquid lipids in variable ratios. NLCs are meant to reduce or eliminate crystallinity within the solidified core, addressing the limits imposed by SLNs' crystalline structure.

The types of NLCs can be summarized as follows:

1. NLC Type I (Imperfect Type): Oil or liquid lipid replaces portion of the solid lipid, resulting in an irregular crystal lattice within the matrix. This form allows for increased drug loading while avoiding a highly organised or ordered matrix, which could expel drug from the core. The defective crystal core consequently allows for greater drug incorporation.
2. NLC Type II (Amorphous Type): Liquid lipid or oil replaces some of the solid lipid, resulting in an irregular crystal lattice within the matrix. This form allows for increased drug loading while avoiding a highly organised or ordered matrix, which could expel the drug from the core. The defective crystal core consequently allows for greater drug incorporation.
3. NLC Type III (Multiple type): Using phase separation techniques, this oil-in-solid lipid or fat-in-water type NLC was developed from water-in-oil-in-water (w/o/w) emulsion

concept. This method increases drug-loading capacity and stability when a medication has higher solubility in oil. When the solid lipid matrix is floated in an aqueous media, tiny oil droplets are evenly distributed throughout, enabling stability and controlled release.

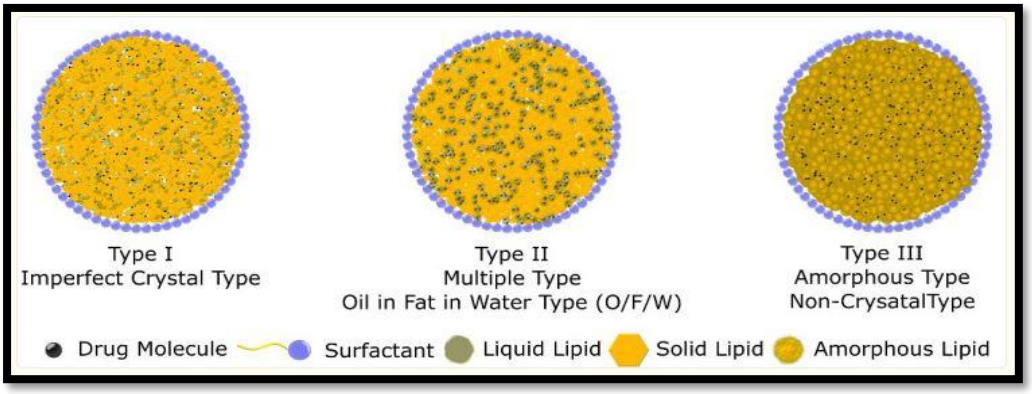

Fig no 02- Types of Nano-structured Lipid Carriers

Background of the study

Solid lipid nanoparticles (SLNs) were the first to be developed as innovative drug delivery vehicles. For targeted drug delivery, incorporating medications into biocompatible lipids at the nanoscale is a potential strategy. Drugs can be delivered via lipid nanocarrier systems in a variety of ways to address physiological circumstances. In contrast to SLNs, nanostructured lipid carriers (NLCs) were created by partially substituting liquid lipids for solid lipids, resulting in a drug-incorporated matrix with improved formulation qualities. Because NLCs have better formulation qualities and are more biocompatible, they are perfect drug carriers, especially when it comes to boosting the oral bioavailability of medications that aren't very water soluble. NLCs are being studied extensively for their ability to target certain areas in a variety of diseases. They allow medications to be targeted to various organs, such as the brain, eyes, and lungs. They can also be target cancer tissues.

Importance to study

Nanostructured lipid carriers (NLCs) are valuable for delivering drugs and active substances through multiple routes:

- **Skin penetration**: NLCs improve the delivery of natural active ingredients, enabling deeper penetration into the skin layers.
- **Oral drug delivery**: NLCs aid in transporting drugs across intestinal membranes, shielding them from enzymatic breakdown and fluctuations in intestinal pH.

- **Targeted delivery**: NLCs facilitate targeted delivery of drugs to specific sites within the body.
- **Controlled drug release**: NLCs enable regulated drug release, providing control over release rates.
- **High drug-loading capacity**: NLCs can carry high amounts of drug.
- **Stability**: NLCs typically exhibit strong stability.
- **Biocompatibility**: NLCs are biocompatible and non-toxic.
- **Ease of preparation**:

NLCs are easy to produce and scale up efficiently.

NLCs consist of both liquid and solid lipids, forming a partially crystallized structure. This disordered lipid matrix increases drug-loading capacity and supports a controlled release profile.

Formulation Techniques

It is possible to produce lipid nanoparticles like SLN and NLC using remarkably comparable techniques. It makes a difference if the formulation contains liquid lipids or not. To create NLCs and SLNs, methods such solvent emulsion, emulsification-ultrasonication, film ultrasonication, and high-pressure homogenisation are frequently employed.

High pressure homogenization (HPH) –

Lipid nanoparticle preparation can be done with high pressure homogenization, which is an effective method. Lipid NP synthesis can be accelerated with the help of HPH. There are two applications for this method, as follows:

Hot HPH

A drug-dispersed lipid must be heated above the melting point of the solid lipid in order allow the liquid and solid lipids to melt.

The drug is then added. A suitable amount of surfactant is dissolved in deionised water to create the aqueous phase, which is then heated to the same temperature as the lipid melt. To create a pre-emulsion, the two phases are then mixed together & homogenised with high shear for a brief period of time at a high temperature. High-pressure homogenisation (HPH) is applied to this pre-emulsion right away for three to five cycles at different pressures. The number of cycles is usually changed according to the target average droplet size of the nano-emulsion.

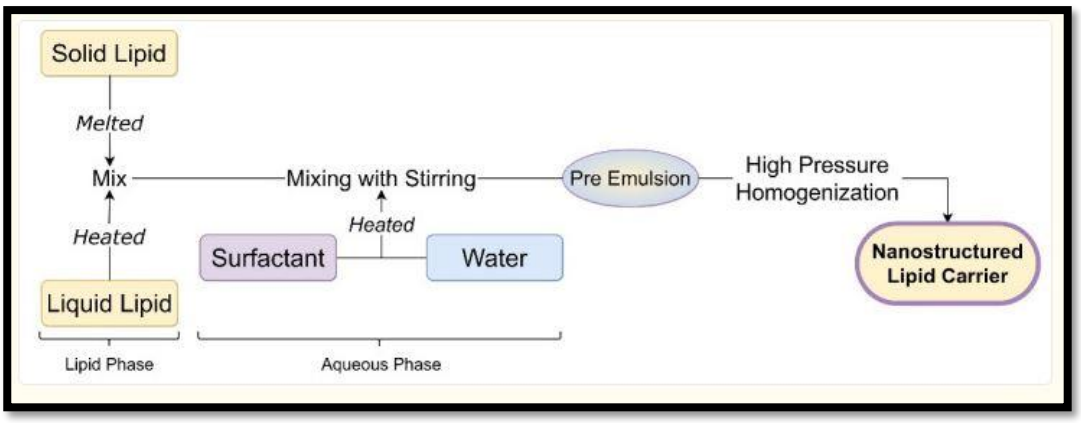

Fig no 03- Hot high-pressure homogenization

Cold (HPH)

There is a drawback to the widely used hot high-pressure homogenization (HPH) method: the high processing temperature may cause hydrophilic and thermolabile medications break down. This is addressed with a straightforward method that involves quickly chilling the nano-emulsion. Using this method, liquid and solid lipids are heated to a temperature higher than melting point of solid lipid. Following dispersion or dissolution of the medication in the heated lipid melt, HPH is applied. Dry ice or liquid nitrogen is used to quickly chill the resulting emulsion. To create a solid mass that is then crushed into microparticles. NLCs are then created by dispersing these particles in a cold aqueous phase with the proper surfactant and exposing them to high-shear homogenization or ultra-sonication.

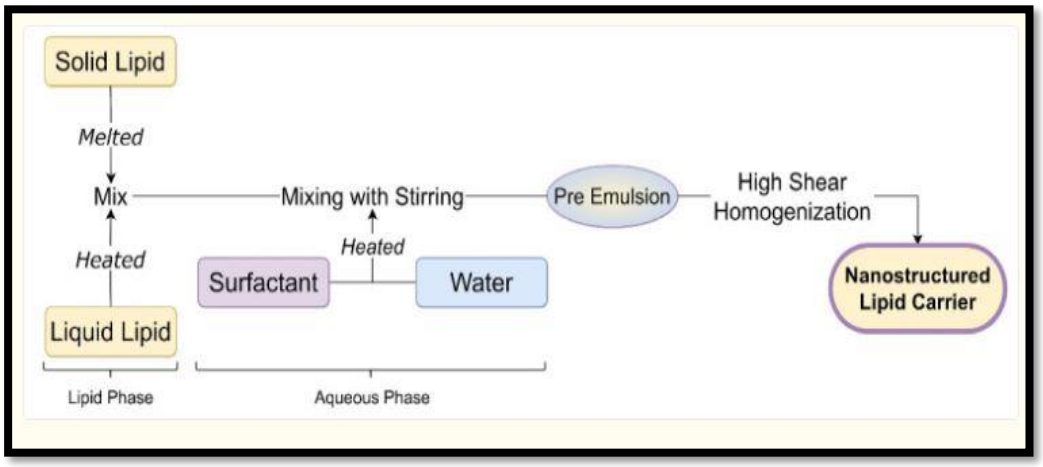

Fig no 04- High speed homogenization

Solvent emulsification evaporation method-

This term and the diffusion approach mentioned above are interchangeable.

Water-immiscible organic solvents, such as cyclohexane or chloroform, are used in this method, to dissolve the drug and lipids rather than a water-miscible organic solvent. Since certain traces may still be present in the finished formulation, the use of organic solvents is a major drawback of the solvent diffusion and evaporation approach.

Solvent diffusion method

Water-miscible organic solvents like methanol, ethanol, acetone, and others are used in solvent diffusion method. The medication and lipids are introduced in one or more organic stages using this approach. The transparent lipid phase is obtained by sonicating this and keeping it at a high temperature. By adding an appropriate stabilizer or surfactant, the aqueous phase is created and kept at the same temperature as the lipid phase. In the aqueous phase, the organic-lipid phase is introduced while being mechanically stirred at a high temperature. This mixture is stirred at room temperature to cool and evaporate the organic solvent and create NLCs.

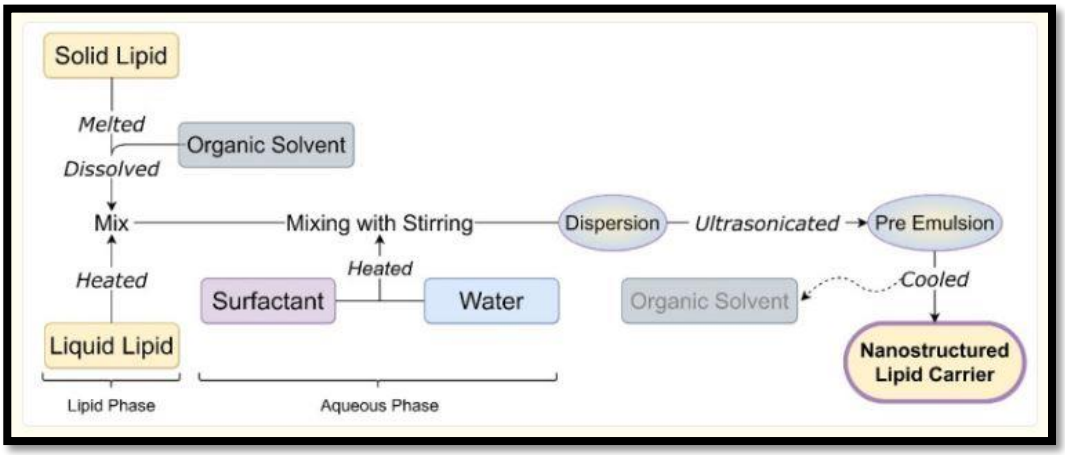

Fig no 05- Solvent diffusion technique

Emulsification-ultrasonicator method

HPH and this approach are relatively comparable. Solid, liquid, and drug lipids are combined and melted at temperatures 5–10 °C above the solid lipid's melting point. The surfactant is heated to the same temperature as the lipid melt after being dissolved in distilled water.

After adding the aqueous phase to the lipid phase, the pre-emulsion is homogenized at high shear by applying the necessary rpm for a predetermined amount of time. After a predetermined amount of time in an ultrasonicator, this emulsion is added to a predetermined volume of distilled water. To get NLCs, this is cooled to room

temperature and solidified. During probe sonication, metal particles may contaminate the formulation.

Film-ultra sonication method

This technique is adapted from vesicular drug delivery system preparation techniques. Ethanol is the preferred organic solvent for dissolving lipids and drugs. An aqueous phase is produced when a surfactant is dissolved in water and kept at a high temperature. This phase is maintained at a high temperature while being swirled to ensure that the drug-lipids mix correctly. The organic phase is removed through the application of suction using a spinning evaporator. A thin layer of drug-lipid blend is typically produced in a heated aqueous phase, which is then gathered and dispersed by sonication. After cooling this mixture to room temperature, distributed solidified NLCs are produced.

Microemulsion method

The medication dissolves in the mixture once the melted lipid is introduced to the heated oil. The surfactant is dissolved in distilled water to create the aqueous phase. The temperature of both phases is raised and kept there. A microemulsions can occur when a lipid phase is introduced to an aqueous phase while being mechanically stirred at the same temperature. While stirring, the warm microemulsions are introduced to cold water (between 2 and 4 °C). In this case, precipitation of microemulsions globules to produce NLCs requires dilution with a considerable volume of cold water. The concentration of actives decreases when a high volume of water is used for dilution. Therefore, additional formulation concentration or lyophilization is needed.

Supercritical fluid (SCF) technology

It is done by melting lipids and solubilizing SCF (ideally carbon dioxide). The solubility of the elements in the SCF determines whether this form is a gas-saturated suspension or a solution. Following that, it is atomized by a nozzle and sprayed into a chamber. Decompression and gas evaporation take place at this phase, creating solid NLCs. Frequently, the creation of hybrid lipid nanoparticles served as the foundation for patent applications. In other words, a polymer is added to the lipid mixture during the NP formation process, which results in reduced drug escape in the dispersion media, control over drug release, and dispersion stability against drug degradation. Lipid nanoparticles have been proposed to be surface coated with various compounds

to enhance their targeting capabilities. Methods such as microemulsions, nanoprecipitation, and HPH can be used to produce such lipid NP. Proteins were similarly enclosed utilizing polymers and lipids without the use of organic solvents. In watery conditions, the lipid bilayer NP system demonstrated enhanced lipid carrier stabilization. Targeting and cellular uptake were found to be improved by the use of cationic polymers.

Hot melt extrusion technology

The majority of the preceding methods for preparing NLC are taken from other nanocarrier systems or from the ways for preparing SLN. With the exception of HPH, commercializing these multi-step techniques is challenging. A more recent technique used to prepare NLCs is hot melt extrusion with a twin screw extruder. In the extruder, there were three feeding ports: one for adding the lipid drug mix, one for adding liquid lipid, and one for adding the aqueous phase. A peristaltic pump was used to transfer heated liquid lipid through the second port after a volumetric feeder had added solid lipid and drug mix to the first port. The melting and mixing part were applied as it moved through the extrusion barrel. Using a peristaltic pump, a heated aqueous phase containing the proper surfactant was added to the third port. The mixture was then mixed at the ideal speed to create a pre-emulsion. That pre-emulsion is extruded into a vessel that is attached to a probe sonicator in order to produce NLCs.

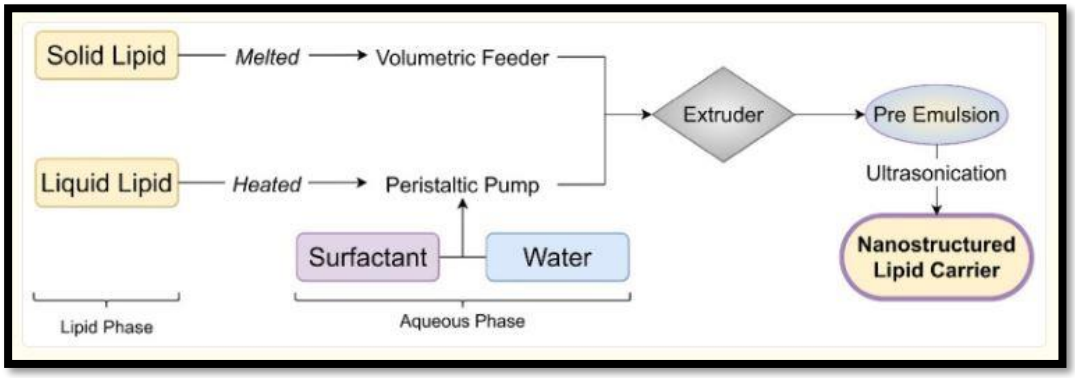

Fig no 06- Hot melt extrusion method

4.9 Solvent Injection Method

Using heat to melt solid lipid, the lipid phase is dissolved in a water-miscible solvent or their combination. Rapid injection of the resulting organic phase into an aqueous phase that contains buffer solution or surfactant is done while swirling continuously. Lipid precipitation and lipid nanocarrier production cause the solvent to disperse. The

emulsifier concentration and solvent diffusion determine particle size. Demonstrates how to use the hot melt extrusion technique to prepare NLC.

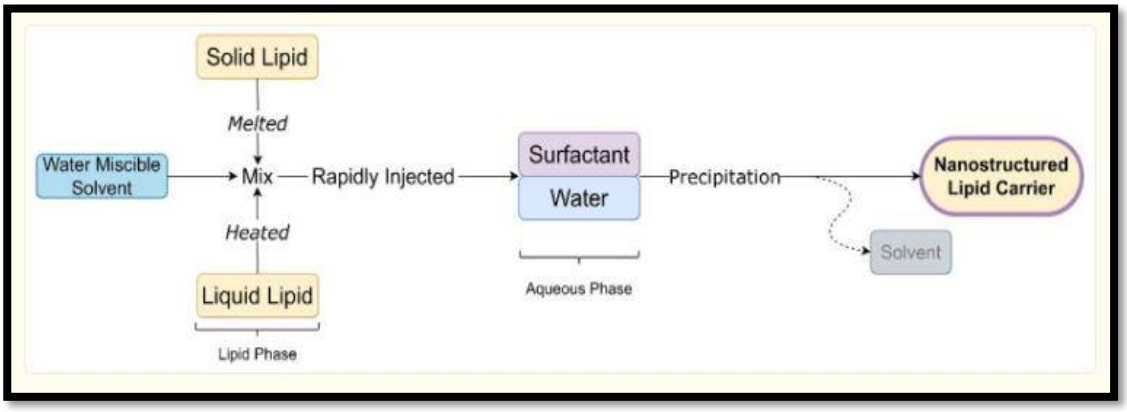

Fig no 07- Solvent Injection method

Evaluations with the specifications

Size of particle

A HORIBA PS 100 Particle Size Analyzer is used to measure the mean particle size in triplicate at 25°C using the principles of light scattering. Distilled water is used to dilute the samples before to testing. The average particle diameter (Z-average) expressed as a percentage of sample volume is how the data are displayed. Additionally, the polydispersity index (PDI), which measures suspension homogeneity, is calculated. Measurements from three different samples are used to compute the mean's standard deviation.

Zeta potential measurement

Utilizing the Zetasizer (HORIBA Z5100), the charge of the particles was assessed. 2 With an electrode potential of 3.3 V, laser Doppler velocimetry and phase analysis are used to quantify light scattering. 0.896 MPa is the dispersion medium's viscosity. To find the mean zeta potential, samples of each formulation were examined.

Entrapment efficiency -

The total drug concentration (A) was determined by sonicating NLCs for five minutes after diluting them with a 0.5 M methanolic HCl solution. A Shimadzu (UV-1800) double beam spectrophotometer was then used to measure the overall drug concentration. For 45 minutes, we centrifuged 1 mL of NLCs at 12,000 rpm to determine the amount of medication that remained unentrapped. 0.1 mL of the

supernatant was diluted with 10 ml. The concentration of unentrapped drug (B) and 0.5 M methanolic hydrochloride solutions were measured using a UV spectrophotometer. To find the medication that was entrapped, the values of A and B were entered into the following equation.

$$\text{Entrapment efficiency (EE \%)} = \frac{\text{Initial drug} - \text{final drug}}{\text{Initial drug}} \times 100$$

Where, A – Initial drug, B – Final drug

FTIR study

Using a probe (BRUKER Alpha II) FTIR Spectrophotometer, FTIR spectra of the medicine, excipients, physical combination, and optimized batch were obtained. Spectral measurements were performed in the 400–4000 cm-1 range following the introduction of around 5 mg of each sample.

X-ray Diffraction (XRD)

The drug, excipients, and physical formulation's X-ray diffraction (XRD) profiles are obtained using the BRUKER D8 ADVANCE X-ray Diffractometer. At a scanning rate of 40 per minute, 5 mg of each sample is exposed to monochromatized Cu-Kα radiation (1.54184 Å) and examined in the 40–1000 Å range. 15 mA and 35 kV are the values for the current and voltage parameters, respectively.

Transmission Electron Microscopy

TEM is used to evaluate the NLCs' forms using a JEOL Model 1230 (Tokyo, Japan). Once the NLCs have been diluted tenfold, they are carefully placed on a copper grid coated with carbon for one minute. Any surplus solution is then carefully removed using filter paper. Imaging is done after the grid has had time to dry. The TEM takes pictures with an acceleration voltage of 200 kV, and imaging viewer software is used to examine the pictures.

In-vitro drug release study

Using an open glass cylinder dissolving equipment, drug release studies are conducted over a 12-hour period. The release barrier is a dialysis membrane (HI Media, Mumbai) with a molecular weight cutoff of 12,000–14,000 Å. A pre-soaked

dialysis membrane is attached to the end of the glass cylinder. The glass cylinder is attached to the stirrer after 2 ml of solution is gently added from the open side each time. The stirrer is rotated at 100 rpm while suspended in 100 ml of synthetic tear fluid (pH 7.4) at 37°C ± 0.5°C. A Shimadzu 1800 UV-Visible Spectrophotometer (Japan) is used to measure absorbance at 295 nm in order to quantify the drug content of the removed samples.

Release kinetic models

A kinetics method to drug discharge has been integrated into three kinetic equations to compute the dynamic study of drug released from NLCs. A variety of criteria were used to calculate the released data that was gathered. Knowing the release method, variables 'n' and time component 'k', the release rate constant, and 'R', the Korsemeyer-Peppas equation was used to get the regression coefficient (R2). These are some examples of kinetic models.

Zero order kinetics

Plotting the drug concentrations against time is part of this concept. The graph was also used to determine the zero order rate constant, K0, and the regression line (R2). This approach is effective in producing long-lasting pharmaceutical effects. This pertains to the delivery of topical low-soluble medications via osmotic systems, matrix tablets, coated forms, and systems.

First order kinetics

The entire amount of medication that was left behind was compared to time using this logarithmic framework to create a figure. Particularly for medications that dissolve under permeable surfaces, this method is helpful for examining the kinetics of hydrolysis and the release patterns of pharmacological dosage forms.

Higuchi kinetics

Plotting the Cube Root of the initial drug amount less the Cube Root of the medication released at time t against time in minutes is how the Hixson-Crowell delivery mechanisms work. The line of regression value (R^2) and the release constant of rate (KHC) were then extracted from the graph.

Korsemeyer Peppas model

As a Korsemeyer-Peppas release mechanism, log accumulated% of drug release was timed using a log plot. Graph was then used to obtain the releasing constant for rate and the line of regression value (R^2).

Stability study

Accelerated stability tests of opaque formulations are conducted using new methods such as Turbiscan and LUMiSizer. Gravitational force is used by Turbiscan technology to speed up particle aggregation and separation. LUMiSizer technology harnesses centrifugal forces for a similar purpose. Near-infrared light transmission through the material is detected using these techniques. The intensity of transmitted light is measured using the instability index (provided by software) to identify sedimentation/creaming, or particle movement and aggregation.

Toxicity study

To evaluate the safety and potential harmful concentration of created NLC formulations, appropriate in vitro and in vivo toxicity studies are conducted. Cell viability assays such as MTT (tetrazolium dye), WST1 and WST8 (water soluble tetrazolium salts), and Lactate Dehydrogenase release (LDH) assay in appropriate cancer cell lines are used to perform in vitro cytotoxicity investigations. It is assessed for compatibility with red blood cells (IV formulations), genotoxicity, cellular inflammatory response, and membrane integrity, cellular uptake of the carrier, and the production and magnitude of reactive oxygen species (ROS). The formulation is given to a suitable animal using the proper method for in vivo studies. Histopathological examinations are used to assess the effects of therapy.

In-vivo study

To determine the drug's absorption, distribution, metabolism, and excretion (ADME) in formulations, in vivo pharmacokinetic studies are conducted to examine the drug's AUC, Cmax, and Tmax. Studies on in-vivo pharmacodynamics are conducted to examine a drug's effectiveness in an appropriate diseased animal model. The effectiveness of NLC drug formulations is assessed and contrasted with that of pure medicines or their conventional forms.

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CHAPTER NO 10- LIPOSOME FORMULATION

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Introduction-

Liposomes are well-recognized and essential nano-sized drug delivery systems. Liposomes have been considered promising and versatile drug vesicles. Compared with traditional drug delivery systems, liposomes exhibit better properties, including site-targeting, sustained or controlled release, protection of drugs from degradation and clearance, superior therapeutic effects, and lower toxic side effects. Liposomes are phospholipid vesicles comprised of cell membrane components and have mimic the structure and functions of cells.

History:

The Greek term "liposome" is made up of two words:"Lipos" means fat and "Soma" means the flesh. The field of liposomology was launched by the British scientist Alec Bangham and colleagues at Babraham Cambridge in the mid-1960s , and they first published the structure of liposomes in 1964. They observed these structures while experimenting with dry phospholipids under an electron microscope. This discovery provided the first tangible evidence supporting the bilayer lipid structure of cell membranes. Over the years, liposomes have evolved and are now extensively used in various fields, including pharmaceuticals and biotechnology.

Scientists and Their Work

Alec Douglas Bangham: Known as the "father of liposomes," Bangham's pioneering work laid the foundation for the development of liposome technology.

Yi Lu and Yongtai Zhang: Researchers who have contributed significantly to the advancement of liposomes as drug delivery systems.

Christian Isalomboto Nkanga and Alain Murhimalika Bapolisi: Scientists and Their Work brief information.

Liposomes are spherical, closed structures composed of phospholipids in the colloidal size range of 5–200 nm and contains one or more concentric/non-concentric membranes, of around 4 mm thickness. The liposomes consist of amphiphilic phospholipids with hydrophilic head and hydrophobic tail, which aids in unique

characteristics such as self-sealing of liposomes in aqueous media. Liposome component composed of two most important substances namely Phospholipid and Cholesterol. They consist of a lipid bilayer surrounding an aqueous core and can vary in size from nanometer to micrometers. Due to their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic substances, liposomes are widely used in drug delivery systems, vaccines, and other medical applications.

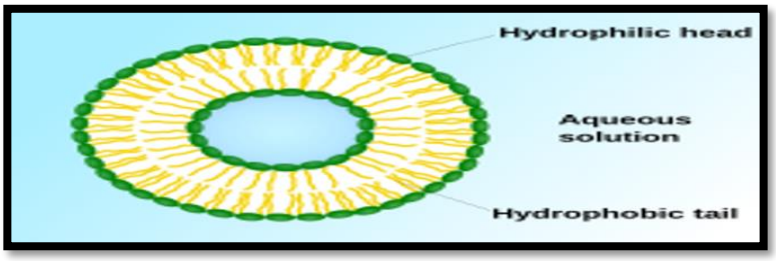

Fig no 01- liposomes structure

Phospholipids:

- Phospholipids are the building blocks of liposomes.
- The biocompatibility and amphiphilicity properties of phospholipids contribute to the formation of liposomes and thereby potentiate their desirability as drug carriers.
- Phospholipids are used in preparation of drug carriers specifically liposomes.
- Phospholipids are amphiphilic in nature, so that they can form bond with both water as well as lipids and helps to increases penetrability of drugs.
- they are classified into classes :
- Phosphatidylcholine (PC), Phosphatidyl ethanolamine (PE), Phosphatidylserine (PS), Phosphatidylinositol (PI) and Phosphatidylglycerol (PG).
- The most used glycerophospholipids in formation of liposomes are Phosphatidylcholine (PC)

Cholesterol: Another component in the formation of liposomes is cholesterol. During the preparation of liposomes, cholesterol molecules position themselves with their hydroxyl group oriented towards the aqueous core whereas the hydrophobic group is inserted in the hydrocarbon core region of the bilayer. Cholesterol increases the rigidity and fluidity of liposome. The cholesterol and phospholipid ration is 2:1 and 1:1 in the liposome preparation.

Advantages:

1. Liposome can carry both water and lipid soluble drugs.
2. Non-ionic in nature.

3. Liposome is biocompatible, completely biodegradable, non-toxic,and non-Immunogenic.
4. Suitable for delivery of hydrophobic, amphipathic and hydrophilic drug.
5. Protect encapsulated drug from the external environment.
6. Liposome reduces toxicity and increase stability via encapsulation.
7. They are increase activity of chemotherapeutic drug.
8. Biodegradable drug can be stabilized from oxidation.

Disadvantages:

1. Leakage and fusion of encapsulated.
2. Short half-life.
3. Stability problems.
4. Allergic reaction may occur to liposome constituents.
5. Problem to targeting to various tissues due to their large size.
6. Phospholipid undergoes oxidation, hydrolysis.

Structures and Main Components of Liposomes

Liposomes can be classified as unilamellar vesicles (ULVs), oligolamellar vesicles (OLVs), multilamellar vesicles (MLVs), and multivesicular liposomes (MVLs) depending on the compartment structure and lamellarity.

The glycerolphospholipid (GP), sphingomyelin (SM), and cholesterol (Chol) are the basic components used in the marketed products. GP contains glycerol, which links a pair of hydrophobic fatty acid chains and a hydrophilic polar head group.

Types of Liposomes :

A] Classification of liposome depending upon size and shape

1. Multilamellar vesicles (MLV)
2. Large unilamellar vesicles (LUV)
3. Small unilamellar vesicles(SUV)

B] Classification of liposome according to composition and application

1. Conventional liposome
2. PH- sensitive liposome
3. Cationic liposome
4. Long circulating liposome
5. Immuno- liposome

C] Classification of liposome according to method of preparation

Classification on based of Structure:

1.Multilamellar vesicles:

MLV have a size greater than 0.1µm and consists of two or more bilayer. Their method of formulation is simple and very easy to carry which includes thin– film hydration method or hydration of lipids in excess of organic solvent. They are mechanically stable on long storage. Due to the large size, they are cleared early or rapidly by the reticuloendothelial system (RES) cells and hence can be beneficial for various targeting the organs of RES. MLV have a moderate trapped volume, i.e., amount of aqueous volume to lipid ratio.

2. Large unilamellar vesicles:

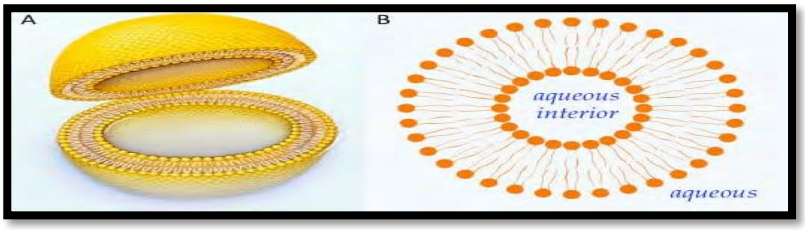

Fig no 02- Large unilamellar vesicles

The large unilamellar vesicles of liposome consist of a single bilayer or single lamella. LUV size is ' > 0.1 micrometer and can reach size up to 1000 nm). They have mainly high efficiency of encapsulation, since ability to hold large volume of solutions in their cavity. They are similar to multilamellar vesicle. Large unilamellar vesicles are prepared from various methods like ether injection, reverse phase evaporation technique and detergent dialysis.

3. Small unilamellar vesicles:

SUV are smaller in size (less than 0.1 µm) when compared to MLV and LUV, and have a single bilayer. They have a low entrapped aqueous volume to lipid ratio and characterized by having long circulation half-life.

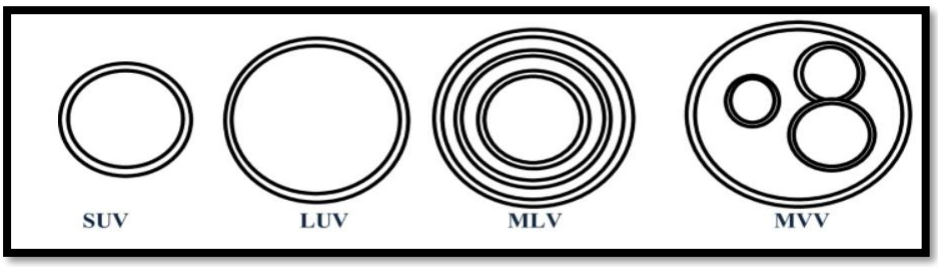

Fig no 03 - Small unilamellar vesicles

B] Classification of liposome according to composition:

1.Conventional Liposomes (CL):

Made up of neutral and negatively charged cholesterol and phospholipids Conventional liposome- based technology is first generation of liposome to be used in pharmaceutical applications. Several attempts to overcome their challenges have been made, specifically manipulation of the lipid membrane.

2.pH sensitive Liposomes: Phospholipids such as DOPE with either

3.Cationic liposomes: Cationic lipid with DOPE .

4.Long Circulatory (Stealth) Liposomes (LCL):

Liposomes that persist for prolong period of time in the blood stream. LCL contains PEG (polyethylene glycol) which is termed pegylation.Pegylation increases circulation of liposomes in the body by reducing its body clearance

5.Immuno liposome: Enhance target site binding. Immuno-liposome (ILs) is generated Immuno-liposome (ILs) is generated by coupling antibodies either directly to liposome lipid bilayer in the presence of PEG chains (type l liposome) or to the distal end of PEG chains (type ll liposome).Coupling antibodies to the lipid bilayer of PEGylated. Liposome can result in reduced antigen binding depending on amount of PEG and length of the PEG chains.

❖ **Method of drug loading during liposome preparation:**

Drug loading in liposomes can be mainly accomplished by passive loading and active loading methods. A diagrammatic representation of drug loading into liposomes explains the development and characterisation of solvent-assisted active loading technology for liposomal loading of poorly water-soluble compounds. High drug loading is desirable to minimize the amount of excipient, reach the desired concentration of therapeutic agents, decrease the dose volume, and reduce dosing time. Two primary techniques are routinely used for drug loading, i.e., passive and active drug loading procedures. Additionally, there are some other drug-entrapment methods, such as a drug–lipid chemical conjugate, the combination of passive and active drug encapsulation

a) Passive loading: includes all techniques in which during liposome preparation the lipid and drug are dispersed in an aqueous buffer, thus achieving entrapment while the liposomes are being formed.

The drug can be encapsulated within the inner aqueous space or embedded in the

bilayer of liposomes by means of covalent, ionic, electrostatic, non-covalent, or steric interactions between drug molecules and lipids.The main disadvantage of this approach is the low encapsulating efficiency, and thus leading to an additional step of free drug removal.

b) Active loading: on the other hand, refers to the entrapment of hydrophilic or hydrophobic drugs in the bilayer or aqueous core of liposomes respectively due to nature of the drug and lipids.

The active drug loading approach, also called remote drug loading, involves loading the drug agent after empty liposomes are produced. The transmembrane gradient of pH or ion concentration is the driving force to promote the drug diffuse across the membrane into the inner core of liposomes. The drug-entrapment process takes around 5 min to 30 min, and a high loading efficiency (above 90%) can be reached.

C] Classification of liposome depending upon production method:

- **The liposome preparation method depends on following parameter:**

1. Physiochemical characteristic of material to be enclosed in liposome,
2. Nature of medium in which lipid vesicles are dispersed,
3. Effective concentration of entrapped substance and its potential toxicity,
4. Optimum size, polydispersity and vesicles for intended application.

A] Passive loading Technique-

a) Mechanical dispersion methods-

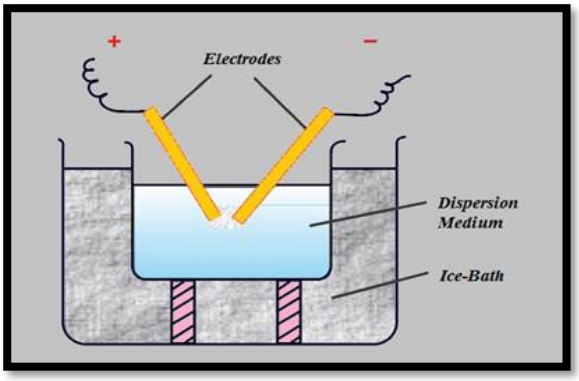

Fig no- 04 Mechanical dispersion method

1.Lipid hydration by hand shaking, non-hand shaking or freeze drying:

- Lipid are dissolved in organic solvents to assure the homogeneous mixing of lipid.
- Organic solvents used are chloroform or chloroform: methanol mixture.
- After lipid are mixed in organic solvent, solvent is removed to yield film.

- For removal of small volume of organic solvents, dry nitrogen is used, for large volume , rotary evaporator is used.
- Film is dried with the help of vacuum pump. Lipid solution frozen by placing the container on block of dry ice or container in dry acetone or alcohol.

2.Micro- emulsification:

- High pressure homogenizer is used for this method. This method is used to prepare SLVS. By using high shear stress lipid composition is micro emulsified.

3.Sonication:

- Sonication method is widely used for the preparation of SUVs. There are 2 sonication techniques used to sonicate MLVs, namely, bath type sonicator or a probe sonicator under substantial atmosphere.
- **Probe sonication:** The sonicator tip is directly dipped into the liposome dispersion. The energy input into lipid dispersion is very high, and the coupling energy at the tip leads to heating. Thus, the vessel should be placed into a water/ice bath throughout the sonication process up to 1 h. More than 5% of lipids can be de-esterified and titanium may pollute the solution.
- **Bath sonication:** Liposome dispersion is taken in a cylinder and is placed into a bath sonicator. In this the temperature should be controlled in contrast to probe sonication. The material being sonicated can be protected in a sterile vessel under inert atmosphere.

3.French pressure cell:

- This method is based on mechanism of high pressure. This method used to preparation of 1-40 ml of homogeneous unilamellar liposomes of intermediate size (30-80 nm).
- The method involves the extrusion of MLV at 20,000 psi at 4^0 C through small orifice.
- The method has several advantages over sonication method.It is simple, rapid, reproducible and involve gentle handeling materials.
- Drawback of this method is that temperature is difficult to achieve and using volume is small.

4.Membrane Extrusion Method

- This method is widely used for the conversion of MLVs into SUVs and LUVs. The liposomes size should be decreased by passing them through the polycarbonate

membrane filter having specific pore size at low pressure (< 100 psi). Before extrusion, LMV are disrupted by freeze–thaw cycles/pre-filtering through large pore size 0.2–1 µm.

b) Solvent dispersion method:

1.Ethanol injection:

- A lipid solution of ethanol is rapidly injected to a vast excess of buffer.
- The MLVs are immediately formed.
- The drawbacks of the method are that the population is heterogeneous (30-110 nm), liposomes are very dilute, it is difficult to remove all ethanol because it forms azeotrope with water and the possibility of various biologically active macromolecules to inactivation in the presence of even low amounts of ethanol.

Ether injection:

A solution of lipids dissolved in diethyl ether or ether/methanol mixture is slowly injected to an aqueous solution of the material to be encapsulated at 55-65°C or under reduced pressure. The subsequent removal of ether under vacuum leads to the formation of liposomes. The main drawbacks of the method are population is heterogeneous (70-190 nm) and the exposure of compounds to be encapsulated to organic solvents or high temperature.

Reverse phase Evaporation:

- First water in oil emulsion is formed by sonication of two phase system containing phospholipid in organic solvent and buffer solution.
- Organic solvents (diethylether or isopropylether or mixture of isopropyl ether and chloroform) are removed under reduced pressure, resulting in formation of viscous gel.
- The liposomes are formed when residual solvent is removed by continuous rotary evaporation under reduced pressure.
- With this method high encapsulation efficiency up to 65% can be obtained in medium of low ionic strength for example 0.01M NaCl.
- The method is used to encapsulate small and large macromolecules.

D. Detergent removal method:

- This method is used for preparing liposomes encapsulating hydrophobic

substances.

- The detergent at their critical micelles concentrations have been used to solubilize lipid.
- As the detergent can be removed by dialysis.
- The advantages of detergent dialysis method are excellent reproducibility and production of liposome populations which are homogeneous in size.
- The main drawback of this method is retention of trace of detergent in liposomes.

Steps:

a Dissolve lipids and the hydrophobic substance in a detergent solution.

b. Remove the detergent using techniques like dialysis or chromatography to obtain liposomes with the encapsulated substance.

1.Dialysis:

The detergent at their critical Michelle concentration (CMC) is used to solubilize lipids. The detergent is detached, the micelles in phospholipid and last combine to form LUVs. The detergent can be removed by dialysis.

2.Detergent removal of mixed micellar:

Mixed micelles are complexes formed by surfactants (detergents) and lipids (fats) during cleaning processes. Removing these micelles is crucial in various industries, such as:

1. Biotechnology (protein purification)
2. Pharmaceutical (drug development)
3. Food processing (cleaning and sanitation)
4. Textile manufacturing (detergent removal)

❖ **Methods for removing mixed micellar detergent**

- **Dialysis:** Using semi-permeable membranes to separate micelles from solutions.
- **Ultrafiltration:** Applying pressure to force micelles through membranes.
- **Gel filtration chromatography:** Separating micelles based on size and molecular weight.
- **Centrifugation:** Sedimenting micelles using high-speed centrifuges.

- **Precipitation:** Adding agents to precipitate micelles out of solution.
- **Adsorption:** Using materials like activated carbon or silica to capture micelles.

D]. Active loading technique:

Active loading is a technique that uses active components (e.g., amplifiers, transistors) to control and modify the behavior of a system, circuit, or signal.

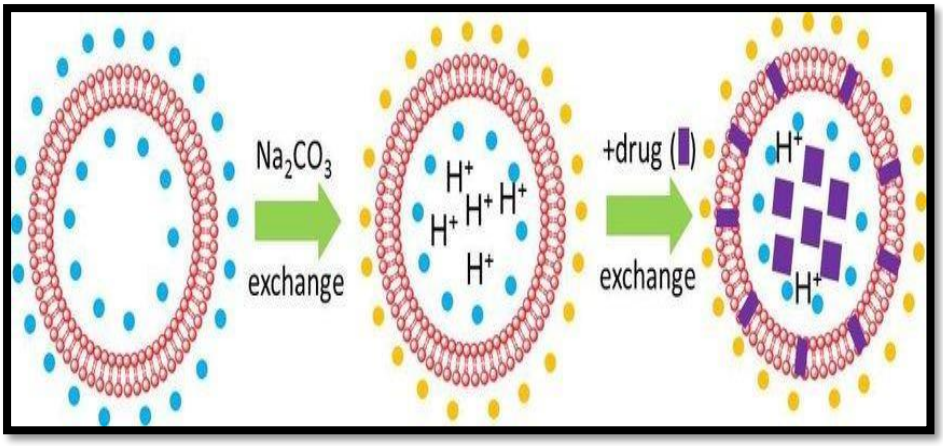

Fig no 05- Active loading technique

Marketed Formulation :

Each of these methods leverages the natural tendency of phospholipids to form bilayers in aqueous environments, resulting in the formation of liposomes with varying sizes and structures. Marketed Formulation of Liposomes in detail. There are several marketed liposomal formulations that have been approved for clinical use. Here are some notable examples:

1. Doxil® (doxorubicin liposome injection)

Indication: Used to treat various cancers, including ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma. Mechanism: Liposomal encapsulation of doxorubicin allows for targeted delivery to tumor tissues, reducing systemic toxicity.

2. Ambisome® (amphotericin B liposome for injection)

Indication: Used to treat fungal infections, including cryptococcal meningitis and visceral leishmaniasis. Mechanism: Liposomal encapsulation of amphotericin B reduces its nephrotoxicity while maintaining antifungal efficacy.

3. Marqibo® (vincristine sulfate liposome injection)

Indication: Used to treat acute lymphoblastic leukemia (ALL) in patients aged 2 years and older. Mechanism: Liposomal encapsulation of vincristine enhances drug delivery to leukemic cells while minimizing systemic side effects.

4. Onivyde® (liposomal irinotecan)

Indication: Used in combination with 5-fluorouracil and leucovorin for the treatment of metastatic pancreatic adenocarcinoma after gemcitabine-based therapy. Mechanism: Liposomal encapsulation of irinotecan improves drug stability and enhances tumor targeting.

5. Vyxeos® (liposomal daunorubicin and cytarabine)

Indication: Used to treat adults with newly diagnosed therapy-related acute myeloid leukemia (AML) or AML with myelodysplasia-related changes. Mechanism: Liposomal encapsulation of daunorubicin and cytarabine allows for co-delivery of both drugs, enhancing their synergistic effect.

Evaluation of liposomes:

1 physical characterisation Parameter : This parameter evaluates size, shape, surface Features, lamellarily, Phase behaviour f drug release profile.

2 chemical characterisation Parameter: This parameter evaluates the purity & potency of Various liposomal constituents.

3 Biological characterisation parameter : safety, & suitability of the formulations for in vivo use or therapeutic application.

Application:

1 They are used as drug / protein delivery vehicles.

2 They are used in antimicrobial, antifungal & antiviral therapy.

3 They are used in tumour therapy.

4 They are used in gene delivery.

5 They are used in immunology.

6 They are used as radiopharmaceutical &radio-diagnostic carrier.

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CHAPTER NO 11- MICROENCAPSULATION

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Introduction-

Microencapsulation is a process in which tiny droplets or particles of a core material (liquid, solid, or gas) are enclosed in a protective coating, forming microcapsules. This encapsulation technique allows the controlled release, protection, and delivery of active ingredients such as nutrients, pharmaceuticals, flavoring agents, or other sensitive substances. The capsules typically range from a few micrometers to several millimeters in size, which is why the process is referred to as "micro" encapsulation.

Microencapsulation can be achieved through various techniques, including coacervation, spray drying, solvent evaporation, extrusion, and more. Each method is chosen based on the nature of the core material, the desired release mechanism, and the specific application requirements.

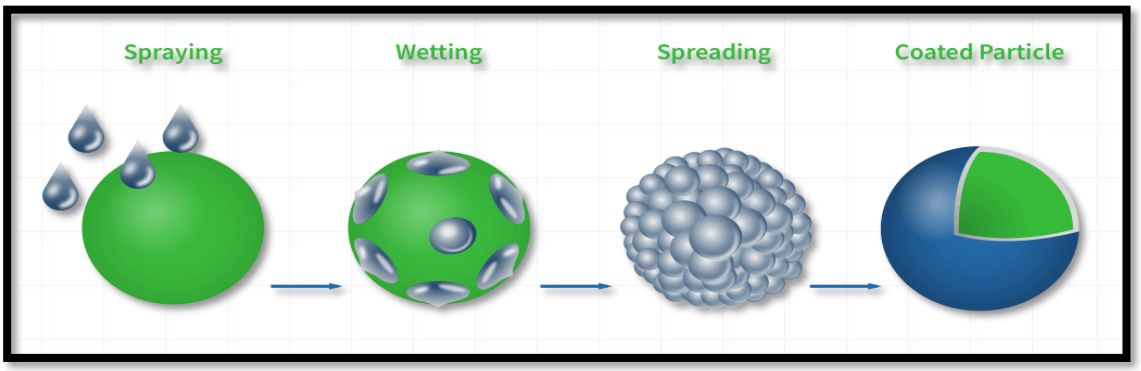

Fig no 01- Microencapsulation

Key Purposes of Microencapsulation-

Protection: The encapsulation process protects sensitive core materials from environmental factors such as air, moisture, temperature fluctuations, or light, which might degrade the active ingredient. This is particularly important for products like vitamins, probiotics, and pharmaceuticals.

Controlled Release: Microencapsulation allows for the controlled release of active ingredients over time. This can be used to create products that release their contents gradually, offering sustained benefits or therapeutic effects.

Improved Stability: Many core materials (such as volatile oils, nutrients, and drugs) are highly unstable when exposed to external conditions. Microencapsulation helps

stabilize these materials, extending their shelf life.

Taste Masking: In the food and pharmaceutical industries, microencapsulation is often used to mask unpleasant tastes or odors associated with certain ingredients, making them more palatable.

Targeted Delivery: Microencapsulation can be tailored to ensure that the encapsulated substance is released at a specific location or under certain conditions, such as a specific pH level in the digestive tract, ensuring more efficient delivery of drugs or nutrients.

Common Applications of Microencapsulation:

- **Pharmaceuticals**: Controlled release of drugs for sustained therapeutic effects, taste masking of bitter drugs, or targeted delivery to specific parts of the body.
- **Food Industry**: Encapsulation of flavors, fragrances, vitamins, and probiotics to protect them from degradation and to release them at the desired time.
- **Cosmetics**: Active ingredients like essential oils, antioxidants, and vitamins can be encapsulated to enhance their stability and release them gradually upon application.
- **Agriculture**: Pesticides, herbicides, and fertilizers are often microencapsulated to release their active ingredients slowly, increasing their effectiveness and reducing environmental impact.
- **Textiles**: Microencapsulation can be used to impart special properties to fabrics, such as releasing insect repellent or fragrances over time.

Microencapsulation Methods:

- **Coacervation**: A process in which two or more polymers phase-separate and form a capsule around the active ingredient. This method is often used for water-soluble materials.
- **Spray Drying**: A technique in which the core material is mixed with a coating substance, then sprayed into a hot gas stream, causing the liquid to evaporate and leaving behind dry microcapsules.
- **Solvent Evaporation**: In this method, a solvent is used to dissolve both the core material and the coating material. Upon evaporation of the solvent, microcapsules form around the core.

- **Extrusion**: A process in which a mixture of core material and coating is forced through a nozzle and hardened into microcapsules.

- **Polymerization**: This method involves polymerizing a material around the core substance to form a capsule.

Early Development and Evolution-

The roots of microencapsulation can be traced back to the 1950s and 1960s, when the technique was first developed and refined for specific applications such as the controlled release of pharmaceuticals and agricultural chemicals. Early research focused on the encapsulation of liquid or solid core materials using different coating materials to achieve desired release profiles or protection.

- **Pharmaceutical Origins**: The initial applications of microencapsulation were in the pharmaceutical industry, where the controlled release of drugs was of significant interest. Early work in this area was driven by the need to improve the bioavailability of poorly soluble drugs, extend the duration of therapeutic effects, or reduce side effects through sustained or targeted delivery. Techniques like spray drying and coacervation were explored during the 1960s and 1970s to encapsulate active pharmaceutical ingredients (APIs) and provide more effective drug delivery systems.

- **Agricultural Uses**: Microencapsulation was also explored in agriculture for the controlled release of pesticides, herbicides, and fertilizers. This approach allowed for a slow release of active ingredients, reducing the frequency of application and minimizing environmental pollution by preventing excessive runoff.

- **Food Industry**: By the 1970s and 1980s, food scientists began to explore microencapsulation as a way to improve the stability and controlled release of flavors, nutrients, and preservatives. The ability to protect sensitive ingredients (like vitamins and probiotics) from heat, oxidation, or moisture degradation, and to release them at specific times (e.g., during digestion), opened up new possibilities in food formulation.

- **Cosmetics and Fragrances**: Similarly, the cosmetics industry adopted microencapsulation to protect sensitive ingredients such as vitamins, antioxidants, and essential oils. Microencapsulation allowed for the gradual release of these ingredients, enhancing the performance and shelf life of cosmetic products.

Scientific Advancements and Techniques:

The progress in microencapsulation technology has been driven by the development of advanced materials and the refinement of techniques for creating capsules that meet specific needs. Several key methods have emerged over time, each offering advantages for different applications:

- **Coacervation (Phase Separation)**: Developed in the 1960s, coacervation involves the phase separation of a polymer in a solution, which forms a shell around the core substance. This method was particularly useful for encapsulating liquids and has been widely applied in pharmaceutical and food applications.

- **Spray Drying**: This technique uses hot air to rapidly dry a solution containing both the active ingredient and a coating material, forming microcapsules. Spray drying is particularly useful for food applications where heat-sensitive ingredients need to be encapsulated.

- **Solvent Evaporation and Emulsion Techniques**: These methods are used to create polymer-based microcapsules, where a solvent is evaporated from an emulsion containing both the core material and the polymer, leaving behind a solid shell around the core. These techniques have been widely adopted in drug delivery systems.

- **Extrusion**: In this process, a core material is extruded through a nozzle or die and hardened into spherical capsules. It is particularly useful for encapsulating solid or semi-solid substances.

- **Polymerization**: Polymer-based encapsulation involves creating capsules by polymerizing monomers around the core substance. This is typically done in the presence of an emulsifier and has been widely applied in pharmaceuticals and biotechnology.

Key Advancements in Microencapsulation Research:

- **Biodegradable and Biocompatible Materials**: Over the last few decades, there has been an increasing focus on the use of biodegradable and biocompatible materials for encapsulation, particularly for pharmaceutical and biomedical applications. Polymers such as poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), and chitosan have gained prominence for their controlled degradation and compatibility with biological systems.

- **Smart and Stimuli-Responsive Systems**: More recently, there has been a surge in research around "smart" microencapsulation systems, which release their contents in response to specific stimuli (e.g., pH, temperature, or enzymes). These systems are particularly useful for targeted drug delivery, where the capsule releases its contents only at the desired site in the body (such as the stomach or intestines).

- **Nanotechnology**: The advent of nanotechnology has significantly advanced the field of microencapsulation, enabling the encapsulation of nanomaterials, drugs, and bioactive compounds at a much smaller scale. Nanocapsules, with sizes ranging from 1 to 100 nanometers, have the potential for high precision in controlled drug delivery, targeted therapy, and diagnostic applications.

Modern Applications:

- **Pharmaceuticals**: Microencapsulation has become essential in drug delivery systems, including sustained-release formulations (e.g., for pain management or chronic diseases), targeted delivery (e.g., cancer therapy), and taste masking (e.g., for pediatric medications).

- **Food and Beverages**: In the food industry, microencapsulation is widely used for encapsulating vitamins, probiotics, omega-3 fatty acids, and flavor compounds. It helps in improving the stability, bioavailability, and controlled release of these ingredients during processing or digestion.

- **Agriculture**: Controlled-release fertilizers, pesticides, and herbicides have been developed using microencapsulation, allowing for more efficient application and reducing the impact on the environment.

- **Cosmetics**: Microencapsulation is used to deliver active ingredients in skincare products, such as antioxidants, moisturizers, and anti-aging compounds, which are released gradually over time when applied to the skin.

the main techniques for formulating microencapsulation:

1. Coacervation (Phase Separation)

Coacervation is one of the oldest and most widely used techniques for microencapsulation, particularly for liquid core materials. This method involves the separation of a polymer solution into two phases—one rich in polymer and the other containing the core material.

- **Process**:

  - A solution of the core material (e.g., oil, drug) is mixed with a polymer solution.

  - A coacervate phase forms when conditions such as temperature, pH, or ionic strength are altered, leading to phase separation.

  - The polymer phase forms a gel-like coating around the core material, which is then hardened.

- **Applications**:

  - Pharmaceutical controlled-release formulations.

  - Flavor and fragrance encapsulation in food and cosmetics.

  - Encapsulation of sensitive nutrients like vitamins and probiotics.

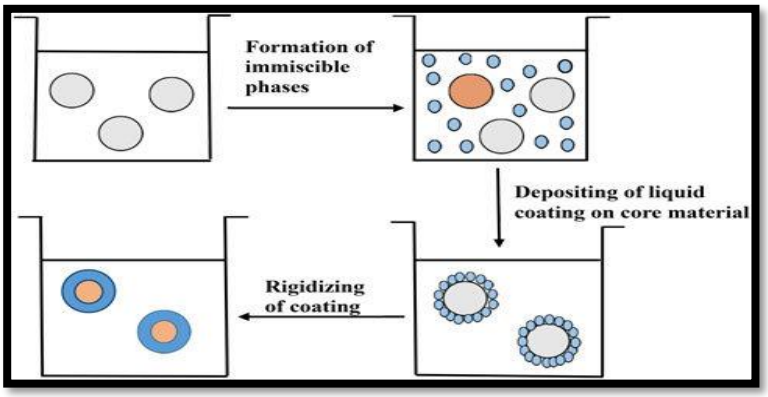

Fig no 02- Coacervation

2. Spray Drying

Spray drying is a fast and widely-used technique that is often applied in food and pharmaceutical industries for the production of powdered microcapsules. It is particularly suitable for heat-sensitive core materials.

- **Process**:

  - A liquid mixture containing the core material and a coating substance is sprayed into a hot gas stream.

  - The solvent (usually water) evaporates rapidly, leaving behind a dry powder composed of microcapsules.

  - The microcapsules are collected in a cyclone separator or bag filter.

- **Applications**:

  - Encapsulation of flavors, colors, and essential oils.

  - Encapsulation of probiotics, vitamins, and other sensitive nutrients in food products.

  - Pharmaceutical applications for sustained release of drugs.

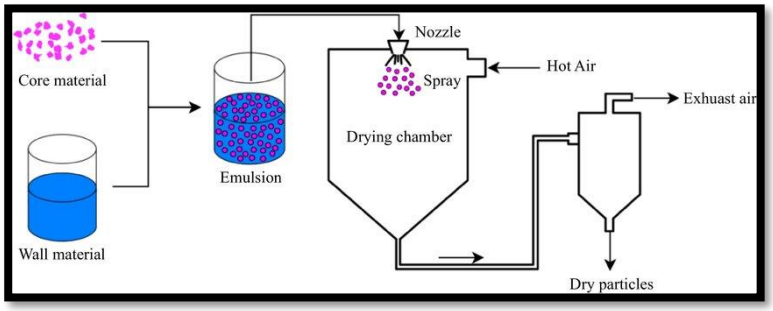

Fig no 03-Spray Drying

3. Solvent Evaporation (Emulsion Technique)

In **solvent evaporation**, an emulsion of the core material and coating polymer is created, followed by the gradual evaporation of the solvent to form microcapsules. This technique is commonly used for the encapsulation of hydrophobic drugs or other compounds.

- **Process**:

  - A solution of the core material and a polymer (e.g., PLGA, poly(lactic acid)) is dissolved in a volatile solvent.

  - This solution is emulsified in an aqueous phase (often with an emulsifier to stabilize the emulsion).

  - The solvent is then evaporated under reduced pressure, leading to the formation of solid microcapsules around the core.

- **Applications**:

  - Controlled drug delivery (e.g., sustained-release formulations).

  - Encapsulation of nutrients or bioactive compounds in the food and cosmetic industries.

  - Encapsulation of hydrophobic substances.

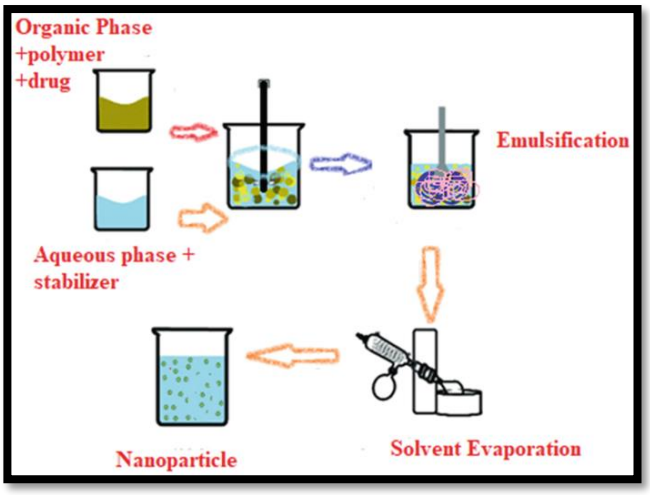

Fig no 04- Solvent Evaporation

- **Extrusion (Hot or Cold)**
- **Extrusion** is a mechanical process in which a mixture of core and shell materials is forced through a nozzle or die to form capsules. It is often used to create spherical capsules and can be used in both hot and cold extrusion techniques.

- **Hot Extrusion**:

  - The core material and coating material are heated until the coating material becomes pliable.

  - The mixture is extruded through a nozzle and cooled rapidly, forming solid microcapsules.

- **Cold Extrusion**:

- The core material and coating material are mixed in their solid form and then extruded at room temperature.

  - The capsules are usually hardened by cooling.

- **Applications**:

  - Pharmaceutical and dietary supplements (e.g., tablets and controlled-release formulations).

  - Encapsulation of solid and semi-solid materials.

  - Encapsulation of hydrophilic and hydrophobic substances.

5. Polymerization (Interfacial or In Situ Polymerization)

Polymerization involves the in-situ formation of a polymer coating around the core material through chemical reactions that occur in the presence of a catalyst or under specific conditions (such as UV light or heat).

- **Process**:
  - The core material is suspended in a solution of monomers.
  - Polymerization occurs at the interface between the core and the surrounding polymer, forming a solid shell around the core.
  - The polymer can be cross-linked to increase the mechanical strength and stability of the capsule.
- **Applications**:
  - Drug delivery systems, especially for targeted or sustained release.
  - Cosmetics and personal care products, where controlled release of active ingredients is required.
  - Encapsulation of bioactive agents for use in agriculture.

6. Fluidized Bed Coating

In **fluidized bed coating**, particles of the core material are suspended in a stream of air, and a coating material is sprayed onto them, forming a shell around the particles. This technique is widely used for coating solid particles.

- **Process**:
  - Core particles are fluidized by a stream of warm air.
  - The coating material (usually a polymer or lipid) is sprayed onto the particles, forming a thin, uniform coating.
  - The coating is hardened by either cooling or curing under heat.
- **Applications**:
  - Pharmaceutical applications (e.g., coating tablets for controlled release).
  - Food industry (e.g., coating of nutrients or flavors).

- Agriculture (e.g., coating of fertilizers or pesticides).

7. Supercritical Fluid Technology (SCF)

Supercritical fluid (SCF) technology uses supercritical carbon dioxide (CO_2) or other gases to dissolve the polymer and form microcapsules. This process avoids the use of organic solvents, making it more environmentally friendly.

- **Process**:
  - Core material and polymer are dissolved in supercritical CO_2.
  - The solution is expanded into a lower-pressure environment, causing the polymer to precipitate and form microcapsules.
  - The microcapsules are then collected and dried.
- **Applications**:
  - Encapsulation of heat-sensitive drugs and nutrients.
  - Cosmetics, where the encapsulation protects and releases active ingredients.
  - Food industry for encapsulation of flavors and bioactive compounds.

8. Nanoprecipitation

Nanoprecipitation is a technique primarily used for creating nano-capsules, in which the core material is dissolved in a solvent, and then the solvent is rapidly mixed with a non-solvent to precipitate the coating material around the core.

- **Process**:
  - A solution of the core substance and polymer is prepared.
  - The solution is then injected into a non-solvent (e.g., water) causing the polymer to precipitate and form nanoparticles with a coating around the core.
  - The microcapsules are then stabilized and collected.
- **Applications**:
  - Nano-drug delivery for cancer therapy or targeted release.
  - Encapsulation of bioactive agents for agricultural applications.

- Development of nanostructured food ingredients.

9. Liposome and Nanoemulsion Techniques

Liposomes and **nanoemulsions** are unique forms of microencapsulation that utilize lipid-based carriers to encapsulate the core material.

- **Liposome Formation**:
  - Liposomes are formed by emulsifying lipids in an aqueous solution. This creates a vesicle with a bilayer membrane that can encapsulate both hydrophilic and hydrophobic core materials.
- **Nanoemulsions**:
  - Nanoemulsions are created by mixing oil and water with surfactants under high pressure to form tiny droplets, which can encapsulate active ingredients in the internal phase.
- **Applications**:
  - Drug delivery, particularly for targeting specific tissues or cells.
  - Cosmetics, for the controlled release of active ingredients such as vitamins and antioxidants.
  - Food industry, for enhancing the bioavailability of nutrients or bioactive compounds.

Evaluation of Microencapsulation

Microencapsulation is an intricate process that requires careful evaluation to ensure the quality, stability, and functionality of the microcapsules. The evaluation of microencapsulation focuses on the assessment of physical, chemical, and release characteristics, among others, depending on the application of the encapsulated material (e.g., pharmaceuticals, food, or cosmetics). Below are key evaluation methods, along with the specifications that are typically examined during the formulation and testing of microencapsulated products.

1. Encapsulation Efficiency (EE)

- **Definition**: Encapsulation efficiency refers to the percentage of the active material (core) that has been successfully encapsulated within the microcapsules compared to the total amount of material initially used for encapsulation.

- **Calculation**:

- EE (%)=(Amount of Active Ingredient Encapsulated /Total Amount of Active Ingredient)×100

- **Specification**:

  - High encapsulation efficiency is desired to minimize wastage of the active material, especially for expensive or sensitive compounds (e.g., pharmaceuticals or nutraceuticals).

  - Typically, an encapsulation efficiency of **>80%** is considered optimal in most formulations.

- **Testing Method**:

  - After the microencapsulation process, the microcapsules are dissolved, and the unencapsulated core material is quantified using techniques such as **UV-Vis spectrophotometry**, **HPLC (High-Performance Liquid Chromatography)**, or **gas chromatography (GC)**.

2. Particle Size and Distribution

- **Definition**: The size and uniformity of the microcapsules are critical in determining their stability, release behavior, and suitability for specific applications. Smaller microcapsules (on the micrometer or nanometer scale) tend to have faster release rates, while larger capsules may offer slower release.

- **Specification**:

  - The particle size can range from **1 µm to 1 mm**, depending on the application. For pharmaceutical or cosmetic applications, **1–100 µm** is commonly desired.

  - **Uniformity of size** is crucial for consistent release profiles.

  - The **polydispersity index (PDI)** should ideally be **< 0.3** to ensure narrow size distribution.

- **Testing Method**:

  - **Laser diffraction** and **dynamic light scattering (DLS)** are commonly used for measuring the particle size distribution.

- **Scanning Electron Microscopy (SEM)** or **Optical Microscopy** can also be used to visually assess size and shape.

3. Morphology and Surface Characteristics

- **Definition**: The morphology of the microcapsules is important because it affects the release mechanism, stability, and the physical handling of the capsules.
- **Specification**:
  - **Shape**: Microcapsules are generally spherical, but they can also be oval or irregular. Spherical shapes are typically preferred for uniform release.
  - **Surface smoothness**: A smooth surface ensures better release characteristics and easier processing.
- **Testing Method**:
  - **Scanning Electron Microscopy (SEM)** or **Transmission Electron Microscopy (TEM)** are used to examine the surface morphology and shape.
  - **Atomic Force Microscopy (AFM)** can be used for detailed surface roughness evaluation.

4. Release Profile (In Vitro Release Testing)

- **Definition**: The release profile describes how the encapsulated material is released from the microcapsule over time, and it is a crucial parameter for assessing the controlled-release properties of the microcapsules.
- **Specification**:
  - For **controlled release**, a gradual release over a specified time period (e.g., 12 hours, 24 hours) is desired.
  - For **targeted release**, the microcapsules should release their content only under specific conditions (e.g., acidic pH for gastrointestinal delivery).
- **Testing Method**:
  - **In Vitro Release Studies**: Typically performed in a simulated environment (e.g., artificial gastric fluid, buffer solutions).

- The release of the active ingredient is monitored at different time intervals using **UV-Vis spectrophotometry**, **HPLC**, or **fluorimetry**.
- **Release Kinetics**: The release data are often fitted to mathematical models (e.g., zero-order, first-order, Higuchi, Korsmeyer-Peppas) to determine the mechanism and rate of release.

5. Stability Studies

- **Definition**: Stability studies are designed to evaluate how the microcapsules perform under different environmental conditions, such as temperature, humidity, and light, over a specified period.
- **Specification**:
  - Microcapsules should show no significant degradation or change in encapsulation efficiency, size, or morphology during storage.
  - For **pharmaceutical or food products**, stability under conditions of **room temperature** (25°C) and **elevated temperature** (e.g., 40–60°C) is tested.
  - **Shelf life** can range from a few months to several years, depending on the application.
- **Testing Method**:
  - Microcapsules are stored under different conditions (e.g., temperature, humidity, light exposure) and periodically assessed for encapsulation efficiency, release profiles, and physical characteristics.
  - **Accelerated stability testing** can be conducted by storing the capsules at higher temperatures and humidity levels to simulate long-term storage.

6. Loading Capacity and Core Material Distribution

- **Definition**: The loading capacity refers to the amount of active ingredient that can be encapsulated in the microcapsules. Uniform distribution of the core material within the microcapsule is crucial for consistent performance.
- **Specification**:
  - High loading capacity is desired for cost-effectiveness, but it should not compromise the stability or release rate.

- Uniform distribution of the active material ensures consistent release.

- **Testing Method**:

- **Gravimetric analysis** or **UV-Vis spectrophotometry** can be used to quantify the core material within the capsules.

- **Cross-sectional microscopy** (e.g., SEM or TEM) can be used to evaluate the distribution of the core material within the shell.

7. Thermal Behavior

- **Definition**: The thermal properties of microcapsules are important for assessing their stability under different temperature conditions and their ability to maintain their structural integrity during processing or storage.

- **Specification**:

- Microcapsules should not show any melting, degradation, or structural changes at typical storage temperatures.

- For controlled-release systems, it is important that the shell remains intact at the intended release temperature.

- **Testing Method**:

- **Differential Scanning Calorimetry (DSC)** is used to evaluate the thermal behavior of microcapsules, including the melting point and glass transition temperature.

- **Thermogravimetric Analysis (TGA)** can assess the thermal stability and decomposition of the microcapsules.

8. Toxicity and Biocompatibility (for Pharmaceutical and Medical Applications)

- **Definition**: For pharmaceutical or medical applications, the toxicity and biocompatibility of the microcapsules are crucial to ensure that the encapsulating materials do not cause adverse effects when administered to the body.

- **Specification**:

- Encapsulation materials should be **non-toxic**, **non-irritating**, and **biodegradable** or **bioabsorbable**.

- **Testing Method**:

- **In vitro cytotoxicity testing** using cell lines to evaluate the effects of the microcapsules on cell viability.
- **In vivo studies** (animal studies) to test the biocompatibility, toxicity, and pharmacokinetics of the microcapsules.

9. pH Sensitivity (for Targeted Delivery)

- **Definition**: For some microencapsulation applications (e.g., for oral drug delivery), the microcapsules are designed to release their contents in response to changes in pH (e.g., in the acidic environment of the stomach or in the neutral pH of the intestines).
- **Specification**:
- Microcapsules should be **pH-sensitive** to ensure that they release the encapsulated material only when they reach the desired pH environment.

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CHAPTER NO 12- MICROSPHERES AS A NOVEL DRUG DELIVERY SYSTEM

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Introduction

Microspheres are solid, approximately spherical nanoparticles ranging from 1 to 1000 µm in size. They can be microcrystalline or contain pharmaceuticals dispersed in a specific solution. The terms microspheres and microcapsules are often used interchangeably. Drugs with brief half-lives that are readily absorbed by the gastrointestinal tract (GIT) are swiftly eliminated from the bloodstream. This challenge has been addressed through the development of oral prolonged or controlled release (CR) formulations, which gradually release the drug into the GIT, maintaining steady plasma drug levels for extended periods. An ideal dose formulation achieves and sustains the required therapeutic drug concentration in plasma throughout the treatment duration. This can be accomplished by administering a conventional dosage form at predetermined intervals and doses.

Microspheres offer localized delivery and are not considered microcarriers, as particles below 100 nm can be transported by lymph into the interstitium. They have the potential to carry harmful substances. When encapsulated, dried microparticles may be classified as solids rather than liquids. The failure of a single subunit does not compromise the entire dosage, as the intake dose is distributed across numerous small, discrete multiarticulate particles, each containing and releasing a portion of the dose.

In dermal applications, these particles are utilized to enhance drug release into the skin. This approach ensures that the medication remains concentrated at the application site, minimizing unnecessary systemic exposure. They function as reservoirs, gradually releasing active ingredients, which reduces unwanted side effects and maintains appropriate therapeutic product concentrations in the skin. Consequently, there are fewer cycles of over- and under-medication. This is

particularly relevant in treating infectious diseases, as it helps reduce antibiotic resistance. Furthermore, these delivery systems can enhance product safety and vehicle integration.

Advantages of Microspheres

- Reducing the size of an insoluble substance can enhance its potency and increase its surface area.
- Consistent drug levels in the human body can improve adherence to patents.
- Reduced risk and dosage requirements.
- Drug delivery methods benefit from polymer-based packaging, which protects medicine from enzymatic breakdown.
- Shorter dosing intervals lead to improved patient compliance.
- Proper drug administration can enhance bioavailability and minimize adverse effects.
- Helps protect the gastrointestinal tract from irritating medications.
- Transform liquids into solids and mask unpleasant tastes.
- If modified, reliable techniques for precise drug delivery to target areas, maintaining desired concentrations without
- Reduce central sensitivity to external stimuli.

Disadvantages of Microspheres

- The altered release of the formulations.
- The release rate of the controlled dosage system, which fluctuates based on various factors such as food intake and intestinal transit levels.
- Variations in release rate between doses.
- Due to the typically higher dose content in controlled-release formulations, any issues with the drug substance's release characteristics could potentially pose a safety risk.

Materials used in the microsphere formulation

Polymers, which are categorized as follows, are primarily employed in the formulation of microspheres.

Synthetic Polymers-

Synthetic polymers are divided into two types:

a. Non-biodegradable polymers

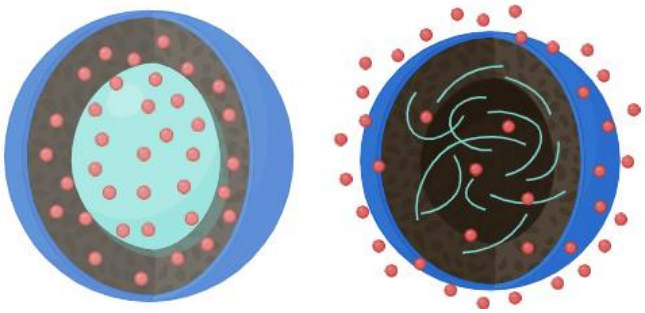
i. Examples include Epoxy polymers, Acrolein Glycidyl Methacrylate, and Polymethyl Methacrylate (PMMA).

ii. Lactides, glycolides and their co-polymers, poly alkyl cyano acrylates, and poly anhydrides are examples of biodegradable polymers.

Natural polymers-

A variety of sources, including carbs, proteins, and chemically modified carbohydrates, are used to obtain them. Additionally, they use proteins like collagen, albumin, and gelatin. Agarose, carrageenan, chitosan, starch, and chemically modified carbohydrates like poly dextran and poly starch are examples of carbohydrate.

Polymeric Microsphere



A. Loaded microsphere **B. Releases microsphere**

Fig no 01- Polymeric Microsphere

Categories of microspheres

Bio-adhesive microspheres-

Bio-adhesive drug delivery systems utilize the adhesive properties of certain polymers that become sticky when hydrated. This adhesion to membranes allows for targeted drug distribution to specific body areas over extended durations. As a result, the reduced dosing frequency enhances drug absorption and bioavailability, leading to improved patient adherence.

Magnetic microspheres

Magnetic microspheres are particles small enough to traverse capillaries without causing blockages (smaller than 4 μm). Their ferromagnetic nature makes them highly susceptible to being captured in micro-vessels and drawn through nearby tissues by a magnetic field of 0.5-0.8 Tesla's. These microspheres play a vital role in precisely localizing drugs at the site of illness.

i. Magnetic therapeutic microspheres
ii. Microspheres for diagnosis

Floating microspheres-

Gastroprotective drug delivery systems are built upon the foundation of non-effervescent floating microspheres. These structures, also known as hollow microspheres, micro balloons, or floating microparticles, are characterized by their lack of a core. These spherical entities are hollow and possess the ability to flow freely, with dimensions ranging from 1 to 1000 μm.

Radioactive microspheres-

The handling of radioactive microspheres generally mirrors that of their non-radioactive counterparts. However, radioactive microspheres incorporate one or occasionally multiple radionuclides in addition to the matrix material that defines the microsphere and grants it targeting capabilities within specific tissues or organs. Despite their presence in minute quantities, radioactive microspheres can deliver high doses of radiation to targeted areas without causing harm to the surrounding healthy tissues.

Polymeric microspheres

Polymeric microspheres can be categorized into two main types:

i. Biodegradable polymeric microspheres
ii. Synthetic polymeric microspheres

Techniques for microsphere production-

The selection of a production method depends on various factors, including the

polymer and drug characteristics, desired particle size, and technological considerations. The chosen process should not adversely affect the drug or protein, should yield reproducible release profiles, and should not compromise the stability of the final product. Various techniques utilize hydrophobic and hydrophilic materials as matrix components in microsphere creation.

Key considerations include-

- The capacity to incorporate relatively small drug doses and maintain stability post-synthesis, ensuring an acceptable therapeutic shelf life.
- Control over particle size and dispersibility for injection into aqueous vehicles.
- Efficient and precisely controlled reagent release over extended periods.
- Biocompatibility of chemical modification responses and controlled biodegradability.

Wax coating and hot melt

This method involves encapsulating core materials by dissolving or dispersing them in melted wax. The molten mixture is then introduced into cold water under vigorous agitation. The mixture is heated for at least an hour, followed by decanting the outer layer (liquid paraffin). The resulting microspheres are immersed in a non-miscible solvent and air-dried. Beeswax and carnauba wax serve as coating materials and can be blended to achieve desired outcomes.

Spray drying technique

This approach is employed to produce drug-loaded polymer nanoparticles. The process involves dispersing raw materials into a liquid coating solution and spraying it into the air for rapid solvent evaporation and surface solidification. Drug-containing microspheres are formed by formulating and spraying organic solvents, polymers in varying weight ratios, and drugs under specific laboratory conditions. While this method is quick and straightforward, the rapid drying process may result in a loss of crystallinity.

Coacervation

This method involves the separation of macromolecular fluid into two non-mixing

material types: a diluted equilibrium layer and a dense coacervate layer rich in macromolecules. Simple coacervation occurs when a single macromolecule is present, while complex coacervation involves two or more oppositely charged macromolecules. The former is triggered by specific factors, such as temperature shifts. Non-solvents or micro-ions facilitate particle dehydration by promoting polymer interactions through polymer solvent engagement. This process can be manipulated to yield various microsphere characteristics.

Solvent evaporation

The solvent evaporation technique is commonly employed to create PLA and PLGA microspheres containing diverse medications. Multiple factors significantly influence microsphere properties, including drug solubility, internal structure, solvent type, diffusion rate, temperature, polymer composition, viscosity, and drug loading. This method is particularly effective for drugs that are insoluble or partially soluble in the continuous phase liquid medium, as the system's ability to produce microspheres relies on successfully entrapping the active ingredient within the particles.

Freeze Drying-

Freeze-drying is an effective method for creating protein API microspheres. This process involves four stages: freezing, sublimation, primary drying, and secondary drying. During the freezing phase, the eutectic point of the components is considered. Throughout the process, cytoprotectants or cryoprotectants stabilize API molecules by removing water, creating a glass matrix, and decreasing intermolecular interactions through hydrogen bonds or dipole-dipole interactions. Although costly, this cycle is suitable for heat-resistant molecules. The solidification resulting from freeze-drying enables particle reconstitution in aqueous media.

Single Emulsion Solvent Evaporation Technique-

This method involves dissolving a polymer in an organic solvent and emulsifying it in an aqueous environment containing an emulsifying agent. The resulting emulsion is stirred for several hours to allow solvent evaporation, then washed, cleaned, and dried in desiccators. Drug microspheres are produced using polymers and an emulsion solvent through the diffusion-evaporation process.

Double Emulsification Method-

The double emulsification technique requires mixing either a w/o/w or o/w/o double emulsion. An aqueous solution of the product is dispersed within a continuous lipophilic organic phase. The primary emulsion is formed when the continuous phase, containing a polymer solution, encapsulates the drug in the dispersed aqueous layer. This pre-formed emulsion is homogenized or sonicated before being added to an alcohol aqueous solution. The resulting drug-filled microspheres exhibited controlled diffusion and erosion, prolonging drug release for 24 hours.

Ionic Gelation Method-

Ionotropic gelation utilizes polyelectrolytes' ability to cross-link in the presence of counter ions, forming hydrogel beads or gelispheres. These hydrophilic, spherical, cross-linked polymeric entities can significantly thicken and gel model biological fluids, and control drug release through polymer relaxation. To create hydrogel beads, a drug-containing polymeric solution is added to an aqueous solution with polyvalent cations. The cations diffuse through the drug-loaded hydrophilic molecules, forming a three-dimensional lattice with ionic crosslinking. Biomolecules can be incorporated into these gelispheres under mild conditions to maintain their three-dimensional structure.

Characterization of microsphere-

Particle size analysis-

The most commonly used method for visualizing microparticles, standard light microscopy (LM), was utilized to measure the dried microsphere using a calibrated optical micrometer.

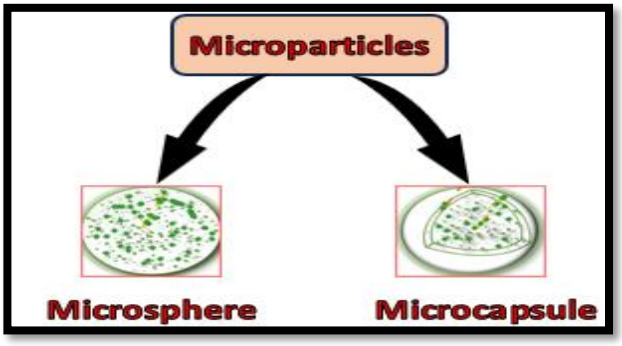


Fig no 02– Diagrammatic representation of microsphere & Microcapsule

Scanning electron microscopy (SEM) study

A scanning electron microscope (SEM) was employed to examine the samples, utilizing a backscattered electron sensor for image analysis and x-ray diffraction analysis (EDXA) to determine the elemental structure when specific elements were identified. This technique involved scanning the sample in parallel lines with a focused electron beam. For SEM characterization, the microspheres were placed on a sample holder and coated with a conductive metal, such as zirconium or platinum, using a sputter coater. Subsequently, a fine, directed electron beam scanned the material. The surface features were determined by analyzing the secondary electrons emitted from the sample's surface.

Flow properties-

The flow characteristics can be evaluated using the Carr's compressibility index, Hausner ratio, and angle of repose at rest. A volumetric cylinder was used to measure the bulk density and tapped density.

Thermal analysis-

Thermal analysis systems routinely examine these changes by applying specified specimen atmospheres and pressures, along with programmed temperature variations for heating and cooling. The most commonly observed properties include subtle changes in heat and enthalpy, weight gain or loss, Young's modulus, thermal expansion or contraction, and gas evolution.

Determination of percentage yield-

The measured quantity of the product, the polymers utilized in the microsphere formulation, and the total number of microspheres produced can all be used to calculate the % yield.

Drug content-

To give the particles time to settle and then wash, the mix should be set aside. After transferring 1 mL of the filtrate into a volumetric flask, the volume was adjusted using

0.1N NaOH. Following the proper diluting, the drug was measured using spectrophotometry.

Determination of drug loading-

The percentage of nanoparticle weight that is bonded to the encapsulated product is known as loading ability, and it is defined as the amount of medication loaded per unit nanoparticle weight. The total amount of drug trapped divided by the total weight of the nanoparticles yields the loading capacity (LC percent). The amount of drug supplied per quantity is represented by the yield, which is expressed as a percentage in the delivery of drugs.

Application of Microspheres-

There are several medicinal microencapsulated products available right now.

Microspheres in vaccine delivery-

A vaccine's safety against microorganisms and their hazardous components is a prerequisite. The same requirements for efficacy, protection, and cost-effectiveness should be met by the perfect vaccine. The issue of safeguarding against negative consequences is a complex one. The way of application is closely related to the safety factor and the degree of antibody response production. The drawbacks of the same traditional vaccines may be addressed using biodegradable delivery technology for intravenous vaccinations. Despite those that provide substantial advantages, there is still involvement in parenteral (subcutaneous, intramuscular, and intradermal) carriers.

Microspheres in Gene delivery-

Viral vectors, non-ionic liposomes as polycation complexes, and microcapsule technologies are all used in genotype medication delivery. Even though viral vectors are quite effective and have a wide range of cell objectives, they are useful for delivering genotypes. Nevertheless, they have harmful consequences and elicit immunological reactions if utilized in vivo. Nonviral delivery methods have been considered for gene therapy in order to overcome the limitations of viral vectors. The advantages of a nonviral delivery system include ease of preparation, the ability to target cells and tissues, a weakened immune system, limitless plasmid size, and large-

scale, reproducible production. For gene delivery applications, polymers will be employed as DNA transporters.

Oral drug delivery-

Rabbits have been used to test the potential of polymer matrix, which typically contains diazepam, as an oral drug delivery system. According to its results, a film with a drug-polymer ratio of 1:0.5 would have been an effective dosage form that was on par with conventional tablet formulations. The polymer's ability to form films may make it possible to manufacture film dosage forms as an alternative to medication tablets. Together with the primary amine groups' reactions, the pH sensitivity begins to distinguish the polymer for use in oral drug administration applications.

Transdermal drug delivery-

The polymer has favorable film-forming properties. Both the thickness of the membrane and the crosslinking of a film affect the release profile from the devices. Additionally, chitosan-alginate polyelectrolyte structures have been made in-situ in microspheres and beads for possible use in surgical instruments, controlled release systems, and packaging. For chemotherapy of inflammatory cytokines, polymer gel beads are an amazing, extremely biocompatible delivery system for drugs like prednisolone, which also exhibits extended-release action to improve treatment efficacy. It was discovered that the properties of the cell wall used also affected the amount of medication outflow. A fantastic all-inclusive method for regulated drug release and release kinetics is a combination of chitosan membrane and chitosan hydrogel that is known to contain lidocaine hydrochloride, a local anesthetic.

Targeting by Using Micro Particulate Carriers-

The idea that one should aim to attract as much attention as possible these days is a well-established orthodoxy. The drug's reaction is dependent on its availability and capacity to interact with the binding site; in general, pellets are confirmed to be made using extrusion/spherization innovation, such as chitosan and microcrystalline cellulose (MCC).

Monoclonal Antibodies-

Targeting microspheres or monoclonal antibodies are examples of biologically immunologic microspheres. The practice of selectively targeting specific organ system sites is one example of this kind of targeting. Monoclonal antibodies are extremely specific substances that attach to a specific area of the body through which absorption takes place.

a. Particular and non-particular adsorption
b. Direct coupling
c. Reagent-mediated coupling

Intratumoral and local drug delivery-

Polymer films were also produced to produce solid lipid nanoparticles at the tumor cells at a therapeutically appropriate intensity. The use of combination with medication in regulated administration across the oral cavity shows promise. For instance, PCL, chitosan, PLGA, and gelatin.

Other applications-

Membrane technology created for mass spectrometry, cell biology, and fluorescently linked immuno-sorbent assays uses microspheres. With encouraging results, yttrium may be utilized for the routine therapy of hepatocellular carcinoma as well as for the pre-transplant management of HCC. Microencapsulation has a wide range of uses in other industries. The most well-known microencapsulated products include carbonless copying paper, photosensitive paper, and microencapsulated scents like "scent-strips" (also called "snap-n-burst") and "scratch-n-sniff"). The gelatin-acacia coacervation complex is typically used to make these additional products. Children's books and the creation of advertisements for food and cosmetic fragrances have both made use of the scratch-n-sniff technique. Additionally, microcapsules are widely used in diagnostic testing; for instance, temperature-sensitive microcapsules are used in temperature-dependent visual cancer detection. In the

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CHAPTER NO 12 - MICROSPHERES

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Introduction

The use of natural excipients as carriers in drug delivery systems is recent trend of oral drug delivery. At present, socio-economic condition of the modern world has elevated the interest of natural polymers. Environmental concerns are also playing considerable role and contributing to the growing interest in natural polymers due to their biocompatibility, biodegradability and low processing cost.

Naturally obtaining polymers are diverse class of macromolecules with a wide range of pharmaceutical applications. Various natural polymers can be classified as proteins-based natural polymers like collagen, gelatin, silk fibroin, fibrin and natural polysaccharides like chitosan, starch, alginate, gellan gum, pectin, gum acacia, gum tragacanth, guar gum. These polysaccharides have some excellent water solubility as well as swelling potential, which eventually are useful for oral controlled drug delivery.

Natural gums

Natural gums are obtained from different parts of the plant. Chemically, these are polysaccharides containing monosaccharides blocks joined in linear as well as branched fashion. Thus, hydrolysis of gums results in formation of various sugar units. Gum acacia and tragacanth are most common gums used in pharmaceutical formulations since long period of time. These gums are produced by the plant as part of protection mechanisms on injury to the plant. The process of formation of gum is termed as gummosis, which indicates breakdown of cell walls.

Many scientific experts have investigated use of natural gums in various drug delivery systems. The gums are commonly used as suspending agent, thickening agent, emulsifying agent, binder, drug release retardant, mucoadhesive agent, gelling agent etc. The commonly used gums and their pharmaceutical applications are represented

in below mentioned table.

Table no 01- Common natural polysaccharides and their use in drug delivery

Name of gum	Botanical name	Constituent	Applications in drug delivery
Gum acacia	*Cyamopsis tetragonoloba (Fabaceae)*	Galactose, Mannose	Suspending agent, emulsifier, tablet binder, demulcent and emollient
Gum tragacanth	*Astragalus brachycalyx (Fabaceae)*	Arabino galactans, Pectinaceous	Suspending agent, emulsifier, demulcent and emollient
Almond Gum	*Prunus dulcis (Rosaceae)*	L-arabinose, L-galactose	Adhesive and suspending agent
Tamarind gum	Tamarindus indica *(Fabaceae)*	Glucosyl: Xylosyl: Galactosyl	Drug release retardant
Grewia gum	*Grewia mollis (Malvaceae)*	Galacturonic acid, Rhamnose	Drug release retardant
Khaya gum	*Khaya grandifoliola (*Meliaceae)	L-arabinose, L-galactose	Drug release retardant
Terminalia catappa gum	*Terminalia catappa (Combretaceae)*	Cyanidin 3-glucoside, Gallic acid	Drug release retardant
Okra gum	*Abelmoschus esculentus (Malvaceae)*	Rhamnose, Glucose	Suspending agent, drug release retardant
Albizia gum	*Albizia zygia (Fabaceae)*	Mannose, Arabinose	Emulsifier
Cashew gum	*Anacardium occidentale (Anacardiaceae)*	Galactose, Rhamnose	Suspending agent, drug release retardant
Bhara gum	*Terminalia bellirica (Combretaceae)*	Gallic acid, Ellagic acid	Drug release retar ant
Cordia gum	*Cordia myxa (Boraginaceae)*	Galactose, Mannose, Rhamnose	Drug release retardant
Honey Locust Gum	*Gleditsia triacanthos (Fabaceae)*	Carbohydrates, Fats, Fibers	Drug release retardant
Tara Gum	*Caesalpinia spinosa (Fabaceae)*	Galactomannans	Drug release retardant

Name of gum	Botanical name	Constituent	Applications in drug delivery
Neem Gum Azadirachta indica	*Azadirachta indica (Meliaceae)*	Galactose, Fucose	Binder
Moringa oleifera Gum	*Moringa oleifera (Moringaceae)*	Glucuronic acid, Galactose	Binder, gelling agent
Gum Damar	*Shorea javanica (Dipterocarpaceae)*	Resins	Drug release retardant
Hakea Gum	*Hakea gibbose (Proteaceae)*	Arabinose, Galactose	Binder, drug release retardant
Olibanum Gum	*Boswellia serrata (Burseraceae)*	Resins, Carbohydrates	Binder, drug release retardant
Alginate	*Laminaria species (Laminariaceae)*	Alginic acid	Stabilizer, suspending agent, emulsifier, gelling agent, tablet coating, tablet binder, matrix in controlled release, bioadhesive enhancer
Xanthan gum	*Xanthomonas campestris*	D-mannosyl, D-glucosyl, as well as D-glucosyluronic acid	Stabilizer, suspending agent, emulsifier, gelling agent, tablet binder, matrix in controlled release, bioadhesive enhancer
Guar gum	*Cyamopsis tetragonoloba (Leguminosae)*	Galactomannans	Suspending agent, emulsifier, gelling agent, thickener, tablet binder, matrix in controlled release, bioadhesive enhancer
Karaya gum	*Firmiana simplex (Malvaceae)*	α-d-galacturonic	Suspending agent, emulsifier, sustained release agent, bioadhesive enhancer
Gum ghatti	*Anogeissus latifolia (Combretaceae)*		Binder and emulsifier
Gellan gum	*Sphingomonas elodea*	Rhamnose, glucuronic acid and glucose	Stabilizer, suspending agent, emulsifier, matrix in controlled release
Locust bean gum	*Ceratonia siliqua (Fabaceae)*	Galacto-mannopyranosyl amine units	Mucoadhesive, colon targeting of drugs
Konjac	*Amorphophallus konjac (Araceae)*	Galactose, Mannose	Gelling agent, drug release retardant

Mucilage

The term mucilage indicates substances which have high water absorbing and swelling capability on contact with water. Several species of mucilaginous species of plants have been used in traditional system of medicine in the world since last 4000 year. Mucilage is metabolic product of the plant formed by various cells. It plays key role in food storage, germination of seeds as well as serve as important component of water storage in plants. Mucilage found in seed endosperms, roots and rhizomes may act primarily as energy reserves

Chemically these are high molecular weight (approx. 200,000 Da) compounds consisting of sugar and uronic acid units. These are generally sulphuric acid esters and have a complex structure of polysaccharide. The high-water absorbing capability of mucilage is due to presence of hydroxyl groups in sugar structure of mucilages. However, upon addition of alcohol, mucilages are precipitated in the form of amorphous or granular mass.

Table no 02- Botanical sources, constituents and pharmaceutical ap plications of common mucilages.

Common name	**Botanical name**	**Constituent**	**Applications in drug delivery**
Mimosa mucilage	*Mimosa pudica (Fabaceae)*	D-glucuronic acid, D-xylose	Drug release retardant
Hibiscus rosa-sinensis	*Hibiscus rosa-sinensis Malvaceae)*	D-glucuronic acid, Rhamnose	Binder and drug release retardant
Asario Mucilage	*Lepidium sativum (Brassicaceae)*	Galactose, Mannose	Emulsifier and suspending agent
Fenugreek Mucilage	*Trigonella foenum-graecum (Fabaceae)*	Galactose, Mannose	Drug release retardant
Aloe Mucilage	*Aloe vera (Xanthorrhoeaceae)*	Galactan, Arabinan, D-glucuronic acid	Drug release retardant
Phoenix Mucilage	*Phoenix dactylifera (Arecaceae)*	Cellulose, Mannose, Pectin	Binder
*Cassia tora*Mucilage	*Senna tora (Fabaceae)*	Tannins, Cinnamaldehyde	Binder and suspending agent
Cocculus Mucilage	*Cocculus hirsutus (Menispermaceae)*	Carbohydrates	Gelling agent

Cordia Mucilage	*Cordia dichotoma (Boraginaceae)*	Carbohydrates	Binder and emulsifier
Ocimum Mucilage	*Ocimum americanum (Lamiaceae)*	Galacturonic acids, Rhamnose	Disintegrating agent

Gum-alginate based microspheres for controlled drug delivery-

Microspheres are spherical, micron sized biocompatible carriers utilize for controlled delivery of encapsulated drugs. The drug loaded in matrix of microspheres is released in controlled manner. Microspheres can be prepared using polymers, proteins and lipids. Recently, natural gum and alginate combination has been explored for fabrication of biocompatible matrix of microspheres. Numerous scientific experts working in pharmaceutical field have investigated various natural gums for formulation of biocompatible microspheres.

Noureen et al. utilized *Prunus armeniaca* gum-alginate combination to enhance bioavailability of tramadol. The tramadol loaded microspheres containing *Prunus armeniaca* gum-alginate was fabricated using ionic gelation method. Infrared spectroscopy was used to confirm drug and excipient compatibility. The microspheres showed sustained delivery of drug following Korsmeyer-Peppas model. In addition to this, formulated microspheres were found to be non-toxic in mice model.

Das et al. used gellan gum and alginate combination for entrapment of metronidazole. The gellan gum-alginate microspheres were crosslinked in present investigation using maleic anhydride. The formulated microsphere released the loaded drug in controlled manner.

Mady et al. successfully utilized two gums i.e., Okra and gellan gums for formulation of metformin hydrochloride loaded microspheres. The drug loaded microspheres containing gums and alginate were fabricated using ionic gelation technique. Fabricated microspheres showed enhanced mucoadhesive potential tested using goat intestinal mucosa. The formulated microcarrier showed acceptable encapsulation efficiency of metformin and sustained drug release behavior for 10 hours. The mucoadhesive potential of natural gums was investigated in present investigation. Thus, natural gums could be viable alternative to synthetic mucoadhesive for

sustained gastrointestinal drug delivery.

Reddy et al. formulated Karaya gum-alginate microbeads for sustained release of D-penicillamine. The drug loaded microbeads showed better swelling index and sustained drug release up to 35 hours.

Abrar et al. formulated famotidine loaded *Acacia nilotica* gum microspheres for controlled gastrointestinal drug delivery. The formulated microspheres showed acceptable physicochemical properties and controlled famotidine delivery in simulated gastric fluid.

Ozoude et al. utilized Khaya gum extracted from *Khaya senegalensis* for sustained delivery of metformin. The Khaya gum-alginate microspheres formulated using ionic gelation technique. The formulated metformin loaded microspheres showed sustained drug release behavior following Korsmeyer-Peppas model.

Mohamed et al. successfully utilized gum Arabic-alginate microbeads for controlled delivery of protein. The ion induced gelation of calcium alginate was used as technique for encapsulation of bovine serum albumin in Arabic gum microbeads. The formulated microbeads showed acceptable encapsulation efficiency, particle diameter and surface characteristics. In addition to this, the swelling index of microbeads was also better. The protein release followed controlled release behavior.

Shwetha et al. utilized Okra gum and alginate combination for controlled delivery of metformin. The microspheres showed acceptable particle size, entrapment efficiency and better swelling index.

Kahima et al. successfully used acacia gum for controlled oral delivery of diclofenac sodium through acacia-alginate beads. Gum acacia-alginate beads were formulated using ionic gelation technique by addition of calcium chloride solution. The formulated beads showed pH dependent swelling ability. The swelling of beads was more at intestinal pH compared to stomach pH because of presence of carboxylic functional groups in gum. The formulated beads showed controlled release of diclofenac sodium by following Hixson-Crowell pattern.

Table 1.3: Overview of natural gum-based microspheres

Gum	Drug	Microcarrier	Outcome
Prunus armeniaca	Tramadol	Microspheres	Sustained drug release and non-toxicity in animal model
Acacia nilotica	Naringin	Microspheres	Sustained drug release
Gellan gum	Metronidazole	Microspheres	Controlled drug release
Okra and gellan gums	Metformin	Microspheres	Better mucoadhesive potential to goat intestinal mucosa
Karaya gum	Penicillamine	Microbeads	Better swelling index and sustained drug release
Acacia nilotica	Famotidine	Microspheres	Controlled drug release
Khaya gum	Metformin	Microspheres	Sustained drug release
Gum Arabic	Bovine serum albumin	Microbeads	Better swelling index
Okra gum	Metformin	Microspheres	Better swelling index
Acacia gum	Diclofenac sodium	Microbeads	Controlled drug release
Locust bean gum	Aceclofenac	Microspheres	Controlled drug release and better reduction of rat hind pow edema induced by carrageenan
Guar gum and xanthan gum	Glipizide	Microspheres	Good mucoadhesive potential
Guar gum	Metronidazole	Microspheres	Sustained drug release

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CHAPTER NO 14- SOLID LIPID NANOPARTICLES: AN OVERVIEW

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Introduction

Nanotechnology has revolutionized the field of drug delivery by enabling the design of nanoscale systems that can enhance the therapeutic efficacy of drugs while minimizing side effects. Nanotechnology involves manipulating materials at the atomic or molecular level to create particles with dimensions typically ranging from 1 to 100 nanometers. These nanoscale drug delivery systems, commonly known as nanocarriers, offer improved solubility, targeted delivery, and controlled drug release, making them highly effective for treating a wide range of diseases. Solid lipid nanoparticles (SLNs) are a novel class of drug delivery systems that have gained significant attention for their potential to enhance the therapeutic efficacy of drugs. SLNs consist of a solid lipid matrix stabilized by surfactants, and they hold promise in overcoming challenges associated with traditional drug delivery methods, such as poor bioavailability, instability, and non-specific targeting. Curcumin is a bioactive compound derived from the rhizome of *Curcuma longa*, commonly known as turmeric, a plant native to Southeast Asia. It is the primary polyphenol responsible for turmeric's distinctive yellow color and has been widely used in traditional medicine, particularly in Ayurvedic and Chinese practices. Curcumin has garnered considerable attention in modern medicine for its broad spectrum of pharmacological activities, including anti-inflammatory, antioxidant, antimicrobial, anticancer, and neuroprotective properties.

Pharmacological potentials of curcumin-

Anti-inflammatory Activity

Curcumin is well-known for its potent anti-inflammatory effects, which are mediated through several pathways:

- **Inhibition of Pro-inflammatory Cytokines**: Curcumin suppresses pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and cyclooxygenase-2 (COX-2), all of which play key roles in chronic inflammation(Mukerjee &Vishwanatha, 2009).

- **NF-κB Modulation**: Curcumin inhibits nuclear factor kappa B (NF-κB), a transcription factor that controls the expression of many inflammatory genes, thus reducing inflammation at the molecular level.
- **Inhibition of COX and LOX Pathways**: It inhibits both cyclooxygenase (COX) and lipoxygenase (LOX), which are enzymes involved in prostaglandin and leukotriene synthesis, contributing to its anti-inflammatory action.

Antioxidant Properties

Curcumin exhibits strong antioxidant capabilities, which protect cells from oxidative damage caused by free radicals(Santos et al., 2021).

- **Neutralization of Free Radicals**: Curcumin directly scavenges reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are responsible for oxidative stress and subsequent cellular damage.
- **Enhancement of Endogenous Antioxidants**: It enhances the activity of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, thus boosting the body's defense against oxidative stress.

Anti-cancer Potential

Curcumin has garnered attention for its anti-cancer properties due to its ability to modulate multiple molecular targets involved in cancer progression(Yike, 2018).

- **Induction of Apoptosis**: Curcumin promotes programmed cell death (apoptosis) in cancer cells by activating both intrinsic (mitochondrial) and extrinsic (death receptor-mediated) apoptotic pathways.
- **Inhibition of Tumor Proliferation**: It inhibits various cell proliferation signaling pathways, including PI3K/Akt, MAPK, and Wnt/β-catenin, which are often overactive in cancer cells.
- **Anti-angiogenic Activity**: Curcumin interferes with angiogenesis, the process of new blood vessel formation that tumors need for growth, by inhibiting vascular endothelial growth factor (VEGF) signaling.

- **Epigenetic Modulation**: Curcumin affects gene expression by influencing DNA methylation and histone modifications, which could be vital for cancer prevention and therapy.

Antimicrobial and Antiviral Activity

Curcumin demonstrates antimicrobial activity against a wide range of pathogens, including bacteria, viruses, and fungi(El-Refaie et al., 2015).

- **Antibacterial Action**: Curcumin inhibits the growth of several bacterial strains, including *Staphylococcus aureus*, *Escherichia coli*, *Helicobacter pylori*, and *Pseudomonas aeruginosa*. It disrupts bacterial cell membranes and inhibits bacterial virulence factors.
- **Antiviral Activity**: It exhibits antiviral properties by interfering with viral entry, replication, and assembly. Curcumin has been shown to be effective against viruses like hepatitis C, Zika virus, and herpes simplex virus (HSV).
- **Antifungal Properties**: Curcumin inhibits the growth of fungi like *Candida albicans*, potentially by disrupting fungal cell membrane integrity.

Neuroprotective Effects

Curcumin has shown promise in protecting against neurodegenerative diseases such as Alzheimer’s, Parkinson’s, and multiple sclerosis.

- **Reduction of Amyloid Plaques**: In Alzheimer's disease models, curcumin reduces the accumulation of beta-amyloid plaques, which are toxic to neurons. It also inhibits the formation of these plaques by modulating enzymes like beta-secretase.
- **Anti-inflammatory and Antioxidant Mechanisms**: Through its anti-inflammatory and antioxidant properties, curcumin protects neurons from oxidative stress and chronic inflammation, both of which are key contributors to neurodegeneration.
- **Inhibition of Neurotoxicity**: Curcumin inhibits the formation of toxic protein aggregates in neurons, particularly α-synuclein in Parkinson’s disease models, thus potentially preventing neuronal death.

Cardioprotective Effects

Curcumin has demonstrated several benefits for cardiovascular health.

- **Improvement in Endothelial Function**: Curcumin enhances endothelial function by increasing nitric oxide (NO) availability, which improves vascular relaxation and reduces blood pressure.
- **Reduction of Atherosclerosis**: It decreases the accumulation of oxidized low-density lipoproteins (LDL) in the arterial walls, thereby reducing the risk of plaque formation and atherosclerosis.
- **Anti-thrombotic Activity**: Curcumin has antiplatelet and anticoagulant properties, which can prevent the formation of blood clots, reducing the risk of stroke and myocardial infarction.
- **Reduction of Heart Failure Risk**: Its ability to reduce inflammation and oxidative stress helps in the prevention of cardiac hypertrophy and heart failure.

Antidiabetic and Hypoglycemic Effects

Curcumin shows potential in the management of diabetes and its complications.

- **Improvement of Insulin Sensitivity**: Curcumin increases insulin sensitivity by modulating pathways like AMPK (adenosine monophosphate-activated protein kinase), thus helping to regulate glucose uptake and reduce blood sugar levels.
- **Reduction of Glycation End-products**: It prevents the formation of advanced glycation end-products (AGEs), which are harmful compounds that form when proteins or fats combine with sugars in the bloodstream, contributing to diabetes complications.
- **Prevention of Diabetic Complications**: Curcumin helps in the management of diabetic nephropathy (kidney damage), retinopathy (eye damage), and neuropathy (nerve damage) due to its antioxidant and anti-inflammatory effects.

Anti-obesity and Metabolic Syndrome

Curcumin aids in weight management and the treatment of metabolic syndrome, a cluster of conditions that increase the risk of heart disease, stroke, and diabetes.

- **Regulation of Adipogenesis**: Curcumin inhibits the formation and accumulation of adipose tissue (fat) by regulating key pathways involved in fat metabolism, such as peroxisome proliferator-activated receptor-gamma (PPAR-γ).
- **Reduction of Inflammatory Markers**: In individuals with metabolic syndrome, curcumin lowers markers like C-reactive protein (CRP) and TNF-α, which are associated with chronic inflammation and insulin resistance.
- **Lipid Modulation**: Curcumin helps regulate cholesterol levels by increasing high-density lipoprotein (HDL) and decreasing LDL and triglycerides.

Gastroprotective Effects

Curcumin has been shown to protect the gastrointestinal tract and aid in the management of various digestive disorders.

- **Protection against Ulcers**: It has protective effects on the gastric mucosa, preventing the formation of gastric and duodenal ulcers. Curcumin inhibits the secretion of gastric acid and enhances mucosal defense.
- **Management of Inflammatory Bowel Disease (IBD)**: Curcumin is effective in reducing the symptoms of IBD, including Crohn's disease and ulcerative colitis, by modulating inflammatory pathways and oxidative stress in the gut.
- **Support for Gut Microbiota**: Curcumin positively influences gut microbiota by promoting the growth of beneficial bacteria and reducing pathogenic strains, contributing to overall digestive health.

Wound Healing and Dermatological Benefits

Curcumin is beneficial in wound healing and has various skin-related applications.

- **Accelerated Wound Healing**: It promotes wound healing by enhancing collagen production, improving the wound closure rate, and reducing oxidative damage at the wound site.
- **Treatment of Psoriasis and Eczema**: Curcumin’s anti-inflammatory and antioxidant properties make it effective in the treatment of skin conditions like psoriasis and eczema, where inflammation plays a major role.
- **Antimicrobial Effects on Skin Infections**: Due to its antimicrobial properties, curcumin can help treat bacterial and fungal skin infections.

Solid Lipid Nanoparticles (SLNs)

Solid Lipid Nanoparticles (SLNs) are an innovative frontier in drug delivery systems that combine the best of both worlds—offering the biocompatibility of lipids with the nanoscale benefits of particle technology(Ganesan & Narayanasamy, 2017). Picture SLNs as minuscule treasure chests, typically ranging between 50 to 1,000 nanometers in size, loaded with therapeutic agents that they protect and transport directly to the target site. These tiny particles are made from solid lipids like triglycerides or waxes, and their structure allows for excellent drug stability, controlled release, and improved bioavailability. Imagine a tiny, secure vault made of natural lipid materials that can slowly release the medication it holds, ensuring a steady therapeutic effect over time. They're perfect for delivering drugs that are otherwise unstable or poorly soluble, as the lipid matrix provides a safe harbor.

SLNs in delivery of curcumin

Curcumin, famed for its powerful anti-inflammatory and antioxidant properties, unlocking its full potential through modern nanotechnology. Curcumin, extracted from turmeric, has long been revered in traditional medicine but faces a major obstacle: poor bioavailability. Solid Lipid Nanoparticles act as a protective armor for curcumin, encapsulating it in a matrix of biocompatible lipids. These lipid warriors are solid at room and body temperature, ensuring that curcumin remains stable, hidden from environmental threats like light and oxygen. With a particle size in the nanometer range (50-1,000 nm), SLNs transport curcumin through the body's various defense mechanisms, enhancing its absorption and therapeutic efficiency(Mei et al., 2003).

Dolatabadi et. al. 2021 explored advanced lipid-based delivery systems designed to enhance the bioavailability and therapeutic efficacy of curcuminoids.The study presents a robust and systematic approach to formulating both SLNs and NLCs for curcuminoid encapsulation. One of the standout features of this research is the pharmacokinetic evaluation conducted in vivo. The study presents convincing data showing that curcuminoids-loaded SLNs and NLCs exhibit enhanced bioavailability compared to free curcuminoids. The extended circulation time, improved absorption, and higher plasma concentrations indicate that both delivery systems significantly increase curcuminoid exposure in the body, potentially enhancing therapeutic efficacy. This study successfully demonstrates the potential of SLNs and NLCs as effective delivery systems for curcuminoids, showing significant improvements in bioavailability

and pharmacokinetics.

Advancement in curcumin delivery through SLNs

In cancer therapy, curcumin-loaded SLNs can deliver the compound directly to tumor sites, exploiting curcumin's ability to induce apoptosis (programmed cell death) in cancer cells while minimizing damage to healthy tissues.

Li et al. 2024 (Li et al., 2024)formulated paclitaxel and curcumin encapsulated SLNs for treatment of lung cancer. This study explores the dual encapsulation of two potent anticancer agents—Paclitaxel and Curcumin within SLNs to achieve targeted therapy for lung cancer. This study provides a promising strategy for improving lung cancer treatment through the co-delivery of paclitaxel and curcumin using solid lipid nanoparticles. The dual-drug approach enhances targeting, reduces side effects, and shows superior anticancer efficacy in preclinical models.

Abudurexiti et al. 2024 (Abudurexiti et al., 2024)designed curcumin loaded SLNs. The work presents an innovative approach to treating cerebral injuries, specifically following intracerebral hemorrhage (ICH). This research focuses on the delivery of two potent therapeutic agents, Curcumin and TGF-β1 siRNA, through a novel transnasal brain-targeting system. By encapsulating these agents in solid lipid nanoparticles (SLNs), the authors aim to improve their bioavailability and therapeutic efficacy directly in the brain.

Aydin et al. 2024 formulated curcumin and termerone encapsulated SLNs. The research work provides a robust foundation for the use of curcumin and turmerone-loaded solid lipid nanoparticles in topical applications. With solid experimental design and promising results from the skin irritation evaluation, the study advances the field of natural compound-based dermatology and paves the way for further research in the use of SLNs for skin therapy.

designed SLNs of curcumin for management of lung cancer. This research addresses these challenges by encapsulating curcumin in solid lipid nanoparticles (SLNs) to create a sustained release system, enhancing its therapeutic efficacy. The methodology is robust, involving the fabrication of SLNs through a high-pressure homogenization technique, ensuring particle size uniformity and stability. The characterization of the nanoparticles, including particle size analysis, zeta potential measurement, and encapsulation efficiency, is thoroughly detailed. The researchers highlight how these parameters are critical for ensuring the SLNs can effectively

deliver curcumin to cancer cells while reducing systemic toxicity.

Gumireddy et al. 2019 designed Resveratrol and curcumin loaded SLNs. The primary aim of the study was to enhance the solubility, stability, and bioavailability of curcumin and resveratrol by encapsulating them into SLNs. The combination of these two potent bioactives in a single nanoparticulate delivery system is particularly novel and potentially synergistic, offering broad therapeutic applications in areas such as skin care, cancer therapy, and anti-aging treatments.

Ji et al. 2014 have successfully improved oral absorption of curcumin through lipid nanoparticles approach. In this formulation, Brij78, a surfactant, and TPGS (D-alpha-tocopheryl polyethylene glycol succinate), a derivative of vitamin E, step into the spotlight as key players. Together, they enhance the stability of curcumin-loaded SLNs, improve curcumin's water solubility, and facilitate better interaction with the intestinal membrane. TPGS, with its dual role as a bio-enhancer and antioxidant, adds an extra layer of protection for curcumin as it navigates the harsh environment of the digestive system.

Kakkar et al. 2011 fabricated curcumin loaded lipid nanoparticles. The study highlights how SLNs provide a novel approach to curcumin delivery. By encapsulating curcumin within lipid matrices, the study suggests an increase in solubility and protection against premature degradation in the gastrointestinal tract. The lipid nanoparticles act as carriers that shield curcumin and enhance its absorption through the intestinal lining, allowing for a more sustained release into the bloodstream.

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CHAPTER NO 15- SOLID LIPID NANOPARTICLES

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1. INTRODUCTION

Over the last two decades, technological advancements have allowed materials to be reduced to micro- to nano-sized particles. When particles are lowered to the nanometer scale, their surface area rises exponentially, radically altering their characteristics. Nanoparticles are particles with diameters ranging from 1 to 1000 nm. While the term "nano" only refers to scale, nanoparticles are used in a variety of industries. Nanomaterial, in particular, with high biodegradability and biocompatibility, are useful as carriers in drug delivery systems for biomedical purposes.

To improve pharmacokinetics (ADME), pharmacodynamics, decrease general toxicity, control antibodies, boost bio-recognition, and maximize therapeutic efficacy, scientists are now working to create new methods. Molecular biology, bio-conjugate chemistry, pharmaceutics, and polymer science are among the multiple disciplines used in these advancements, which are referred to as innovative drug delivery systems (NDDS).

Nanoparticles, erythrocytes, hydrogels, implants, liposomes, microspheres, and transdermal patches are examples of NDDS. Because nanoparticle-based drug delivery systems may address complex biopharmaceutical and pharmacological criteria, they have demonstrated promise in the treatment of chronic problems. The combination of nanotechnology with advances in functional proteomics, genomics, bioinformatics, and combinatorial chemistry has sparked widespread interest among scientists.

This collaboration has hastened the development of new medicine delivery methods. NDDS are crucial for delivering medications that present obstacles that regular drug delivery systems cannot simply overcome. The therapeutic effectiveness of these medications is highly influenced by their pharmacokinetics and mode of administration. Solubility, crystallinity, toxicity, and hydrophilic-lipophilic balance (HLB) value are all factors that influence pharmacokinetics. Understanding biopharmaceutics, pharmacokinetics, and route of administration, as well as absorptive surface area and drug transport pathways inside the body, are critical

components of optimal medication absorption and delivery.

Drug metabolism and elimination are highly impacted by qualities such as solubility, crystallinity, and hydrophilic-lipophilic balance (HLB), which are critical in developing effective formulations for active pharmaceutical ingredients (APIs). The HLB scale divides drugs into two categories: hydrophilic and lipophilic. Lipophilic compounds, in particular, provide a substantial difficulty due to their low solubility, hampering efforts to develop safe, effective, and inexpensive delivery systems.Despite these obstacles, pharmaceutical researchers have made substantial progress, with solid lipid nanoparticles emerging as a critical solution for hydrophobic medication formulations. They are extremely effective at medication delivery, reducing toxicity and achieving sustained release. Nanoparticles are regarded as a more adaptable drug delivery system than liposomes. Nanoparticle-based drug delivery systems are successful because they can cross anatomical barriers, preserve nanoscale stability, and enable controlled release.

However, obstacles still exist. The scarcity of safe, regulatory-approved polymers, as well as the expensive costs of producing nanoparticles, have hampered their use in clinical practice. Continued research in safe polymer formulation and cost-effective manufacturing will be required to broaden the clinical application of nanoparticle-based drug delivery systems.

Lipid-based carriers have become a viable answer to the drawbacks of polymeric nanoparticles, especially when it comes to the delivery of lipophilic medications. SLNs are very appealing for enhancing the efficacy of medications, neutraceuticals, and other physiologically active substances because of these characteristics.For intravenous applications, SLNs are particularly well-suited as innovative colloidal drug carriers. Physiological lipids are distributed throughout an aqueous or surfactant-containing solution to form them.

Reduced cytotoxicity and scalable production techniques are two important reasons why SLNs are better than polymeric nanoparticles. In reality, several polyester polymers have demonstrated substantial cytotoxicity when internalized by cells, despite the fact that they are frequently employed in implants. Furthermore, producing polymeric nanoparticles on a big scale is difficult and frequently expensive and complex. Since the 1990s, studies have concentrated more on SLNs as a scalable and safer substitute for drug delivery using nanoparticles. It has long been recognized that solid lipid formulations, such lipid pellets used in oral delivery (like Mucosolvan® retard

capsules),

Phospholipids are advantageous for lipid-based systems such as SLNs because they offer amphiphilicity, biocompatibility, and multifunctionality. SLNs avoid the problems of other lipid-based systems, like liposomes and lipospheres, which frequently have difficult manufacture and poor entrapment efficiency. The typical spherical shape of SLNs ranges from 50 to 1000 nm in diameter. Active pharmaceutical ingredients (APIs), emulsifiers, solid lipids, and a suitable solvent system are essential elements in SLN formulations.

Depending on their degradability and mode of administration (parenteral, oral, ocular, or topical), nanocarrier-based drug delivery systems can be categorised. High drug loading, low immunological response, controlled release, targeted tissue distribution, maximum bioavailability, the capacity to transport difficult medications (such as lipophilic or amphiphilic compounds), and patient compliance are all characteristics of the perfect nanoparticulate delivery system.

All of these features are offered by SLNs, which combine the benefits of liposomes, microemulsions, and polymeric nanoparticles. Furthermore, SLNs exhibit better stability, pharmacokinetic acceptability, and efficient therapeutic agent integration with surface modification, which makes them perfect for intravenous applications.

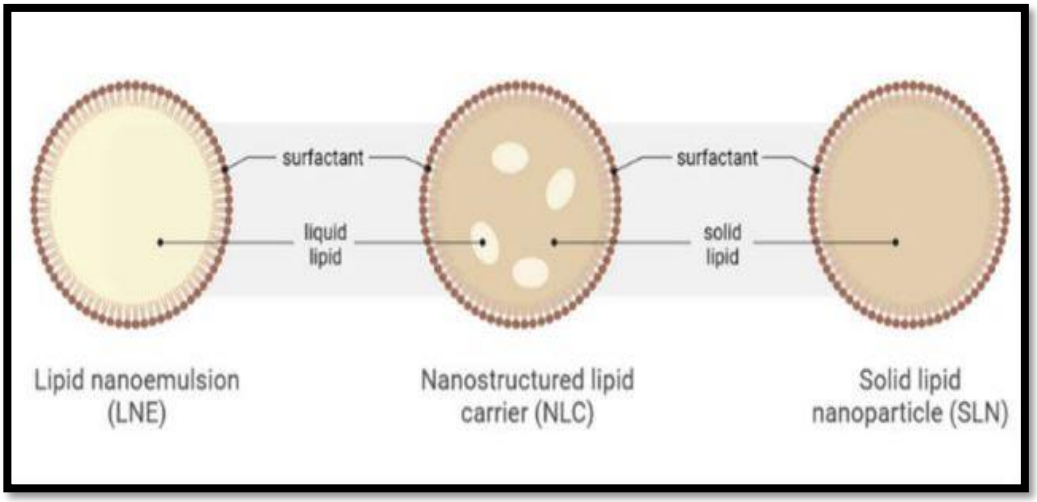

Fig no 01- Schematic representation of structure of solid lipid nanoparticles

Additionally, inclusion complexes with substances like cyclodextrin, which improve physicochemical, bioavailability, and solubility, can help SLNs. Drugs included in SLNs have a better release profile thanks to these complexes. Since lipid modification causes less gelling or degradation, SLNs are more stable than other nanoparticle

formulations and can be kept for years. Improved drug bioavailability, toxicity management, pharmacokinetic and pharmacodynamics modulation, and reduced immunogenicity are the main objectives of SLNs in drug delivery. In chemotherapy, where resistance, poor specificity, and instability are problems with standard drug administration, this is very helpful.

One way to lessen these problems is to encapsulate chemotherapeutic drugs in SLNs. The use of SLNs in chemotherapy, parasitic infection treatment, and tuberculosis treatment is growing thanks to new generations of SLNs, such as long-circulating SLNs. According to studies, SLNs can successfully target malignant cells, showing encouraging outcomes for diseases including colorectal cancer and melanoma. Additionally, SLNs have demonstrated efficacy in transferring genetic material. DNA can be securely delivered to target areas using cationically modified SLNs, which also have low cytotoxicity and excellent transfection efficiency.

Advantages of SLNs

- SLNs are inherently capable of dispersing contract measures to distribute site-specific medications.
- The processes that are employed to make traditional emulsions are important.
- You can use stop-drying to create powdered details.
- Establishing a regulated and gradual release of dynamic medicine is feasible.
- High levels of functional compounds were attained.
- Possible is lyophilisation.
- More control over the release kinetics of the encapsulated chemical.
- The same raw components required for an emulsion are required here.

Disadvantages of SLNs

- Not enough capacity to load medications.
- There is a significant amount of water in the dispersions (70–99.9%).
- During storage, the likelihood of medication ejection during polymerisation.
- Polymeric transformation may result in the possibility of drug ejection during SLN storage.

2. Background of the study

One innovative drug delivery method that shows great potential for treating a variety of illnesses is solid lipid nanoparticles (SLNs). SLNs are made up of solid lipids, such

stearic acid, triglycerides, and fatty acids, that are stabilised by surfactants and in which the medication is either dissolved or distributed. These nanoparticles have minimal toxicity, good biocompatibility, and physiological tolerance.

They are stable colloidal carriers that stay solid at body temperature as well as room temperature. SLNs can transport a wide range of physicochemical properties, such as proteins, peptides, thermolabile compounds, and drug with poor pharmacokinetic profiles. In addition to decreasing enzymatic degradation, they improve medication solubility, stability, and cellular absorption. SLNs are a promising platform for enhancing the effectiveness and distribution of different medicines because of these characteristics.

3. Importance of study

The novel medication delivery system known as solid lipid nanoparticles (SLNs) has enormous promise for improving the treatment of disease. Stabilised by surfactants and composed of solid lipids including stearic acid, triglycerides, and fatty acids, SLNs can contain medications in either dissolved or dispersed forms. These nanoparticles are renowned for their exceptional physiological compatibility, minimal toxicity, and poor biocompatibility. They are also very stable colloidal carriers, staying solid at body and room temperatures.

Drugs having a variety of physicochemical characteristics, including as proteins, peptides, thermolabile chemicals, and those with restricted pharmacokinetic profiles, can be transported via SLNs because of their great adaptability. Enzymatic degradation is decreased, stability is increased, cellular absorption is facilitated, and drug solubility is improved. With these qualities, SLNs are a promising and efficient way to improve the therapeutic efficacy and delivery of different medications.

4. Formulation Techniques

4.1 High shear homogenization

The high-shear homogenization method was first used to create solid lipid nanodispersions and is still often employed because of its ease of usage and accessibility. But occasionally, this technique introduces microparticles, which degrades the quality of the dispersion. In order to produce SLNs, melt emulsification is used for high-speed homogenization; zeta potential and particle size are greatly influenced by emulsification time, stirring rate, and chilling conditions. Here, lipids such trimyristin, tripalmitin, and a combination of mono-, di-, and triglycerides (Witepsol W35, Witepsol H35) were combined with glycerol behenate and poloxamer 188 as

steric stabilizers at a concentration of 0.5% w/w respectively.

4.2 Hot homogenization

Hot uniformity, like emulsion uniformity is done at temperatures over the melting point of lipids. First, the drug-loaded lipid melt and the aqueous emulsifier phase are combined to formulate a pre-emulsion at the same high temperature using a high-shear mixing equipment, such as a Silverson-type homogenizer. The final product is dependent on the quality of this pre-emulsion; the best results are obtained with droplet sizes as small as a few micrometers.

After the pre-emulsion forms, high-pressure uniformity is applied at temperatures over the lipid melting point. Higher processing temperatures often lead to smaller particle sizes because they reduce the viscosity of the lipid phase; however, they potentially increase the risk of drug and lipid carrier degradation.

For better results, the process usually involves multiple cycles through the high-pressure homogenizer (HPH), with three to five passes being the norm. At 500 bar, each pass elevates the sample temperature by around 10°C. Most methods use three to five homogenization cycles at pressures between 500 and 1500 bar. The high kinetic energy of the particles can lead to particle coalescence and larger particles, even though additional homogenization cycles can produce smaller particles.

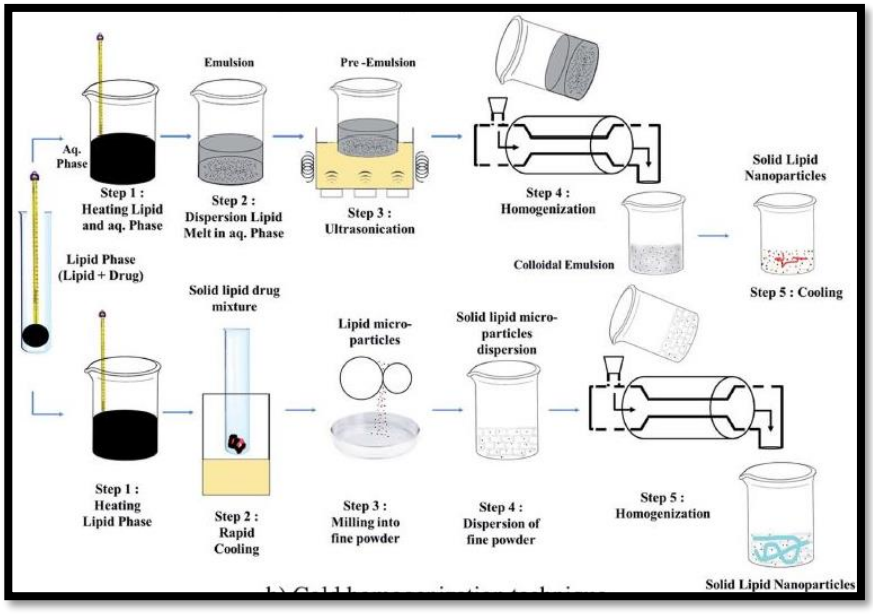

Fig no 02- Hot and cold homogenization technique

4.3 Cold homogenization

In the cold homogenization procedure, which is done with solid fat and is comparable

to milling a suspension under high pressure, the solid condition of the lipid must be maintained by strict regulation of the temperature.

In order to overcome the main drawbacks of hot homogenization, cold homogenization was created. These include:

1. Temperature-induced degradation of the drug,
2. Loss of drug through partitioning into the aqueous phase, and
3. Uncontrolled polymorphic changes in the lipid due to complex crystallization, which can lead to structural modifications or supercoiled melts.

Similar to hot homogenization, the first stage in cold homogenization is the drug's solubilization or dispersion in the melted lipid. The procedures then diverge, though. Liquid nitrogen or dry ice are frequently used to quickly chill the drug-loaded lipid melt, guaranteeing uniform drug dispersion throughout the lipid matrix. Using ball or mortar milling, the drug-containing solidified lipid is next ground into microparticles, usually with a size range of 50 to 100 microns.

Cooling increases lipid brittleness, which facilitates particle milling even more. After being distributed in a chilled emulsifier solution, the microparticles are homogenized under high pressure at room temperature or below, with careful temperature control to offset heat produced during processing. Larger particles with a wider size distribution are often produced by cold homogenization as opposed to hot homogenization.

SLN prepared by solvent emulsification/ evaporation

To produce colloidal dispersions via precipitation in an oil-in-water (o/w) emulsion, the lipophilic material is dissolved in a water-immiscible organic solvent, such as cyclohexane, and then emulsified into an aqueous phase. A dispersion of nanoparticles is created when the lipid precipitates in the aqueous media when the solvent evaporates. Lecithin and sodium glycocholate were used as emulsifiers, and cholesterol acetate was used as a model medication to produce particles with an average diameter of 25 nm. This result was replicated by Siekmann and Westesen, who obtained lipid acetate microspheres with an average size of 29 nm.

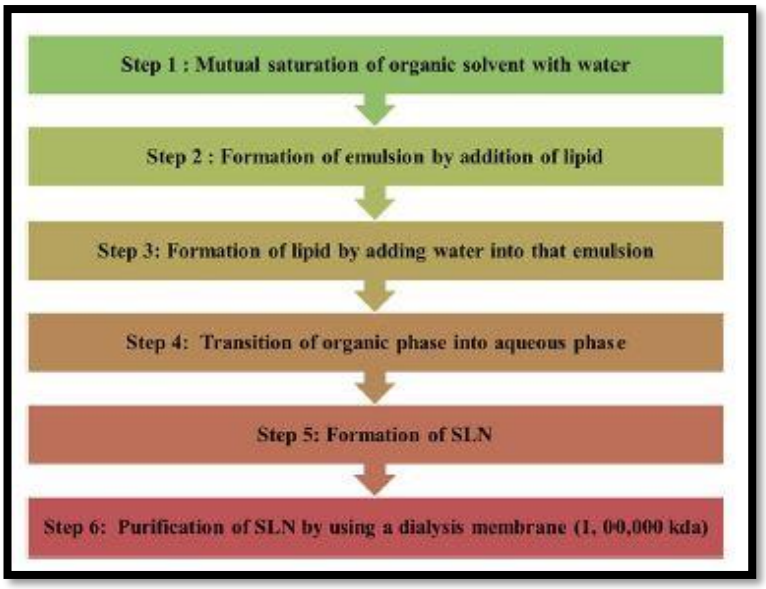

Fig no 03- Preparation method of solvent emulsification method

4.5 Micro emulsion based SLN preparations

Swirling a clear, optically transparent fluid at 65–70°C can also create solid lipid nanoparticles (SLNs). An emulsifier (such as polysorbate 20, polysorbate 60, soy phosphatidylcholine, or sodium taurodeoxycholate), co-emulsifiers (such as sodium monooctylphosphate), water, and a low-melting fatty acid (such as stearic acid) are usually included in this mixture. Next, while stirring constantly, the heated microemulsion is dissolved in cold water (between 2 and 30°C).

Typically, the hot microemulsion to cold water volume ratios fall between 1:25 and 1:50.The composition of the microemulsions significantly impacts this diluting process. The droplet structure of the microemulsion allows for the formation of submicron particles without the requirement for additional energy. French scientists like Fessi used similar techniques to generate polymer nanoparticles by diluting polymer solutions in water.

The pace of distribution has a significant impact on the particle size. More lipophilic solvents produce larger particles of the polymer, whereas solvents that disperse rapidly into the aqueous phase (like acetone) produce smaller particles. Similarly, the hydrophilic co-solvents in microemulsions probably help generate lipid nanoparticles, which is similar to how acetone helps form polymer nanoparticles.

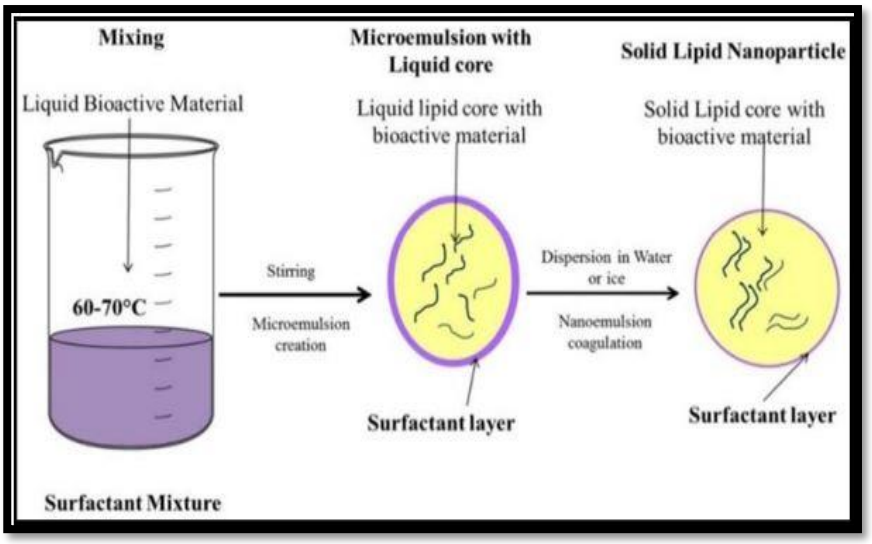

Fig no 4- Preparation of SLN by microemulsion technique

SLN preparation by using supercritical fluid

The main advantage of using this relatively new technique to produce solid lipid nanoparticles (SLNs) is that no solvents are used during processing. Several variations of this platform technology are available for producing both powders and nanoparticles. Supercritical carbon dioxide solution (RESS) rapid expansion is one technique for creating SLNs. For this method, 99.99% pure supercritical carbon dioxide is a great solvent option.

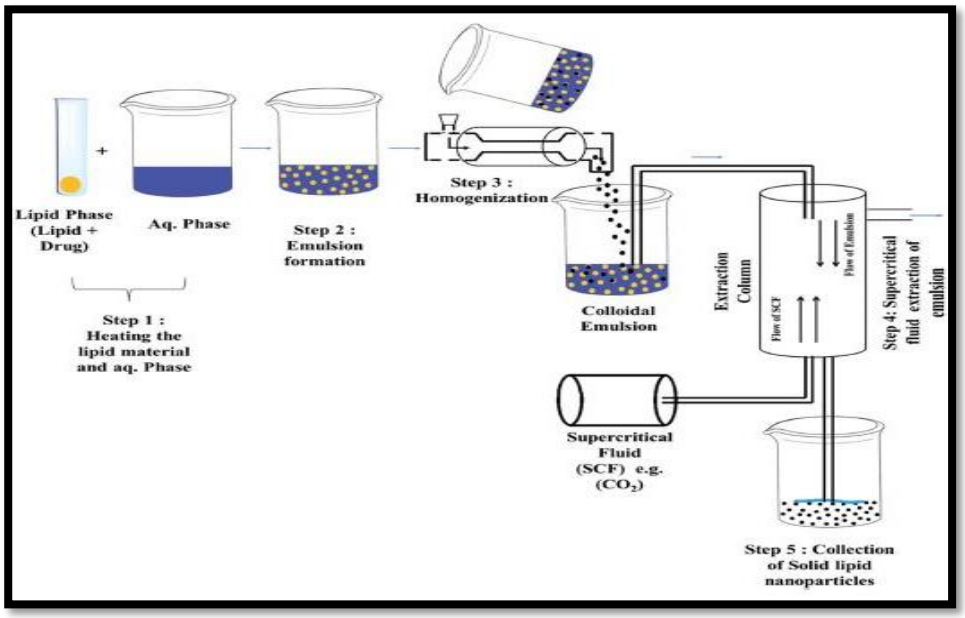

Fig no 05- Critical fluid technique for the preparation of solid lipid nanoparticles.

4.7 Spray drying method

This method can be utilized to create a pharmaceutical product from an aqueous solid lipid nanoparticle (SLN) dispersion and is more cost-effective than lyophilization. However, the process's high temperatures, shear pressures, and partial melting of the particles could lead to particle aggregation. Lipids that melt at a temperature higher than 70°C are recommended for spray drying. The best results were achieved when SLN was present at a concentration of 1% in a trehalose solution in water or 20% in ethanol-water combinations (10:90 v/v).

Double emulsion method

The cutting-edge method of solvent emulsification evaporation is used to create solid lipid nanoparticles (SLNs) loaded with hydrophilic drugs. The medication is encapsulated with a stabilizer in a water-in-oil-in-water (w/o/w) double emulsion to prevent the drug from partitioning into the external aqueous phase during the solvent evaporation process. A more cutting-edge method for creating SLNs is electrospray. This technique produces spherically distributed, narrowly dispersed SLNs that are less than 1 mm by using electrodynamics atomization. The direct manufacturing of SLNs in powder form is made possible by this approach, which is noteworthy.

Ultra sonication or high speed homogenization

Additionally, solid lipid nanoparticles (SLNs) can be produced by high-speed stirring or sonication, both of which need common laboratory apparatus. The drawbacks of this method include the possibility of a broader particle size distribution that can extend to the micrometer range, which over time may result in particle growth and physical instability. Furthermore, there is a chance that the ultrasonication process will contaminate the metal. High-speed stirring and ultrasonication have been investigated by several research groups as a way to overcome these problems and produce a stable formulation, especially when done at high temperatures.

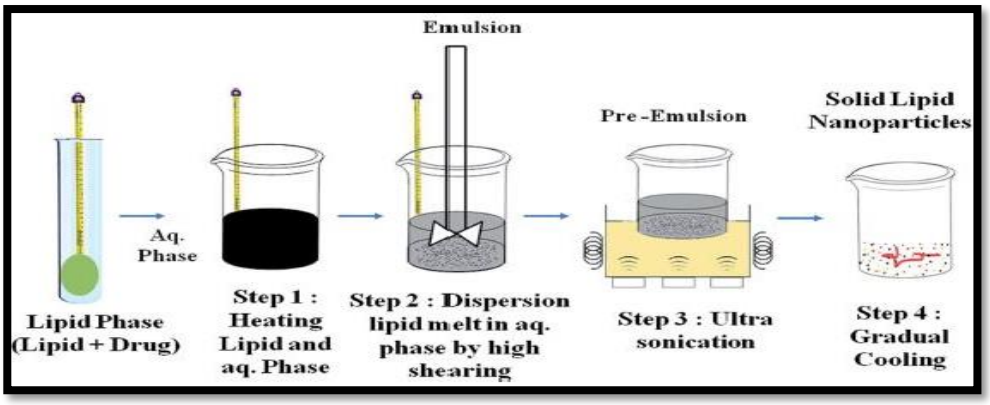

Fig no 06- Preparation of SLN by ultrasonication method

Preparation of semisolid solid lipid nanoparticles

Another method for creating solid lipid nanoparticles (SLNs) is sonication or high-speed stirring, which use tools that are easily found in most labs. This strategy does have some disadvantages, though, such as a larger particle size distribution that may extend into the micrometer range, which could lead to physical instability and possible particle growth over storage. Additionally, there is a chance that metals could contaminate the ultrasonication process. In order to overcome these obstacles and improve formulation stability, a number of research teams have looked into combining high-speed stirring with ultrasonication, particularly at high temperatures.

Electrospray technique

Using electrodynamics atomization, a new and creative method for creating solid lipid nanoparticles (SLNs), narrowly dispersed spherical SLNs smaller than 1 mm are produced. SLNs can be directly produced in powder form using this approach.

Oil/water (o/w) microemulsion breaking technique

First, the drug, the surfactant, and co-surfactant are combined with the lipid melt and heated to a temperature equal to the lipid's melting point to form a microemulsion. The final step involves dispersing the resulting microemulsion in water that ranges in temperature from 2 to 100°C.

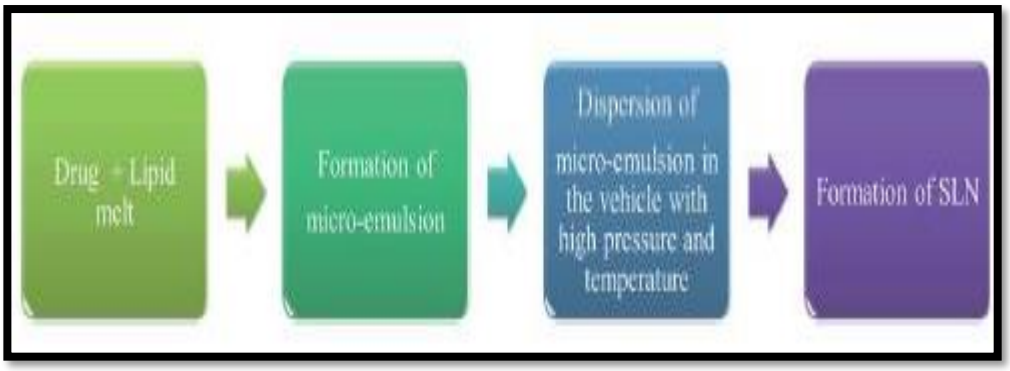

Fig no 07 Preparation of SLN by oil/water (o/w) microemulsion breaking method

Solvent injection method

This procedure involves dissolving lipids in a solvent that dissolves in water, after which they are inserted by a needle into a swirling aqueous solution that might or might not contain surfactants. The kind of injection solvent used, the lipid content, the volume of injected lipid solution, and the viscosity and diffusion characteristics of the lipid solvent phase into the aqueous phase are all significant variables influencing the generation of nanoparticles with this technique.

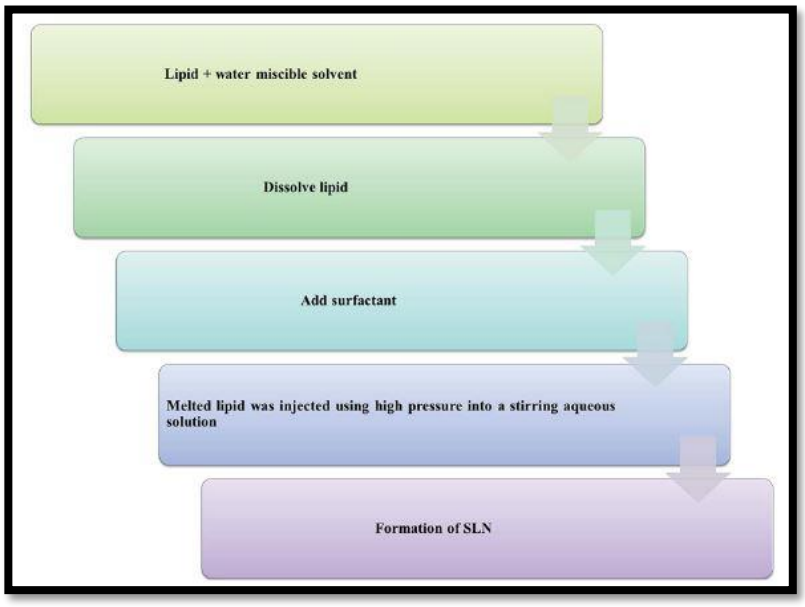

Fig no 08- Preparation of SLN by solvent injection method

Film ultrasound dispersion

Following the decompression, turning, and dissipation of the natural arrangements made of lipid and medication, a lipid film is framed, in which a watery arrangement holds the emulsions. Ultrasound is used as the last test to diffuse the SLN with the tiny

and homogenous molecular measurement.

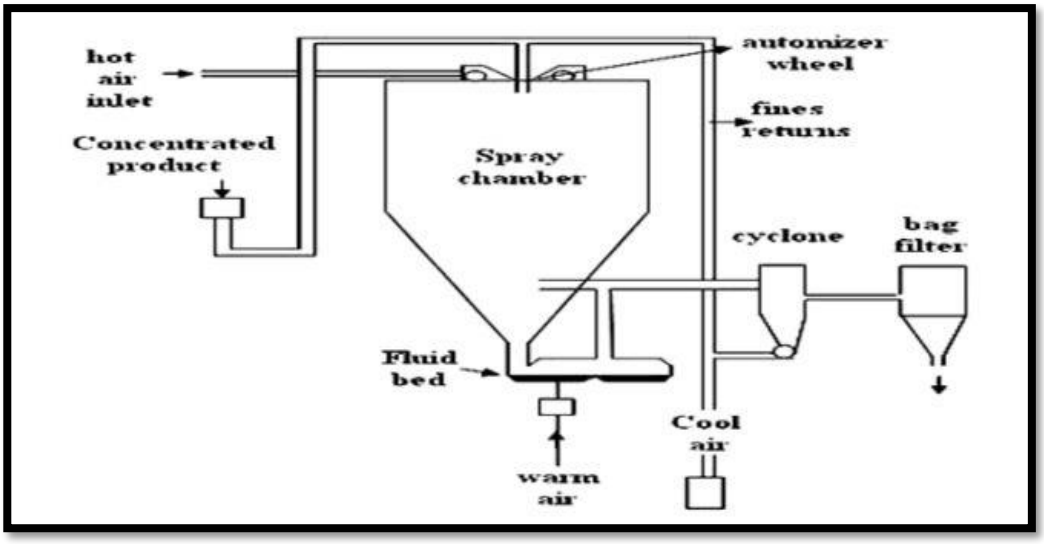

Fig no 09- Preparation of SLN by Film ultrasound dispersion

Evaluations with the specifications

Following production, solid lipid nanoparticles (SLNs) require extensive chemical and physical characterisation. The small size, complexity, and dynamic nature of SLNs make characterisation challenging. Particle size, surface shape, zeta potential, drug release profile, degree of crystallinity, and entrapment efficiency (% EE) are all significant evaluation variables. Particle size, charge, and polydispersity index can be measured using techniques such as photon correlation spectroscopy (PCS), dynamic light scattering (DLS), and quasi-elastic light scattering (QELS). Due to their great sensitivity and analytical speed, these methods are helpful for characterising SLN. Differential scanning Calorimetry (DSC) can be used to measure the glass and melting point temperatures and the associated enthalpies in order to evaluate the polymorphism alterations and crystallinity of lipids. With changes in chemical signals reflecting molecular dynamics and the physicochemical state of the components within the nanoparticles, nuclear magnetic resonance (NMR) can also reveal information about the size and qualitative properties of nanoparticles.

For SLN quality control, it is crucial to assess a number of factors, such as particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), coexistence of other colloidal structures (such as micelles and liposomes), drug content, in vitro drug release, and surface morphology. To study particle size and distribution, a variety of techniques can be employed, including atomic force microscopy (AFM), transmission electron microscopy (TEM), scanning electron

microscopy (SEM), photon correlation spectroscopy (PCS), scanning tunnelling microscopy (STM), and freeze fracture electron microscopy (FFEM).

Particle size and zeta potential

Laser diffraction (LD) and photon correlation spectroscopy (PCS) are two of the best methods for routinely measuring particle size. Because it is difficult to evaluate small nanoparticles and requires electrolytes, which might destabilize colloidal dispersions, the Coulter method is not as commonly used to measure the sizes of solid lipid nanoparticles (SLNs). PCS, sometimes referred to as dynamic light scattering, quantifies variations in scattered light intensity brought on by particle motion. Although it is limited in its ability to identify bigger microparticles, this approach is efficient for characterizing nanoparticles with sizes ranging from a few nanometers to around 3 microns.

By examining how the diffraction angle varies with particle radius (Fraunhofer spectra), on the other hand, LD makes it possible to see larger particles. At greater angles, light is scattered more intensely by smaller particles than by bigger ones. Covering a wide size range, from nanometers to lower millimeters, is one of LD's main advantages. Further increasing LD's sensitivity to tiny particles is the development of polarization intensity differential scattering (PIDS) technology. For a more thorough study, it is recommended to combine PCS with LD.

Both approaches detect light scattering effects that are used to determine particle size, but it's vital to remember that none "measures" particle size directly. Non-spherical particle morphologies can cause uncertainty since platelet structures can emerge during lipid crystallization and may be found in SLNs. Additionally, samples with several populations of varying sizes may be difficult for both PCS and LD to handle. Other techniques could be useful to supplement these methods. Light microscopy, for example, can quickly determine the presence and features of microparticles, but its sensitivity is limited in the nanometer range. The shape of the particles can be directly determined by electron microscopy, but researchers need to be aware of possible artefacts that could occur during sample preparation, such as changes in particle shape brought on by solvent removal.

Since a high value usually denotes particle disaggregation in the absence of complicating factors like steric stabilizers or hydrophilic surface appendages, zeta potential is an essential characteristic of SLNs. Zeta potential is often measured with a

zeta meter.

Atomic force microscopy (AFM)

This method involves scanning a material with a probe tip that is sharp on an atomic scale. The interactions between the tip and the surface are used to generate a topographical map. In contact mode, the probe is moved along the sample; in non-contact mode, it hovers slightly above the sample. Atomic force microscopy (AFM) has several sub-techniques, which are distinguished by the type of force employed while scanning.

This technique makes AFM a useful analytical tool by enabling ultrahigh resolution and mapping based on a variety of features beyond size, such as colloidal attraction and resistance to deformation. Particle size is the main variable in static light scattering (SLS), an ensemble technique that gathers and analyses the pattern of light scattered from a particle solution using basic electromagnetic equations. Although SLS is quick and reliable, it requires more cleaning than dynamic light scattering (DLS) and demands that the optical characteristics of the particles being investigated be known beforehand.

Dynamic light scattering (DLS)

Quasi-elastic light scattering (QELS) and photon correlation spectroscopy (PCS) are other names for dynamic light scattering (DLS), which measures variations in scattered light intensity on a microsecond period. Light dispersed by individual particles affected by Brownian motion interferes to produce these oscillations. Before being fitted to an exponential function or a variant of it, the data is processed by compiling an autocorrelation function. The diffusion coefficient(s) of the particles are related to the relevant decay constant(s) that were found by this fitting. It is possible to determine the particle size from this diffusion coefficient under the conventional assumptions of spherical shape, low concentration, and known viscosity of the suspending medium. DLS's sensitivity, quick analysis, and lack of calibration needs are among its benefits.

X-ray diffraction (powder X-ray diffraction) and differential scanning calorimetry (DSC)

The presence or absence of crystal planes in a solid can be determined by the geometric scattering of radiation from those planes, which in turn allows the degree of crystallinity to be evaluated. Even while DSC is usually applied to bulk materials, it can

also reveal information on the kind and species of crystallinity present in nanoparticles. In order to assess the crystalline properties of the nanoparticles, the glass transition and melting point temperatures as well as the enthalpies that go along with them are measured.

Static light scattering

Static light scattering (SLS) is an ensemble technique that fits the pattern of light scattered from a particle solution to fundamental electromagnetic equations where size is the primary variable. Although this method is fast and accurate, it needs to be cleaned more thoroughly than dynamic light scattering (DLS) and requires knowledge of the particles' optical properties in advance. Acoustic spectroscopy, another ensemble approach that determines particle size by fitting the data to relevant physical equations, is used to detect the attenuation of sound waves. It can also detect the oscillating electric field created by charged particles moving in response to sonic energy, providing crucial information about the particles' surface charge.

5.6 Nuclear magnetic resonance (NMR)

Nanoparticles can be evaluated for size and quality using nuclear magnetic resonance (NMR). While the sensitivity to molecular mobility delivers information about the physicochemical condition of the constituents within the nanoparticle, the chemical shift offers selectivity.

STERILIZATION OF SLN

In order to be administered intravenously or through the eyes, Solid Lipid Nanoparticles (SLNs) need to be sterile. Because of the high temperatures attained during autoclaving, a hot oil-in-water (o/w) microemulsion may occur inside the autoclave, which could change the size of the hot nanodroplets. The SLNs reform when they are slowly cooled down later, although some of the nanodroplets may combine to generate larger SLNs than those that were first created. Furthermore, the quantity of surfactants and co-surfactants in the hot system is decreased because SLNs are cleaned prior to sterilization, which could result in inadequate stabilization of the nanodroplets.

Morphology of SLN

Nanoparticles can be directly observed using Scanning Electron Microscopy (SEM)

and Transmission Electron Microscopy (TEM), with SEM being especially useful for analyzing morphology. In contrast, TEM has a smaller size detection limit and is a useful tool for validating other characterizations techniques. Users must take into account the tiny sample size usually analyzed and the possible impact of vacuum conditions on the nanoparticles, even if it offers extensive structural information.

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CHAPTER NO 16- DRY SYRUP

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Introduction of Dry Syrup-

Dry syrups are dry mixes that require water to be added while dispensing. Dry syrups demonstrate appropriate chemical stability of the medicine during shelf life while reducing the end product's weight. Suspensions are commercial dry formulations that must be diluted with water before dispensing them.

Dry powders for oral suspension are powder combinations that must be reconstituted with water before dispensing and are mostly used in kids. These are referred to as dry syrups or reconstitutable oral suspensions. Due to its ease of administration, the dry syrup recipe is appropriate for both children and the elderly. The oral route is the primary method of delivery.

Fig no 01- Dry Syrup

Oral dose forms are preferred due to their ease of administration, patient compliance, and formulation stability. Tablets and capsules, the most common oral dose form, have the disadvantage of being unpleasant to swallow in dosage forms designed specifically for paediatric and elderly patients. In recent years, modern scientific and technological advancements in the pharmaceutical area have generated a surge of interest in reconstitutable oral suspensions. Dry syrups are dry mixes that require water to be added while dispensing. Dry syrups demonstrate appropriate chemical stability of the

medicine over shelf life while lowering the end product's weight. Furthermore, dry syrups have a better bioavailability than tablets and capsules because they dissolve in water outside of the oral cavity and enter the gastrointestinal tract immediately.

Dry syrup consists of finely separated insoluble particles ranging from 0.5-5 μ that should be distributed in an appropriate medium. Dry syrups are dryness concoctions that must be diluted with water when dispensed. Dry syrup is commonly used to provide antibiotics, child medications, and several moisture-sensitive medicines. Dry syrups are a solid dose form that can be reconstituted. by adding water to administer via the oral route. The majority of the medications are antibiotics, with some being moisture sensitive or paediatric. Drugs are accessible as dry syrup. Many preparations, such as amoxicillin trihydrate, erythromycin, cefixime dry syrup, cefpodoxime dry syrup, cefuroxime dry syrup, amoxycillin dry syrup, amoxycillin and potassium clavulanate dry syrup, colistin sulphate dry syrup, cefadroxil dry syrup, etc. Dry syrup manufacture is especially advantageous because it is easily weighed and packaged, as well as handy to transport. Dry syrup are a broad category of dry syrup used to treat a variety of diseases. Examples of dry powder combinations include Cloxacillin Sodium for Oral Solution, USP (Teva), and an anti-infective antibiotic.

ii) Penicillin V Potassium Oral Solution, USP (Veetids, Geneva) is an anti-infective antibiotic.

iii) Potassium chloride for oral solution, USP (K-LOR, Abbott) is a potassium supplement.

Advantages of dry syrup-

- Use the appropriate unit dosage form.
- Easier to transport and more stable than traditional dose forms.
- Has a more refined appearance compared to powder mixtures.
- Simple to administrate.
- Ideal medication form for paediatrics.
- Single-dose sachets ensure accurate dosage.
- Physical parameters such as temperature, sedimentation rate, and liquid flow qualities do not significantly affect drug dose.
- Colored, flavored, sweetened formulation is advantageous for administration to the pediatric population.

Disadvantages of Dry Syrup

- Following re-establishing dried syrup, caking may occur during storing.
- Possibility of error in single dose.
- Dry syrup might deteriorate.
- Caused by the impact of biphasic characteristics,
- Measure viscosity, dispersion, and sedimentation rate.

SUSPENSION

A pharmaceutical suspension is described as a coarse dispersion in which its inner component is evenly dispersed across the outer phase.

CLASSIFICATION OF SUSPENSION-

Based On Route of Administration

- Oral suspension
- Topical suspension
- Parenteral suspension

Based On Proportion of Solid Content

- Dilute suspension (2 to10%w/v solid)
- Concentrated suspension (10 to 50% w/v solid)

Based On the Electro Kinetic Nature of Solid Particles

- Flocculated suspension
- Deflocculated suspension

Based On Size of Solid Particles

- Colloidal suspension (< 1 micron)
- Coarse suspension (>1 micron)
- Nano suspension (10 mg)

Based on Method of Administration

- Dry powder for reconstitution
- Ready to use suspension

Based on Release

- Conventional suspension
- Sustained release suspension

Qualities of ideal oral suspension

1. The fragmented particles should not settle easily, and the settled particles should re-disperse suddenly.

2. When the particles settle, no cake should develop.
3. Mixture is simply poured.
4. It needs to be both physically and chemically stable.
5. It must be tasteful.
6. It should be devoid of grinding particles.

Advantages of Sustained/Controlled release drug delivery system over the conventional dosage form

Sustained release drug delivery is novel drug delivery system which has many advantages over conventional dosage form.

- Decreased dosage frequency owing to delayed release.
- Dose reduction
- Improved compliance among patients.
- Reduced gastrointestinal irritation leading to less local and systemic adverse effects.
- Consistent medication concentrations in blood plasma.
- Reduces chances of toxicity due to overdose
- Improved therapy led to lower healthcare expenses.
- Reduces the fluctuation of peak valley concentration
- Avoid nighttime dosage.

DESIRED ATTRIBUTES FOR RECONSTITUTED SUSPENSION

The combination that is dry must have an acceptable concentration of each element. If the mixture is not uniform, it results in an incorrect dose. The powder blend must be easily and quickly disseminated in an aqueous vehicle. To provide a precise dose, the reconstitution must be simple and straightforward for the patient to pour. The increased viscosity induced by chilled temperature storage after restoration should not interfere with the dose delivered to the patient. The finished product should have an acceptable flavour, aroma, and appearance.

Reasons for formulation of such suspensions

The most prevalent rationale for the development of suspensions for reconstitution is the drug's insufficient chemical stability in an aqueous carrier. In such circumstances,

dissolution or even suspension of the medicine leads to an extremely limited shelf life. For example, reconstituted penicillin solutions have a maximum shelf life if 14 days. However, the commercially produced dry mixture has a minimum shelf life of two years. Another rationale for developing suspensions for reconstitution is to avoid the physical stability issues that are common with regular suspensions. These issues include the possibility of enhanced drug solubility due to pH changes caused by chemical degradation, component incompatibility, viscosity changes, polymorphic form conversion, crystal development, and caking.

Because the aqueous vehicle is removed, reconstitution formulation reduces the weight of the final product, potentially lowering transportation costs. The dry combination can be sent regardless of seasonal temperatures because its physical stability is less sensitive to temperature fluctuations than typical suspensions.

- The powder blend should be a homogenous combination with the right concentration of each element.
- During reconstitution, the powder blend should distribute promptly and fully in the aqueous vehicle.
- To ensure accurate and uniform dosing, reconstituted suspensions should be conveniently poured by the patient.
- The final outcome should have an acceptable appearance, smell, and taste.

Desired attributes

During production, the dry blend, or mixture, must be consistent and contain the appropriate concentration of each ingredient. It must not segregate into a non-uniform mix, or dosing mistakes may occur. During reconstitution, the powder blend should distribute promptly and fully in the aqueous vehicle. The reconstituted suspension must be easily redisposed and poured by the patient to ensure a precise and uniform dose. After reconstitution, the high viscosity generated by chilled storage conditions should not interfere with dose administration by the patient. The finished product must have an acceptable appearance, taste, and odour.

Excipients used

Excipients are should be chosen based on their appropriateness for reconstitution and the physical characteristics of the powder mixture. Excipient selection criteria are based on both reconstitution compatibility and the desired morphological type of

powder mixture.

- Using too many excipients can lead to safety issues.
- All excipients that should disperse quickly upon reconstitution. This criterion removes numerous suspending agents.
- Many preservatives are unsuitable.
- Using excipients with multiple functions can reduce the number of excipients needed. For example, sucrose is employed as a sweetener, suspending agent, and diluent.

Granule disintegrant

Granule Binder

It helps decrease particles settle in suspensions and is also employed as a suspension stabilizer. For example, the high-molecular-weight povidone, also.

Suspending agents

Suspending agents suited for use in suspensions for reconstitution can be easily disseminated during reconstitution through vigorous hand shaking. The combination of microcrystalline cellulose and sodium CMC is a typical suspending agent. Several popular suspending agents are ruled out because they require hydration, increased temperatures, or high shear mixing for proper dispersion. Some of the recommended suspending agents include (Gums) Acacia, Carboxymethylcellulose sodium, Iota carrageenan, microcrystalline cellulose with carboxymethylcellulose sodium, Povidone, Propylene glycol alginate, Silicon dioxide, Sodium starch glycolate, Tragacanth, and Xanthan gum.

A popular suspending agent consists of microcrystalline cellulose and sodium carboxymethylcellulose (CMC). Natural gums are usually anionic and contain tree exudates and seaweed extracts.

Sweeteners

Sweeteners are commonly used to mask disagreeable tastes and improve patient acceptability. Some medications have a harsh and bland taste. To disguise this flavour, sweeteners are utilised. For example, sucrose, mannitol, and dextrose are regularly used suspending agents in this form of suspension.

Wetting agents

During suspension, they are hydrophobic, reject water, and are difficult to wet. Surfactants are often utilised to improve the dispersion of hydrophilic medicines. The

formulator must choose the right wetting agent to ensure optimum medication dispersion at the lowest effective concentrations. Excess wetting agent can cause froth and leave an unpleasant taste. Polysorbate 80 is a chemical that is a commonly used wetting agent. It is nonionic and chemically compatible with both cationic and anionic excipients and medications. It is utilised in concentrations less than or equal to 0.1%. Another popular wetting ingredient is sodium lauryl sulphate. This substance is anionic and may interact with cationic medicines.

Other excipients

Other excipients include buffers, preservatives, flavours, and colours. Flocculating agents are rarely employed in suspensions for reconstitution since these products are often redispersed frequently enough to avoid caking. Buffers are used to keep all excipients at their optimum pH. Suspension pH is frequently altered to ensure that the medicine is insoluble. Polymeric suspending agents, on the other hand, have the highest viscosity at the pH where they are most soluble. Sodium citrate is a common buffer used in suspensions for reconstitution.

Preparation of dry mixture

- Powder blends
- Granulated products
- Combination products

Powder blends

Powder blends, also known as powder mixtures, are created by blending dry conditions mixture's additives in powder form. Excipients in modest quantities may necessitate a two-stage mixing operation. Such excipients can be used with a portion of a large excipient to improve dispersion. For example, milled sucrose has a wide surface area that allows for the adsorption of modest amounts of flavor oils. The second stage involves mixing the remaining excipients. The primary criterion when choosing an adequate mixer is that it produces a homogeneous mixture quickly and dependably.

Advantages

- Requires minimal capital equipment and energy.
- The absence of heat and solvents reduces the risk of chemical and physical stability issues.
- Dry mixtures might have low moisture levels.

Disadvantages

- Prone to uniformity issues. The two most significant properties for combining these kinds of powders are particle size or powdered flow.
- Active component is lost during mixing.
- Mixing can result in considerable loss of strong drugs at low doses.

Combination product

The powdered and granulated excipients that can be blended to overcome some of the drawbacks of granular products. The majority of the dilution agents can be added after granulation, which may require less energy and devices. Heat-sensitive excipients, like tastes, may additionally be included after the granulation has dried to avoid exposure to high temperatures.

Disadvantages

- Risk of variation.
- Control the particle size of each fraction.

Processing the dry mixture

- Ensure efficient mixing.
- Determine an appropriate mixing time.
- Minimize heat and humidity during mixing.
- Control temperature/humidity changes. A typical rule is 700 degrees Celsius at <40% relative humidity.
- Protecting the finished batch from dampness. Store in walled containers with silica desiccant bags.
- A test for batch homogeneity. Test at the top, middle, and bottom of the dried mixture.

Evaluations of oral reconstitute system

For example, re-constitutional swallowing suspensions of cephalexin monohydrate and piperine.

Drug content

A single injection (3.4 g of the formulation per 5 mL) is comparable to 0.125g of Cephalexin. The drug was extracted in 100 mL of distilled water and filtered through a 0.22 µm nylon filter membrane. The solution had been diluted to 10 ml with a solution of distilled water, and its absorbance was measured at λmax 260 nm using a Hitachi U-2800 UV a spectrum analyser. The drug concentration was estimated using the

calibration curve in distilled water.

pH

The pH of the regenerated suspension was evaluated using a pH meter (Systronic pH system 361). A glass rod had been dropped into a suspension of 100 mg of medication in a 50 ml beaker.

Viscosity

Overall rheologic properties of the created suspensions in terms of viscosity were determined using the steady shear method, which measured the "non-Newtonian viscosity". Rheology of all suspensions was done with an RVT Brookfield viscometer from Choksi Lab (Indore, M. P.). All measurements were taken after removing all thickness from the suspension.

Packaging and storage

1) Dry powders should be put in a wide-mouth container with enough free space above the liquid.

2) Placed in an airtight amber glass jar to protect it from extreme heat and light.

3) The packaging should include the phrase "shake well before use" to achieve uniform particle distribution.

4) The dry powders used for oral recombination should be kept at room temperature.

5) Single-dose packing uses sachets comprised of four layers of aluminium foil.

ICH guidelines (Q6A) for re-considerable oral suspensions

The appropriate ICH Expert Working Group created this Guideline, which was subject to consultation by regulatory bodies in accordance with the ICH Process. At Step 4 of the Process, the final document is proposed for approval by regulatory authorities in the European Union, Japan, and the United States.

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CHAPTER NO 17- GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

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Introduction

Gastroretentive Drug Delivery Systems (GRDDS) are specialized formulations that extend a drug's retention time in the stomach, thereby increasing bioavailability and therapeutic efficacy. These systems are especially useful for drugs with a narrow therapeutic index, which require a specific site of absorption or have low solubility in the intestinal environment. The primary idea behind GRDDS is to improve drug delivery by ensuring that the dosage form stays in the stomach for an extended period of time. This approach uses a variety of physiological factors and formulation technologies to achieve targeted drug release and absorption. Many GRDDS formulations are buoyant, which implies they can float on the gastric contents. This property prevents rapid gastric emptying, allowing the dosage form to remain in the stomach for longer. Some GRDDS are designed to swell when in contact with gastric fluids, increasing their size and improving mucoadhesion to the gastric mucosa. This improves drug retention and allows for a more controlled release. GRDDS can be engineered to provide a controlled or sustained release of the drug. This reduces the need for frequent dosing while maintaining therapeutic drug levels over time. By prolonging gastric retention, GRDDS can improve drug targeting to the stomach or upper gastrointestinal tract. This is especially useful for drugs that have a significant first pass.

Drugs that are suited for gastroretentive drug delivery systems (GRDDS) usually have certain properties that make them perfect for gastric retention. This includes:

1.Poor solubility in alkaline conditions. e.g., omeprazole with ranitidine.
2. Limited Therapeutic Index, e.g., include digoxin and lithium.
3. Drugs with local stomach action. e.g., antacids and sucralfate.

4. Drugs have shorter half-lives. e.g., include propranolol and theophylline.
5. Biopharmaceutical Classification System (BCS) Class II and IV drugs. e.g., Ibuprofen (Class II), Valacyclovir (Class IV).
6. High first-pass metabolism. e.g., morphine and nitro-glycerine.

Using GRDDS, these medications can improve absorption, effectiveness, and patient compliance.

Anatomy and Physiology of the Stomach

Structure of the Stomach

The stomach is a muscular, hollow organ situated between the oesophagus and the small intestine, primarily responsible for the digestion of food. Its unique anatomy is critical to its functions, which include mechanical breakdown, mixing of food with digestive juices, and controlled release into the small intestine.

Sections of the Stomach:

Fundus: The uppermost portion of the stomach, which acts as a storage area for undigested food and gases released during digestion. It is richly supplied with blood vessels and contains gastric glands that secrete digestive juices.

Body (Corpus): The central and largest section of the stomach, responsible for the majority of digestive processes. The body contains numerous gastric glands that secrete pepsinogen (inactive form of the enzyme pepsin), hydrochloric acid (HCl), and intrinsic factor, which is essential for vitamin B12 absorption.

Antrum: -The lowest part of the stomach, which grinds food to a liquid form (chyme) and makes sure that it passes through into the small bowel from time to time via an eccentric little valve at its end called pyloric sphincter. The antrum has a crucial function in the mixing and propelling of food, and also hormone secretion (gastrin, which is involved in gastric acid production).

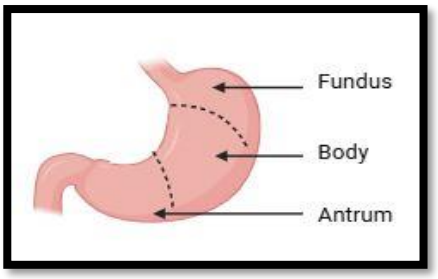

Fig no 01- Anatomy of Stomach

Functions of the Stomach:

Mechanical Digestion: The muscular walls of the stomach contract to mix food with gastric juices, facilitating mechanical breakdown.

Chemical Digestion: The acidic environment (pH 1.5 to 3.5) is essential for activating pepsinogen to pepsin, which begins the digestion of proteins. Gastric acid also helps kill pathogens present in food.

Storage: The stomach acts as a reservoir, allowing for the gradual release of chyme into the small intestine, which is crucial for effective nutrient absorption.

Regulation: The pyloric sphincter controls the passage of chyme into the duodenum, ensuring that the small intestine is not overwhelmed.

Physiological Factors

Understanding the physiological environment of the stomach is essential for optimizing drug delivery, as various factors can influence the absorption of orally administered drugs.

Gastric pH:

- The pH of gastric juice is highly acidic, usually ranging from 1.5 to 3.5 during fasting. This acidic environment is essential for protein digestion and act as a barrier against pathogens. However, the pH can increase significantly (up to 5 or more) after food intake or under certain pathological conditions.

- The solubility of many drugs is pH-dependent. Acidic drugs can be easily dissolve in the stomach, while basic drugs may face solubility challenges. Formulations that consider this pH variability can improve the stability and absorption of drugs.

Transit Time:

- Gastric emptying time can vary significantly among individuals and is influenced by factors such as the composition of the meal (fats, proteins, carbohydrates), volume, and temperature. In general, liquids empty faster than solids.
- The average gastric emptying time is approximately 2 to 4 hours for solids and around 30 to 60 minutes for liquids. Drugs that cause longer dissolution times may benefit from formulations designed to extend gastric retention.

Secretion of Gastric Fluids:

- The stomach secretes various components, such as gastric acid, pepsinogen, intrinsic factor, and mucus etc. These components play an important role in digestion and protection of the gastric mucosa.
- **Gastric Acid (HCl)**: Essential for activating digestive enzymes and providing an optimal pH for pepsin activity. Its secretion is regulated by neural and hormonal signals, especially gastrin.
- **Pepsinogen**: Secreted by the chief cells (gastric), it is activated to pepsin in the presence of acid and is essential for protein digestion.
- **Intrinsic Factor**: A glycoprotein necessary for the absorption of vitamin B12 in the small intestine.
- **Mucus**: It is secreted by goblet cells and protects the stomach lining from the corrosive effects of gastric acid and mechanical injury.

2. Gastric mortality and gastric empty rate

There are two different patterns of GIT secretion and mortality in the fed and fasting states. The status of feeding affects the drug's bioavailability when taken orally. An interdigestive series of electric events known as the migrating motar complex or interdigestive myoelectric cycle characterizes the fasting state (Figure

It can be divided into **four** stages:

Phase 1 (basal phase)

Phase 2 (preburst phase)

Phase3 (burst phase)

Phase 4

After ingesting a meal, the pattern of contraction shifts from a fed to a fasted. This is known as the digestive motility pattern. These contractions reduce the size of food particles, which are then propelled to the pylorus in a suspended form. During the fed state, the onset of the migrating motor complex (MMC) is delayed, resulting in a slower gastric emptying rate.

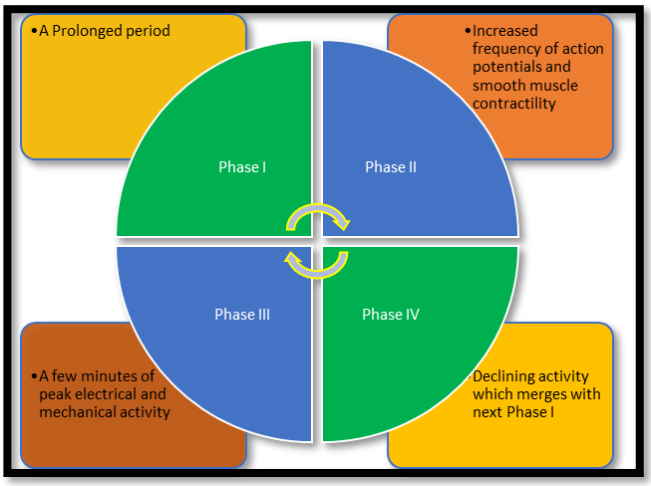

Fig no 02- Gastric Motility and Gastric Emptying

3.Factors Influencing the Gastro retentive System

GRDDS is impacted by different factors which are set out below:

- **Density**: It depends on the density of drug that influence its gastric retention time. This is always lower density than
- **Gastric content**. The shape and size of the drugs also play an important role in making them work effectively. Drugs of diameter 9.5 mm
- **Dosage form shape** – The tetrahedron and ring-shaped dosage form has more half-lives than any other dosage form of same size.
- **Half-life and nature of meal**: Food in stomach influences the gastroretentive drug delivery system. Feeding of incorporating indigestible polymers or salts of

fatty acids can alter stomach mortality from the fasted to fed state so that reduce the gastric emptying rate and prolonged drug releasing.

- **Caloric Composition**: Added GRT with meals that are rich in protein and fats up to 4 to 10 hr.
- **Frequency of feed** — when successive meal is given the GRT can increased over 400 minutes. Because MMC are so infrequent, this means you might have just an open feeding window to be left with one meal.
- **Age** — GRT can be extended to seniors, particularly those over the age of 70.
- **Posture** – GRT can be altered compared with the upright ambulatory state of the patients to that from a supine state.
- **Biological factors**– Diabetes and Obesity.

Background of Gastroretentive Drug Delivery Systems (GRDDS)

The development of gastroretentive drug delivery systems (GRDDS) emerged from the need to improve the bioavailability of drugs that have specific absorption sites in the gastrointestinal (GI) tract, particularly in the stomach and upper intestine. Conventional oral dosage forms often face challenges like rapid gastric emptying, variability in gastric pH, and patient compliance issues, leading to suboptimal outcomes.

Physiological Considerations

1. **Gastric Retention**: The stomach plays an important role in the drug absorption of certain medications. Drugs that require an acidic environment for solubility or are primarily absorbed in the stomach benefit from prolonged gastric retention.
2. **Gastric Motility**: Understanding the gastric emptying process is vital for designing GRDDS. Factors that influence gastric emptying include:
    - Size and density of the dosage form.
    - Presence of food in the stomach.
    - viscosity of the formulation and its adherence to the gastric mucosa.
3. **pH Variability**: The pH of the stomach varies from 1.2 to 4, influenced by food intake and circadian rhythms. Formulations that can adapt to these pH changes can enhance drug solubility and stability.

Technological Advances

The development of GRDDS has been facilitated by advances in materials science and pharmaceutical technology. Key developments include:

1. **Floating Drug Delivery Systems (FDDS)**:

These systems are designed to float on the surface of gastric fluids, utilizing buoyant materials or gas-generating agents. With this technology allows for extended retention time in the stomach.

2. **Bioadhesive Systems**: These systems utilizing mucoadhesive polymers, these systems adhere to the gastric mucosa, enhancing retention and allowing controlled drug release.
3. **Swellable Systems**: These formulations increase in size upon contact with gastric fluids, slowing down their transit through the stomach.
4. **Magnetic Systems**: Some advanced GRDDS incorporate magnetic materials, allowing external magnets to help retain the dosage form in the stomach.
5. **3D Printing Technologies**: Recent innovations in additive manufacturing allow for precise control over the geometry and release profiles GRDDS.

2.3 Clinical Relevance

GRDDS are particularly advantageous for:

- **Drugs with Narrow Therapeutic Indices**: Drugs that require precise dosing benefit from the controlled release capabilities of GRDDS.
- **Drugs that Undergo First-Pass Metabolism**: Prolonged gastric retention can improve the systemic availability of drugs susceptible to extensive hepatic metabolism.
- **Chronic Conditions**: For diseases requiring consistent therapeutic levels (e.g., hypertension, diabetes), GRDDS can reduce dosage frequency and improve patient compliance.

Importance of Gastroretentive Drug Delivery Systems (GRDDS)

The study of gastroretentive drug delivery systems (GRDDS) is essential due to several key factors that significantly impact therapeutic efficacy, patient compliance, and overall healthcare outcomes. Below are some key aspects highlighting the significance of GRDDS, along with relevant references.

1. Enhanced Bioavailability

GRDDS can improve the bioavailability of drugs that are better absorbed in the gastrointestinal tract or have poor solubility in the intestinal environment. Promoting the retention time in the stomach, GRDDS facilitate better absorption and therapeutic efficacy.

2. Controlled Release of Medications

GRDDS are designed to provide controlled or sustained release of drugs, which helps maintain therapeutic drug levels over an extended period of time. This reduces the frequency of dosing, improving patient compliance.

3. Targeted Drug Delivery

Certain medications, especially those used for local treatment of gastric conditions (e.g. Ulcers), benefit from being retained in the gastric region. GRDDS can deliver the medication directly to where it is needed most, enhancing the localise therapeutic effects.

4. Improved Patient Compliance

GRDDS improve patient compliance by reducing dosing frequency and providing a more consistent release of medication, GRDDS enhance patient compliance. This is particularly important for chronic conditions where maintaining steady drug levels is crucial.

5. Minimized Side Effects

GRDDS minimize peak plasma concentrations through controlled release, thereby reducing the risk of side effects associated with rapid drug absorption. which is particularly beneficial for drugs with a narrow therapeutic range

6. Application in Chronic Diseases

GRDDS are particularly useful for the management of chronic diseases where consistent therapeutic levels are required. The ability to provide sustained release can lead to better disease management and outcomes.

7. Advancements in Pharmaceutical Technology

Research into GRDDS advances innovation in pharmaceutical formulations and technologies, leading to new materials, methods, and approaches that can be applied across various drug administered systems.

4.Gastroretentive Drug Delivery Systems (GRDDS) Techniques: Methods of Preparation- Gastroretentive drug delivery systems (GRDDS) are designed to prolong the retention time of drug formulations in the stomach, enhancing bioavailability and therapeutic efficacy. Below, we detail various techniques for formulating GRDDS, providing a stepwise explanation of the preparation methods along with a flowchart for clarity.

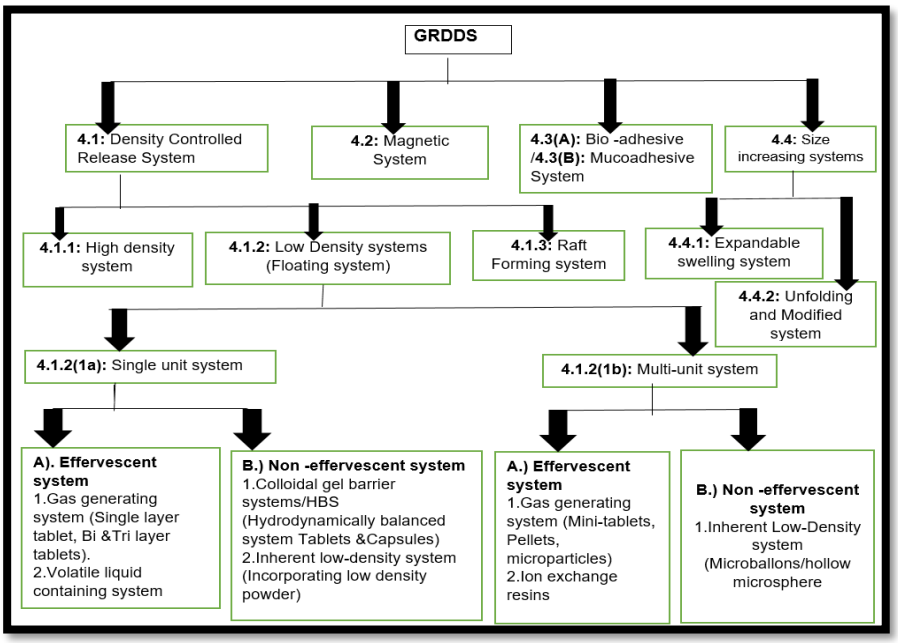

Fig no 03- GRDDS Approaches

Density controlled Release system

In the context of gastroretentive drug delivery systems (GRDDS), a density-controlled release system (DCRS) is certain techniques used to regulate the release and retention of medications in the upper gastrointestinal tract or stomach. GRDDS seeks to increase a drug formulation's duration of residence in the stomach, which can enhance bioavailability, especially when taking medications that need extended release for therapeutic efficacy or are poorly absorbed in the lower gastrointestinal (GI) tract.

High Density system:-

In this dosage form, the density of the formulation is higher than the density of the normal stomach content. These dosage forms are made by either mixing heavy inert materials like titanium dioxide, iron oxide, or zinc powder with the medicine or coating it with a heavy core.

These systems have several limitations, such as being unavailable on the market and being challenging to produce in large quantities due to the difficulty in incorporating high-density materials uniformly, as well as the need for specialized equipment to ensure proper formulation and controlled drug release. Furthermore, there may be concerns regarding the safety and biocompatibility of certain heavy materials used in these formulations**.**

A high-density system uses a dense dosage form (e.g., metal, glass) that remains in the stomach due to its high weight, promoting prolonged gastric retention.

Preparation Steps:

1. **Select Materials:**
   Choose high-density materials (e.g., barium sulphate, zinc, titanium dioxide) and suitable excipients (e.g., HPMC, gelatine).
2. **Formulation of Drug:**
   Blend the drug with excipients and high-density agents.
3. **Tablet/Pellet Formation:**
   - Compress the formulation into tablets or form pellets.
   - Methods: Direct compression, extrusion-spheronization.
4. **Coating (Optional):**
   Apply a coating for controlled drug release, using polymers like ethyl cellulose or HPMC.
5. **Quality Control:**
   Check tablet/pellet size, release profile, density, and mechanical strength.

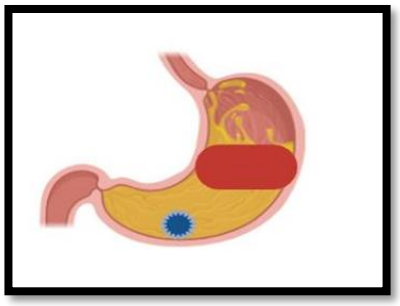

Fig no 04- High Density System

Floating Drug Delivery Systems (FDDS)

Overview: FDDS utilize buoyancy to remain afloat in the gastric contents, prolonging gastric retention.

Preparation Steps:

1. **Selection of Polymers**: Choose hydrophilic and swellable polymers (e.g., HPMC, sodium alginate) that can form a gel upon contact with gastric fluid.
2. **Drug Mixing**: Mix the drug with the selected polymers in a suitable ratio (typically 1:1 to 1:5).
3. **Addition of Gas Generating Agents**: Incorporate agents like sodium bicarbonate or citric acid that release gas upon reaction with gastric fluid.
4. **Granulation**: Use wet granulation or melt granulation to form granules or pellets. If using wet granulation:
    - Mix the powder blend with a granulating solvent (e.g., ethanol).
    - Pass the mixture through a sieve and dry to obtain granules.
5. **Spherical or Tablet Forming**: Compress the granules into tablets using a tablet press or shape them into spheres.
6. **Coating (Optional)**: Apply an enteric coating if delayed release is desired.
7. **Quality Control**: Evaluate buoyancy, drug release, and physical properties.

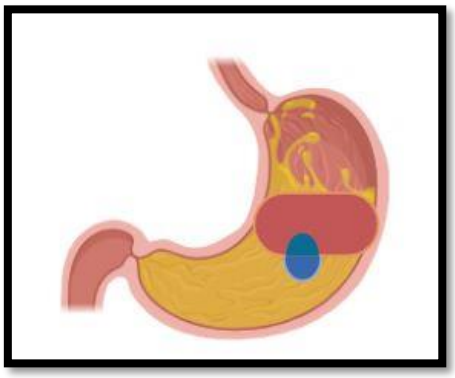

Fig no 05- Floating Drug Delivery System

Single-Unit Pellet Systems (SUPS)

Formulation of pellets for controlled or sustained drug release.

Preparation Steps:

1. **Select Materials:** Choose excipients and polymers (e.g., HPMC, ethyl cellulose).
2. **Mix Drug & Excipients:** Blend the drug with chosen excipients.
3. **Pelletization:**
    - Extrusion-Spheronization (form cylinders, then round them).
    - Alternatively, spray-dry or coat pellets.
4. **Drying:** Remove moisture by drying.
5. **Quality Control:** Check pellet size, release rate, and mechanical properties.

Multi-Unit Pellet Systems (MUPS)

MUPS consist of small pellets that can float or adhere to the gastric mucosa, allowing for prolonged release.

Preparation Steps:

1. **Selection of Materials**: Choose suitable excipients and polymers (e.g., ethyl cellulose, HPMC).
2. **Drug Mixing**: Blend the drug with the selected excipients.
3. **Pelletization**: Use techniques like:
    - **Extrusion-Spheronization**: Extrude the blend through a die to form cylinders, then spheronize to form pellets.

- **Pan Coating**: Coat existing pellets with the drug formulation.

4. **Drying**: Dry the pellets to remove moisture.
5. **Quality Control**: Assess pellet size, drug release rates, and buoyancy.

(A). Effervescent System

GRDDS effervescent systems typically contain an effervescent agent, such as an acid (e.g., citric acid) or a base (e.g., sodium bicarbonate), which reacts in the acidic environment of the stomach to produce carbon dioxide (CO2). It is designed to improve drug retention in the stomach and provide controlled drug release. These systems utilize effervescence (gas generation) to increase buoyancy and help the composition remain floating on top of the gastric contents, thereby increasing gastric retention time. It also facilitates a controlled, gradual release of drugs over time. These effervescence systems are further classified into different types.

1.Volatile liquid containing System

The GRT of a drug delivery system can be maintained by incorporating an inflatable chamber containing a liquid, for example**:** Ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device, consisting of polyvinyl alcohol and polyethylene, gradually dissolves, releasing gases and gases from the inflatable chamber. After a certain time, to permit the spontaneous ejection of the inflatable system from the stomach.

2. Gas generating system

This system uses effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to release CO2, which penetrates the gel layer of the system, decreasing its specific gravity and causing it to float above the gastric contents.

(B). Non-effervescent System

The non-effervescent system is based on the polymer swelling mechanism on the mucosal layer of the GIT. The most commonly used excipients are hydrophilic resins, polysaccharides and matrix-forming materials such as polycarbonate, polyacrylate, as well as bio adhesive molecules such as chitosan.

1.Colloidal gel Barrier System

Colloidal gel barrier systems (also known as hydrodynamic balance systems, HBS) are a type of non-effervescent gastric retention system that use a gelling and swelling mechanism to maintain buoyancy and extend gastric retention time. These systems are usually provided in tablet or capsule form and are designed to float in the stomach, absorb gastric fluids, and form a gel-like barrier around a drug core.

2.Inherent Low-Density System (Incorporating Low-Density Powders)

Inherent low-density systems are a type of non-effervescent gastroretentive system. These systems use low density materials to achieve buoyancy and extend gastric retention time. The low-density formula is designed to float on the surface of gastric contents due to its reduced density compared to gastric fluids. This approach avoids the need for effervescence, but also allows the drug form to remain in the stomach longer.

Raft Forming System

A raft-forming system refers to a specialized formulation that helps retain a drug within the stomach for prolonged periods. This system takes advantage of the unique physical properties of certain materials to form a "raft" or floating layer on the stomach's surface, thereby improving the drug's residence time.
This mechanism is particularly useful for drugs that need to be released slowly or locally in the stomach or upper gastrointestinal tract. A dosage form that forms a gel-like raft on top of the stomach contents, ensuring prolonged gastric retention and controlled drug release.

Preparation Steps:

1. **Select Materials:** Use gelling agents (e.g., alginates, gellan gum) and effervescent agents (e.g., sodium bicarbonate).
2. **Formulate Drug:** Mix the drug with gelling agents and excipients.
3. **Tablet/Pellet Formation:** Compress or mould into tablets or pellets.

4. **Raft Formation:** In the stomach, the formulation reacts with stomach acid to form a gel-like raft that floats.
5. **Quality Control:** Ensure raft stability, drug release, and mechanical properties.

Magnetic System

A magnetic system uses an external magnetic field to retain a dosage form in the stomach, enhancing drug retention for extended release.

Preparation Steps:

1. **Select Materials:** Choose magnetic materials (e.g., iron oxide) and suitable polymers (e.g., HPMC, ethyl cellulose).
2. **Formulation of Drug:** Blend the drug with excipients and magnetic agents.
3. **Pelletization/Tablet Formation:**
    - Prepare pellets or tablets incorporating the magnetic material.
    - Methods: Direct compression, extrusion-spheronization.
4. **Coating (Optional):** Coat the pellets or tablets with a polymeric film for controlled release.
5. **Quality Control:** Check for size, drug release, magnetic properties, and mechanical strength.

Mucoadhesive Systems

Mucoadhesive systems specifically target the gastric mucosa, using polymers that promote adhesion.

Preparation Steps:

1. **Selection of Mucoadhesive Polymers**: Choose polymers such as sodium alginate or polyvinyl alcohol.
2. **Drug Incorporation**: Mix the drug with the mucoadhesive polymer.
3. **Preparation of Hydrogel**:
    - Dissolve the polymer in an appropriate solvent.
    - Mix thoroughly until homogeneous.

4. **Molding or Shaping**: Pour the mixture into molds to form desired shapes (e.g., tablets, beads).
5. **Drying**: Dry the formed shapes to remove excess solvent.
6. **Adhesion Testing**: Evaluate the mucoadhesive strength through in vitro studies.
7. **Quality Control**: Check drug release profiles and physical properties.

Size Increasing System

Size-increasing systems in gastric drug delivery systems (GDDS) are made for remaining in the stomach for a long time, ensuring sustained medication release. In order to achieve gastric retention, these systems make use of the physiological conditions of the stomach to expand their size or volume. In order to get better therapeutic results and regulated drug release, the goal is to extend the dose form's residence period in the stomach.

Swellable Drug Delivery Systems

Swellable systems are designed to expand in the gastric environment, increasing their retention time.

Preparation Steps:

1. **Selection of Swellable Polymers**: Choose polymers like HPMC, sodium alginate, or Carbopol known for their swelling properties.
2. **Drug Mixing**: Blend the drug with the selected swellable polymers in appropriate ratios.
3. **Preparation of Granules**: Use a wet granulation method:
   - Mix the powder blend with a granulating solution (e.g., water, ethanol).
   - Pass through a sieve to obtain granules.
4. **Drying**: Dry the granules to remove excess moisture.
5. **Compression**: Compress the dried granules into tablets or shape them into beads.
6. **Quality Control**: Evaluate swelling behaviour, drug release profiles, and mechanical strength.

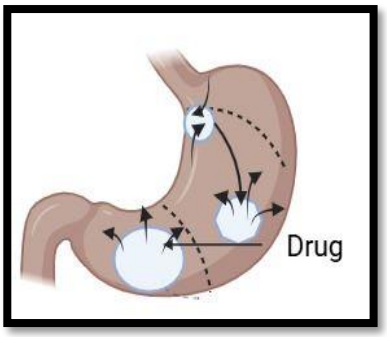

Fig no 06- Swellable System

Unfolding and Modified System in GRDDS

To ensure prolonged retention in the stomach and prevent rapid gastric emptying, a modified unfolding system is made to expand or unfold when it comes into contact with stomach fluids.

Preparation Steps:

1. **Select Materials**: Choose polymers and excipients (e.g., HPMC, guar gum, sodium CMC) that allow expansion in the stomach.
2. **Formulate Drug & Excipients**: Mix the drug with excipients to create the compact formulation.
3. **Tablet/Pellet Formation**: The drug mixture is compressed or moulded into a small dosage form.
4. **Unfolding/Expansion in Stomach**: Upon contact with stomach fluids, the dosage form expands or unfolds to increase size and reduce gastric emptying rate.
5. **Quality Control**: Test for correct expansion, drug release rate, size increase, and mechanical properties.

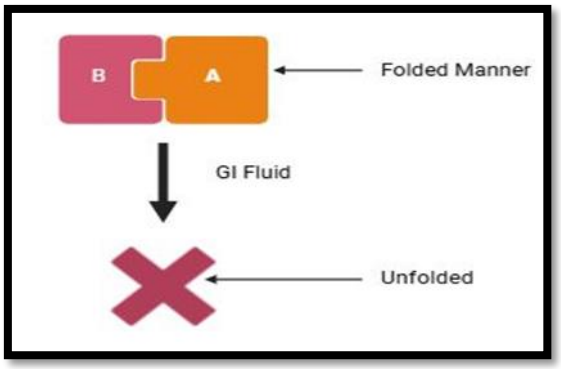

Fig no 07- Unfolding System

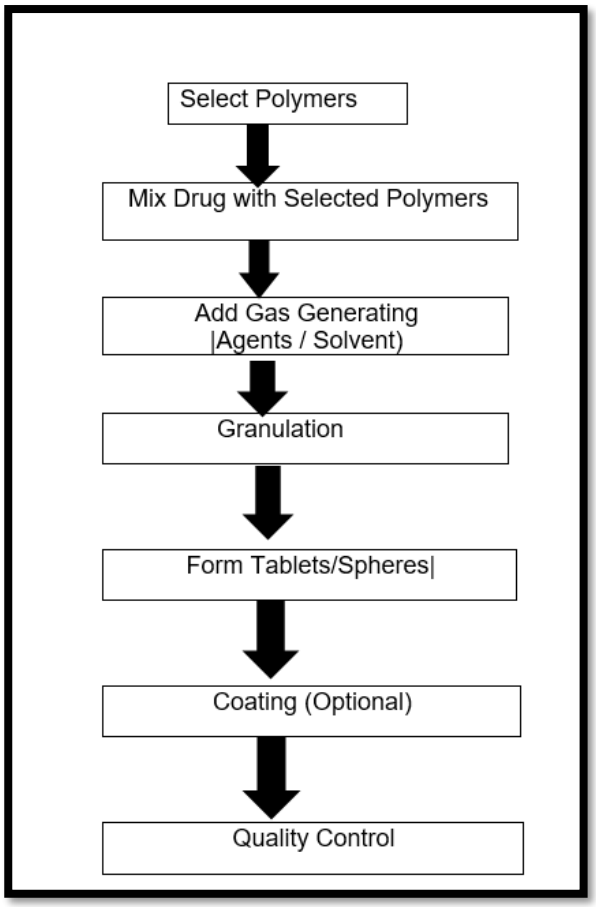

Fig no 08- Flowchart of GRDDS Techniques

This systematic approach to GRDDS formulation highlights the various methods available, along with their specific steps and considerations, ensuring a comprehensive understanding of how to develop effective gastric drug delivery systems.

Evaluation of Gastroretentive Drug Delivery Systems (GRDDS)

Evaluation of gastroretentive drug delivery systems (GRDDS) is essential to ensure their efficacy, stability, and patient compliance. Different parameters and tests are used to assess their effectiveness. The detailed evaluation method and its features are as follows:

In Vitro Drug Release Studies

To determine the rate and extent of drug release from the GRDDS.

Method:

- **Apparatus:** Use USP apparatus II (paddle method) or USP apparatus I (basket method).
- **Medium**: Typically, simulated gastric fluid (SGF) is used (pH 1.2) for the first few hours, subsequently simulated intestinal fluid (SIF, pH 7.4).

Procedure:

1. Place the dosage form in the container containing the medium.
2. Maintain the temperature at 37 ± 0.5 °C and mix at 50-100 rpm.
3. Take samples at predetermined intervals (e.g., 1, 2, 4, 6, 8 hours).
4. Take the samples using UV-Vis spectrophotometry or HPLC.

Characteristics:

1. Cumulative percentage of drug released vs. time.
2. T50% (time to reach 50% drug release).
3. Higuchi or Korsmeyer-Peppas models for kinetic analysis.

Floating Ability Studies

To evaluate the buoyancy of the GRDDS in gastric conditions.

Method:

- **Medium**: Use SGF (pH 1.2).

- **Procedure**:
    1. Place the formulation in a glass beaker filled with SGF.
    2. Observe the time required for the dosage form to float on the surface.
    3. Measure the floating duration (how long the system remains buoyant).

Characteristics:

- Buoyancy lag time: The Time required for the system to float.
- Duration of floating: Total time the system remains buoyant.
- The percentage of the dosage form (i.e. floating after a specific time) (e.g., 12 hours).

Swelling Studies

To evaluate the ability of the GRDDS to swell in gastric fluid, which aids in retention.

Method:

Medium: Use SGF (pH 1.2).

Procedure:

1. Weigh the dry dosage form and immerse it in SGF.
2. Remove it at predetermined time intervals, gently blot it to remove excess fluid, and weigh again.
3. Calculate the swelling index (SI) using the formula:

SI=100 (w_t -w_0)/w_0 = where W_t is the weight swollen tablet at time t and W_0 is the initial weight of dry tablet.

Characteristics:

- Swelling index vs. time.
- Maximum swelling capacity.

Mechanical Strength Testing

Ensure the physical integrity and stability of the GRDDS during handling and administration.

Method:

1.Use a hardness tester or tablet hardness tester.

2.Place the dosage form in the apparatus and apply pressure until it fracture is broken.

Specifications:

- Hardness (typically measured in kg/cm²).
- Friability test: % loss in weight after 100 rotations in a friabilator.

In Vivo Studies

To evaluate the pharmacokinetics and therapeutic efficacy of the GRDDS.

Method:

- **Animal Model**: Use an appropriate animal model. (e.g., rabbits, dogs).
- **Procedure**:

1. Administer the GRDDS and monitor for gastric retention with imaging techniques (e.g., X-ray, MRI).
2. Collect blood samples at specific time intervals to analyse drug concentration

Stability Studies

To evaluate the stability of the GRDDS under different conditions over time.

Method:

- **Conditions**: Evaluate under accelerated conditions (e.g., 40°C/75% RH).

- **Procedure**:

1. Samples are stored specified conditions and analyse at specified time intervals (e.g., 0, 3, 6, and 12 months).
2. Check for physical changes, drug release, and degradation.

Characteristics:

- Retention of drug content (typically ≥90% after 6 months).
- Evaluation of appearance, pH, and dissolution profile.

Mucoadhesion Testing

To evaluate the ability of the GRDDS to adhere to the gastric mucosa, extend its retention time.

Method:

- **Procedure**:

1. Use a texture analyser or a mucoadhesion tester.
2. The small part of gastric mucosa in contact with the formulation and apply a controlled force.
3. Measure the force required to release the formulation.

Specifications:

- Mucoadhesive strength (measured in grams).
- Compliance period

The evaluation of GRDDS encompasses various in vitro and in vivo methods to ensure their effectiveness, stability, and safety. Each evaluation method provides crucial information regarding the performance of the delivery system, helping in the optimization of formulations for improved patient outcomes. These tests are vital to meet regulatory standards and enhance the therapeutic efficacy of oral drug delivery systems.

CHAPTER NO 18- NANOEMULSION

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Introduction

Nanoemulsions, also referred to as mini-emulsions, are advanced colloidal dispersions of oil and water, stabilized by surfactants and cosurfactants. These systems exhibit unique properties such as thermodynamic stability, transparency (or translucency), and droplet sizes typically below 100 nm. Their multiphase nature, with dispersed phase droplets ranging from 5 to 200 nm, results in low interfacial tension between oil and water phases, distinguishing nanoemulsions by their clarity and exceptional stability. Transparency arises when droplet size is less than 25% of the wavelength of visible light. Nanoemulsions can form spontaneously or with minimal energy input, further adding to their versatility.

The composition of nanoemulsions allows for three principal types to form:

- **Oil-in-water (O/W) nanoemulsions**: Oil droplets dispersed in a continuous aqueous phase.
- **Water-in-oil (W/O) nanoemulsions**: Water droplets dispersed in a continuous oil phase.
- **Bi-continuous nanoemulsions**: Interconnected microdomains of water and oil within the system.

In all these forms, the interface is stabilized by carefully selected surfactants and cosurfactants, ensuring system stability. While terms like submicron emulsion and tiny emulsion are sometimes used interchangeably with nanoemulsion, the latter stands out due to its specific droplet size range and advanced functional properties.

Nanoemulsions are highly versatile, capable of being administered through various routes such as oral, topical, intravenous, intranasal, pulmonary, and ophthalmic delivery. They are adaptable into multiple dosage forms, including liquids, creams,

sprays, gels, and aerosol foams. Their application spans industries, including pharmaceuticals, cosmetics, and pesticides, where they serve as aqueous bases for organic actives, offering superior solubilization compared to micellar systems and greater kinetic stability than coarse emulsions. In pharmaceutical contexts, nanoemulsions improve drug targeting, protect active ingredients from environmental degradation (e.g., oxidation, pH, hydrolysis), and enhance bioavailability through improved permeability and retention.

Despite their numerous advantages, nanoemulsions come with challenges. They are unsuitable for dissolving materials with high melting points and require strictly non-toxic (preferably GRAS) excipients for human applications. Additionally, the need for high surfactant concentrations in some low-energy nanoemulsion systems may cause biomembrane fluidization, limiting their internal applications. These considerations are critical when evaluating their viability in drug formulation and delivery.

In this chapter, we explore the principles, preparation, types, and diverse applications of nanoemulsions, while addressing their limitations and potential in advancing drug delivery systems.

Background

The development of nanoscale biocompatible systems for encapsulating, distributing, and protecting fragile bioactive components has gained significant attention globally. Among these systems, **nanoemulsions** have emerged as a promising solution, leveraging biological amphiphiles and natural oils to encapsulate active substances. Their potential applications span multiple industries, including food, pharmaceuticals, and cosmetics. With formulations based on biocompatible and non-toxic ingredients, nanoemulsions offer versatile solutions for delivering drugs and bioactive compounds via diverse administration routes.

Key Aspects of Nanoemulsions

1. Drug Delivery:

Nanoemulsions are effective in delivering active pharmaceutical ingredients (APIs), enhancing the solubility and bioavailability of hydrophobic drugs and bioactive food components as shown in Table 1.

2. Safety

Composed of water, oil, and surfactants that are safe for human consumption, nanoemulsions are generally recognized as safe (GRAS), making them suitable for pharmaceutical and food-grade applications.

3. Preparation

Nanoemulsion preparation typically involves combining surfactants with the oily phase, followed by dispersion in an aqueous phase using high or low-energy methods.

4. Applications

Nanoemulsions are utilized across various fields, including material synthesis, food, cosmetics, and pharmaceuticals. Their ability to encapsulate and stabilize active ingredients underpins their wide-ranging utility.

Table no 01- Comparison of Nanoemulsions with Other Emulsions

Property	Macroemulsions	Nanoemulsions	Microemulsions
Size	1–100 µm	20–500 nm	10–100 nm
Shape	Spherical	Spherical	Spherical, lamellar
Stability	Thermodynamically unstable; weakly kinetically stable	Thermodynamically unstable; kinetically stable	Thermodynamically stable
Preparation Method	High & low energy methods	High & low energy methods	Low-energy methods
Polydispersity	Often high (>40%)	Typically, low (<10–20%)	Typically low (<10%)

Nanoemulsions bridge the gap between macroemulsions and microemulsions, combining small droplet sizes and kinetic stability with versatile preparation methods, making them highly adaptable for scientific and industrial applications.

Importance to study:

Nano emulsions offer a plethora of advantages over traditional emulsions, making them a cutting-edge solution in drug delivery, food, cosmetics, and material science

as shown in table 2. Their nanoscale properties result in improved stability, enhanced bioavailability, and the ability to deliver both hydrophilic and lipophilic active compounds efficiently as shown in figure 1.

Key Advantages of Nanoemulsions

1. **Enhanced Stability and Reduced Agglomeration**
   - Small particle size and reduced surface tension between the oil and aqueous phases minimize the likelihood of creaming, sedimentation, or precipitation.
2. **Increased Interfacial Area**
   - The emulsifier-stabilized oil-water interface facilitates exceptional solubilization capacity for both hydrophilic and hydrophobic actives.
3. **Improved Bioavailability**
   - Nanoemulsions enhance drug solubility, promote rapid absorption via enterocyte internalization, and facilitate the crossing of biological membranes through reversible alteration of cellular structures.
4. **Targeted and Precise Delivery**
   - Nanoemulsions are effective carriers for delivering drugs to specific and targeted sites, ensuring high therapeutic efficacy with minimal side effects.
5. **Multifunctionality**
   - Multilayered nanoemulsions (MLNEs) allow customization of surface properties such as composition, structure, charge, permeability, and reactivity, offering solutions tailored to diverse applications.
6. **Environmental and Commercial Feasibility**
   - Nanoemulsions can be converted into powdered forms using spray drying techniques, making them more versatile for commercial products like food, cosmetics, and pharmaceuticals.
7. **Oxidation and Hydrolysis Protection**
   - Nanoemulsions protect sensitive drugs in the oil phase of oil-in-water (O/W) systems from degradation by air or water.
8. **Low Energy Requirement**
   - Nanoemulsions often require less energy for preparation compared to traditional systems, making them cost-effective.

Table no 2: Comparison of Nanoemulsion Benefits over Traditional Emulsions

Nanoemulsion Benefit	Comparison with Traditional Emulsions
Boosts absorption rate	Enhanced cellular uptake and solubilization.
Reduces absorption fluctuation	Ensures consistent drug delivery.
Solubilizes lipophilic drugs	Greater solubilization efficiency than micellar systems.
Enhances bioavailability	Improves systemic drug absorption.
Enables multiple administration route	Oral, topical, intravenous, intranasal, etc.
Facilitates rapid drug absorption	Accelerates therapeutic effects.
Provides flavor masking	Makes medicines more palatable.
Protects against oxidation and hydrolysis	Prevents degradation of sensitive actives.
Ensures thermodynamic stability	Resists phase separation over extended periods.
Reduces adverse effects	Allows dose reduction due to enhanced efficacy.

Furthermore, they can serve as the building blocks for designer advanced materials withunique properties.

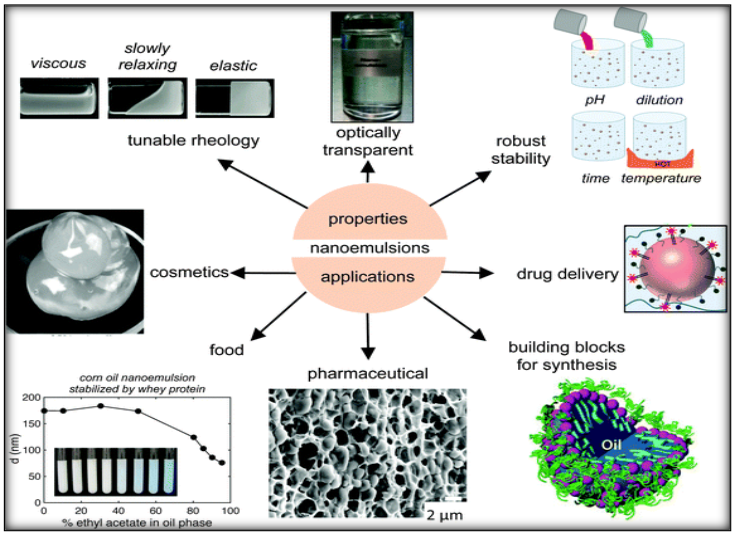

Figure no 01- Characteristics and Applications of Nanoemulsions

Applications and Functional Properties of Nanoemulsions

Droplet Size and Optical Properties

Nanoemulsions typically feature droplets with diameters around 100 nm. Due to their

small size, nanoemulsions often appear transparent, as the droplet size is significantly smaller than the wavelength of visible light. However, by tuning droplet size, nanoemulsions can range from transparent to milky white. Their strong stability, with shelf lives spanning months to years, and reduced sensitivity to pH, temperature, and dilution changes make them ideal for industries such as food and cosmetics.

Tunable Rheology

The rheological properties of nanoemulsions can be adjusted by altering droplet size, dispersed phase volume fraction, and additives like salts or depletion agents. Nanoemulsions can exhibit higher elasticity compared to macroemulsions, with elasticity values aligning with the Laplace pressure of an undeformed droplet. For instance, by modifying the number of passes through a high-pressure homogenizer (HPH), nanoemulsions can transition from a flowing fluid to a gel-like system. This tunable rheology is crucial in the cosmetics industry, where the product's texture and flow behavior influence consumer perception.

1. Nanoemulsions in Drug Delivery

Nanoemulsions are utilized across various drug delivery methods, including:

- **Topical:** The oil-in-water (O/W) continuous phase offers a gentle medium that can dissolve biopolymers like alginate to modify texture, while the dispersed phase improves solubility for lipophilic drugs. Studies indicate that nanoemulsions enable better permeation of hydrophobic drugs compared to suspensions.
- **Ophthalmic, Intravenous, Internasal, and Oral Routes:** Nanoemulsions enhance the bioavailability of water-insoluble drugs due to their lipophilic properties, tunable charge, and rheology.

2. Nanoemulsions in the Food Industry

Nanoemulsions enable the incorporation of poorly water-soluble bioactives into "smart foods." For example, nanoemulsions stabilize **β-carotene**, a health-benefiting pigment, using emulsifiers like β-lactoglobulin. Techniques such as evaporative ripening, microfluidization, and high-pressure homogenization have been employed to enhance bioaccessibility in digestive-like environments. Similarly, nanoemulsions have been used to deliver **curcumin**, an anti-inflammatory compound, effectively.

3. Nanoemulsions in Crystallization and Pharmaceuticals

Nanoemulsions facilitate size-controlled crystallization of poorly water-soluble APIs within a polymer matrix, offering an innovative approach to avoid polymorphic transitions and high-energy grinding. For example:

- APIs are encapsulated in nanosized anisole droplets within an alginate-based hydrogel matrix.
- Controlled evaporation of the hydrogel produces crystals with precise size (330 nm–420 µm) and high loading (up to 85% w/w).

This method offers a continuous, low-energy solution for pharmaceutical crystallization, addressing limitations of traditional techniques.

Techniques for Nanoemulsion Preparation:

Nanoemulsions are created using **high-energy** and **low-energy methods**, each offering unique benefits depending on the application as shown in figure 2. These methods influence the droplet size, stability, and overall properties of the nanoemulsion as shown in table 3.

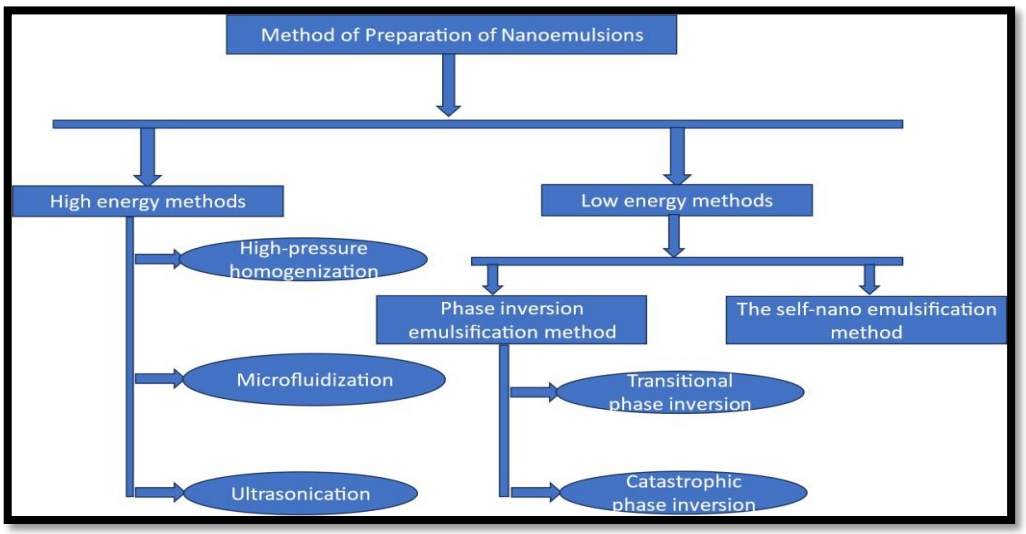

Fig no 02- Method of preparation of nano emulsion

High-Energy Methods:

High-energy techniques utilize mechanical energy to create intense disruptive forces, breaking larger droplets into nanoparticles. These methods ensure precise control

over droplet size, stability, and emulsions' rheological properties.

High-Pressure Homogenization

- Utilizes a piston or homogenizer to create nano-sized droplets (as small as 1 nm).
- Involves forcing the oil and aqueous phases through a small orifice under high pressure (500–5000 psi), resulting in intense turbulence and shear forces.
- Produces monomolecular layers of droplets with strong stability.
- **Key Factors:**
  - **Homogenization Pressure:** Typically ranges between 100 and 150 bars, influencing droplet size.
  - **Number of Cycles:** More cycles reduce particle size, monitored by the polydispersity index (PDI).
- **Drawbacks:** High energy consumption and temperature rise during processing.

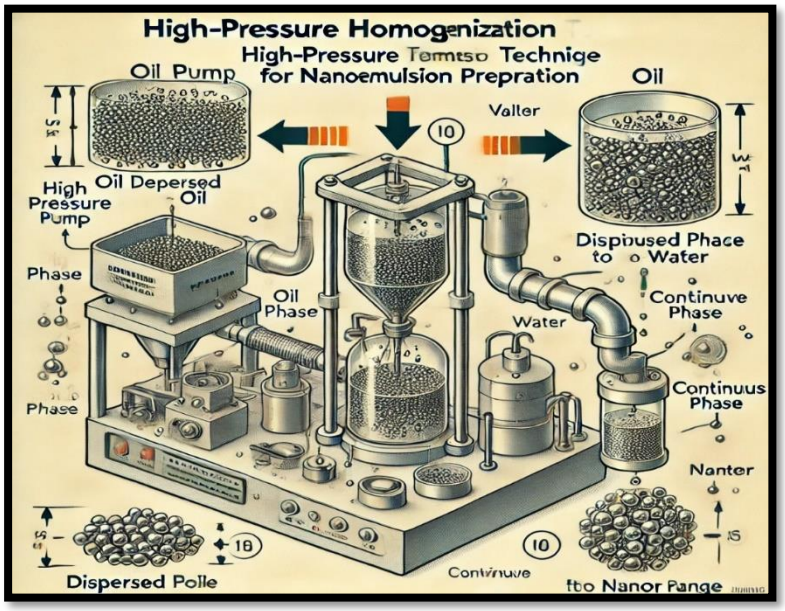

Fig no 03- High Pressure Homogenization

ii. Microfluidization

- Involves pushing fluids through microchannels at very high pressures (500–20,000 psi).

- Macroemulsions (oil and water phases) collide in an interaction chamber, generating forces like shearing and cavitation that form stable nanoemulsions as shown in figure 4.
- Produces smaller and more uniform droplets than homogenizers.Requires lower surfactant concentrations, making it ideal for food-grade applications.

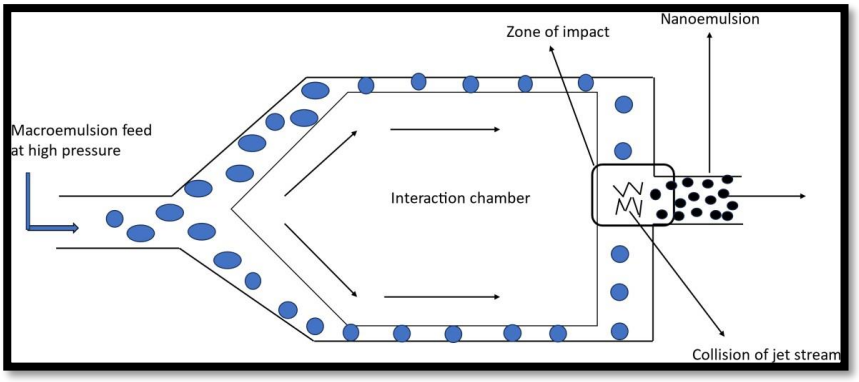

Fig no 4- Microfluidization process

iii. Ultrasonication

- Employs ultrasonic sound waves to reduce droplet size via cavitation forces.
- Cavitation bubbles collapse with high energy, producing stable nanoemulsions as shown in figure 5.
- The system includes a water jacket to maintain an optimal temperature during processing.

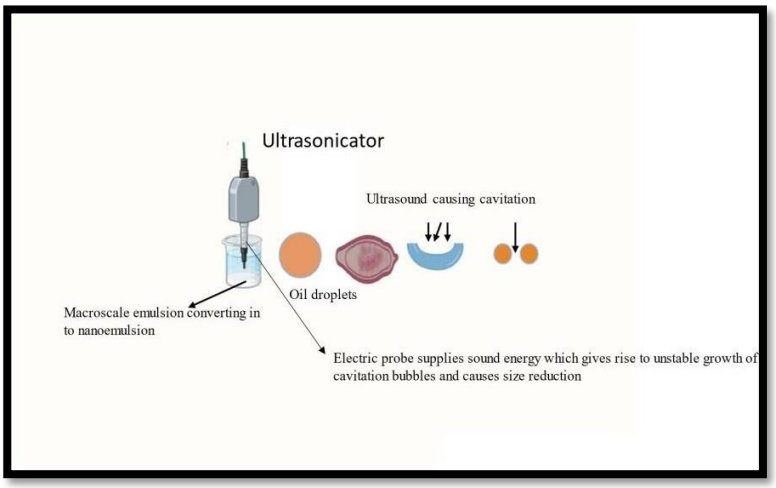

Fig no 5- Ultrasonication

2. Low-Energy Methods

Low-energy methods rely on the system's inherent chemical energy, requiring minimal external agitation. These methods include **phase inversion emulsification** and **self-emulsification**, commonly used for non-food applications due to the need for higher surfactant concentrations.

i. Phase Inversion Emulsification

- Relies on changes in the spontaneous curvature of surfactants induced by temperature or composition as shown in figure 6.
- Subcategories:
  - **Phase Inversion Temperature (PIT):** Uses temperature changes to transition between oil-in-water (O/W) and water-in-oil (W/O) emulsions.
  - **Phase Inversion Composition (PIC):** Gradual addition of water to an oil-emulsifier mixture creates kinetically stable nanoemulsions with droplets as small as 50 nm.

ii. Catastrophic Phase Inversion (CPI):

- Occurs by adding the dispersed phase to the continuous phase, resulting in sudden phase transitions.
- Leads to bicontinuous or lamellar structures when water is continuously added to an oil-emulsifier mixture under controlled stirring.

iii. Emulsion Inversion Point (EIP):

- A variation of CPI, where water droplets aggregate to achieve phase inversion.

iv. Self-Nano Emulsification (SNEDDS):

- Surfactant and co-solvent molecules rapidly migrate from the dispersed phase to the continuous phase, creating nanoemulsions.

- SNEDDS (Self-Nano Emulsifying Drug Delivery Systems) involve isotropic mixtures of oil, surfactant, co-surfactant, and drugs, forming nanoemulsions upon dilution in aqueous fluids as shown in figure 7.

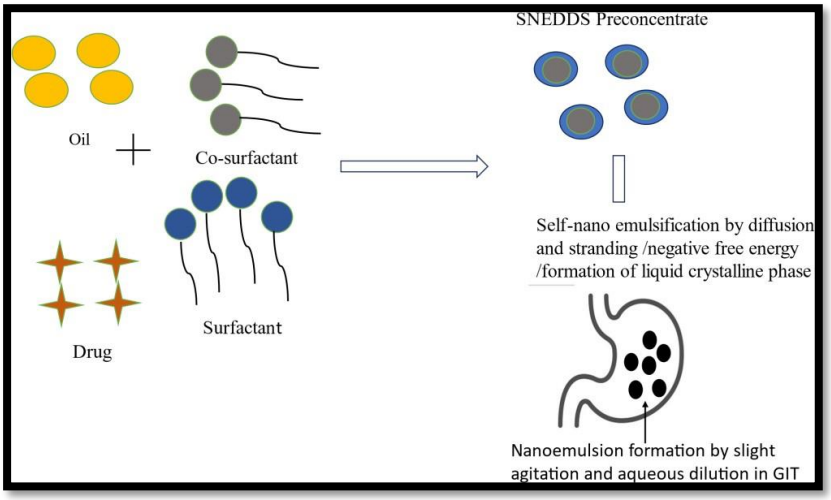

Fig no 06- Self nano emulsion

Table 3 Summery of technique of preparation for nanoemulsion

Method	Mechanism	Applications	Key Advantages	Limitations
High-Pressure Homogenization	High turbulence and shear forces	Pharmaceuticals, cosmetics	Very small droplet size; high stability	High energy consumption; heat generation
Microfluidization	High-pressure collision of macroemulsions	Food, cosmetics	Uniform particle distribution; low surfactant use	Complex equipment setup
Ultrasonication	Cavitation via ultrasonic sound waves	Pharmaceuticals, cosmetics	Precise size control	Requires temperature regulation
PIT (Low-Energy)	Temperature-induced phase transition	Non-food emulsions	Energy efficient	Requires high surfactant concentrations
PIC (Low-Energy)	Gradual addition of water to oil-emulsifier	Cosmetics, pharmaceuticals	Kinetic stability; fine droplet size	Thermodynamic instability
SNEDDS (Low-Energy)	Spontaneous nanoemulsification	Drug delivery	Simple preparation; clear O/W systems	Limited to hydrophilic drugs

Nanoemulsion Evaluation

1. Encapsulation Efficiency Determination

To determine the encapsulation efficiency (EE) of a nanoemulsion, the drug is extracted into a suitable buffer after ultrasonically dispersing a weighed quantity of the formulation in an organic solvent. The extract is spectrophotometrically analyzed at the drug's λmax after proper dilution against a blank. Encapsulation efficiency (EE) and loading efficiency (LE) are calculated using the formulas:

- **LE (%)** = (Drug content in product (mg) / Total product weight (mg)) × 100
- **EE (%)** = (Drug content in product (mg) / Total drug added (mg)) × 100

Alternatively, reverse-phase high-performance liquid chromatography (HPLC) can also be used to determine drug content, as demonstrated by Singh et al., who reported a 95% encapsulation efficiency for primaquine.

2. Particle Size and Polydispersity Index (PDI) Determination

Photon correlation spectroscopy (PCS), typically using a Malvern Zetasizer, is employed to measure particle size and PDI by analyzing the changes in light scattering caused by Brownian motion. PCS calculates particle size based on the correlation of fluctuations in laser scattering intensity, producing a histogram of line width distribution corresponding to particle size.

3. Zeta Potential Determination

The zeta potential is a measure of the surface charge of particles in a dispersion, predicting stability. Nanoemulsions are diluted and assessed using the Malvern Zetasizer, which measures electrophoretic mobility. A zeta potential of ±30 mV or higher is indicative of good stability. For example, Đorđević et al. reported a zeta potential of -50 mV for a risperidone nanoemulsion, ensuring its stability.

4. **In Vitro Drug Release Study**

In vitro drug release studies evaluate nanoemulsion performance. A USP dissolution apparatus is used, and formulations are enclosed in dialysis membranes placed in a dissolution medium. The study is conducted at 37±0.5°C with samples withdrawn at intervals, diluted, and analyzed spectrophotometrically to calculate drug release percentages over time.

5. **In Vitro Skin Permeation Studies**

Using Keshary-Chien diffusion cells, skin permeation studies are conducted with rat abdominal skin as a barrier between donor and receptor chambers. The receptor chamber, containing a buffer solution, is maintained at 37°C and stirred at 300 rpm. Samples from the receptor chamber are periodically withdrawn, replaced with fresh solution, and analyzed, often by gas chromatography.

6. **Stability Studies**

Stability studies assess nanoemulsion resilience under different environmental conditions as per ICH guidelines. Samples stored at freeze (-20±5°C), refrigeration (5±3°C), and ambient (25±2°C/60±5% RH) conditions are examined over time for encapsulation efficiency, particle size, and drug release profiles. Singh et al. demonstrated that nanoemulsions retained their viscosity, drug content, and particle size during stability tests.

Conductance Measurement

Conductivity studies differentiate between oil-in-water (O/W) and water-in-oil (W/O) nanoemulsions. O/W emulsions exhibit high conductivity, while W/O emulsions are non-conductive. Phase inversion and droplet interactions can be detected using a conductometer to measure changes in conductivity.

7. **In Vivo Studies**

In vivo studies utilize animal models tailored to the drug's therapeutic activity. For instance, Srilatha et al. used diabetic rat models to study the antidiabetic effects of

glipizide nanoemulsions, observing significant glucose level reductions over 12 hours. Pharmacokinetic studies also show that atorvastatin nanoemulsions have improved bioavailability compared to the pure drug.

8. **Refractive Index Measurement**

The refractive index, indicative of transparency and light transmission, is measured using an Abbe refractometer at 25±0.5°C. A nanoemulsion is considered transparent if its refractive index matches water (1.333). Harika et al. reported that the amphotericin B nanoemulsion had a comparable refractive index, confirming its optical clarity. Nanoemulsions offer promising potential as efficient drug delivery systems, capable of enhancing drug bioavailability and therapeutic outcomes under various evaluation parameters.

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CHAPTER NO 19- NANO SUSPENSION

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Introduction:

In the evolving field of pharmaceutical science, nanosuspensions have emerged as a revolutionary approach to drug delivery. A nanosuspension is a submicron colloidal dispersion of solid drug particles within an aqueous medium, with particle sizes below 1 μm. These finely dispersed systems are stabilized using surfactants and polymers and produced using specialized techniques. Their versatility allows for application across multiple administration routes, including oral, topical, parenteral, ocular, and pulmonary, making them a highly adaptable tool in modern therapeutics.

The primary advantage of nanosuspensions lies in their ability to address challenges associated with poor solubility and limited bioavailability of drugs. By modifying the pharmacokinetics of a drug, nanosuspensions enhance its safety and efficacy. This approach is particularly beneficial for compounds characterized by high log P values, elevated melting points, and large dose requirements, which are otherwise difficult to formulate using traditional methods.

Nanosuspensions also offer the potential to reduce conventional oral dosages by improving adsorption and absorption rates. Fundamental principles, such as the Nernst-Brunner & Levich adaptation of the Noyes-Whitney equation, underscore this advantage by demonstrating how a reduction in particle size increases the surface area and dissolution rate. Additionally, the Ostwald-Freundlich equation illustrates how smaller particle sizes elevate dissolution pressure, further enhancing saturation solubility. Depending on the production method, nanosuspensions may alter the crystalline structure of drug particles, increasing their amorphous fraction and solubility.

Another notable characteristic of nanosuspensions is the inherent adhesiveness of nanoparticles, which facilitates better tissue interaction and promotes effective drug

delivery. Importantly, nanosuspensions differ from other nanoparticulate systems such as solid lipid nanoparticles and polymeric colloidal drug carriers. While solid lipid nanoparticles involve lipidic matrices and maintain drugs in a lipid form, nanosuspensions retain the drug in a crystalline or amorphous state to optimize dissolution and bioavailability.

This chapter explores the transformative potential of nanosuspension technology in improving the dissolution, absorption, and overall efficacy of challenging drug molecules, including "brick dust" compounds with poor solubility profiles. By leveraging these systems, pharmaceutical research can achieve significant advancements in developing more effective and patient-friendly therapeutic options.

Background of Nanosuspensions in Pharmaceutical Development-

The increasing prevalence of poorly water-soluble drugs has posed significant challenges in pharmaceutical formulation. Over 40% of active pharmaceutical ingredients (APIs) exhibit poor solubility in water, creating difficulties in developing effective traditional dosage forms. This issue is especially pronounced for Biopharmaceutics Classification System (BCS) Class II drugs, which exhibit low solubility in both aqueous and organic solvents. For compounds with high log P values—insoluble in water but soluble in oils—formulation as nanosuspensions has emerged as a promising solution.

Early Challenges in Solubility and Bioavailability-

Traditional strategies to enhance solubility and bioavailability include co-solvency, salt formation, liposomal systems, emulsions, and solid dispersions. While effective for some APIs, these methods often prove unsuitable for drugs with unique physiochemical properties, including high melting points, high doses, and complex permeability issues. Furthermore, weakly water-soluble drugs often exhibit challenges such as poor bioavailability, unpredictable dose-response relationships, and fed/fasted variability, limiting their therapeutic effectiveness.

Nano suspensions as a Formulation Breakthrough-

Nanosuspensions were developed as a versatile formulation approach to address

these limitations. By reducing drug particles to the nanometer range (below 1 μm), nanosuspensions improve solubility and dissolution rates, thereby enhancing bioavailability. Unlike lipid-based systems, nanosuspensions maintain the drug in a stable crystalline or amorphous state, effectively increasing the rate of dissolution while avoiding the use of harsh excipients. Additionally, they allow for rapid drug release, achieving maximal plasma levels quickly, which is especially advantageous for oral and intravenous applications.

Evolution of Nanosuspension Technology

1. **Initial Exploration of Nanoscale Drug Delivery**
   In the 1980s and early 1990s, researchers began exploring nanoscale particle reduction as a means to enhance drug solubility. Early work demonstrated that smaller particles resulted in higher surface area-to-volume ratios, boosting dissolution rates and bioavailability.
2. **Development of Stable Nanosuspensions**
   By the late 1990s, stable nanosuspensions were introduced as a liquid-phase suspension of nanoscale drug particles. Techniques such as high-pressure homogenization, wet milling, and precipitation were optimized to produce uniform, stable nanosuspensions that resisted aggregation.
3. **Commercial Success and FDA Approvals**
   The early 2000s marked a significant milestone with FDA approval of nanosuspension-based drugs. Rapamune (sirolimus), approved in 2000, was the first commercial nanosuspension formulation designed to improve bioavailability. Other successful examples, such as Emend (aprepitant) and Tricor (fenofibrate), showcased the commercial viability of nanosuspension technology.
4. **Technological Advancements and Expanded Applications**
   Innovations such as spray drying and supercritical fluid techniques further improved the stability and efficiency of nanosuspensions. Beyond solubility enhancement, nanosuspensions have been employed for targeted drug delivery, particularly in oncology and immunotherapy, where precise delivery can minimize side effects and optimize therapeutic outcomes.
5. **Contemporary Uses in Advanced Therapies**
   Nanosuspensions now extend beyond conventional small-molecule drugs to include gene therapies, vaccines, and biologics. Their ability to stabilize complex molecules

has opened new avenues for delivering therapeutic agents in fields such as oncology, infectious diseases, and personalized medicine.

Importance to study:

The study of nanosuspensions holds critical importance in the development of novel drug delivery systems (NDDS), which are designed to enhance therapeutic efficacy by improving drug stability, solubility, and targeted delivery. Traditional drug delivery methods often fail to achieve optimal bioavailability due to challenges such as poor solubility, rapid metabolism, or systemic side effects. Nanosuspensions, as a specialized form of NDDS, address these limitations by reducing drug particle size to the nanometer scale, thereby overcoming solubility challenges and significantly enhancing drug dissolution and absorption.

1. **Enhancing Bioavailability**

   Nanosuspensions improve bioavailability by increasing the surface area of drug particles, which accelerates dissolution and absorption. This property is particularly crucial for drugs with low aqueous solubility, allowing for more efficient therapeutic action. By encapsulating drugs in stable nanoscale suspensions, the risk of degradation during absorption is minimized, ensuring that the active pharmaceutical ingredients (APIs) are delivered effectively to their target sites.

2. **Targeted and Controlled Drug Delivery**

   One of the defining features of nanosuspension-based systems is their ability to provide controlled and targeted drug delivery. By modifying particle characteristics, these systems can be engineered to release drugs at specific sites or over extended periods, reducing the frequency of dosing and improving patient compliance. For example, in oncology, nanosuspensions can concentrate anticancer agents in tumor tissues while minimizing exposure to healthy cells, thereby reducing systemic toxicity and enhancing therapeutic outcomes.

3. **Addressing Complex Diseases**

   Complex diseases such as cancer, neurological disorders, and inflammatory conditions require advanced drug delivery strategies. Nanosuspensions offer the ability to co-deliver multiple therapeutic agents or combine drugs with targeting biomolecules like antibodies, making them indispensable for treating conditions where single-drug regimens are insufficient. Their versatility also allows for

incorporation into multi-modal therapies, improving specificity and efficacy.

4. **Customization and Personalization**

   The shift toward personalized medicine demands drug delivery systems that can be tailored to individual patient profiles. Nanosuspensions offer flexibility in formulation, allowing for customization based on factors such as genetic predisposition, disease severity, and patient preferences. Furthermore, advancements in artificial intelligence and data analytics enable nanosuspensions to be optimized for personalized dosage regimens, maximizing therapeutic benefits while minimizing risks.

5. **Economic and Healthcare Impact**

   By enhancing the solubility and bioavailability of drugs, nanosuspensions can reduce the dosage required and minimize side effects, leading to improved treatment adherence and fewer hospitalizations. This reduction in treatment-related complications translates into significant cost savings for healthcare systems. Additionally, their potential to repurpose poorly soluble drugs into effective formulations extends the lifespan and utility of existing pharmaceuticals, providing economic benefits to both patients and healthcare providers.

6. **Driving Technological Innovation**

   The field of nanosuspensions exemplifies how emerging technologies such as nanotechnology, smart polymers, and 3D printing can revolutionize drug delivery. These innovations enable the creation of dynamic systems capable of responding to environmental stimuli, such as pH or temperature, for enhanced drug release profiles. For instance, nanosuspensions incorporated into gastroprotective drug delivery systems can delay drug release for improved absorption, catering to specific therapeutic needs.

Technique for the formulation:

In pharmaceutical research, a range of techniques has been developed to formulate nanosuspensions, offering a more economical and technically straightforward alternative to traditional colloidal drug carriers such as liposomes. These methods are particularly suited for poorly soluble drugs and aim to produce physically stable formulations. The approaches can be broadly classified into **top-down**, **bottom-up**, and **hybrid** strategies, each with unique mechanisms and applications as shown in

figure no. 1.

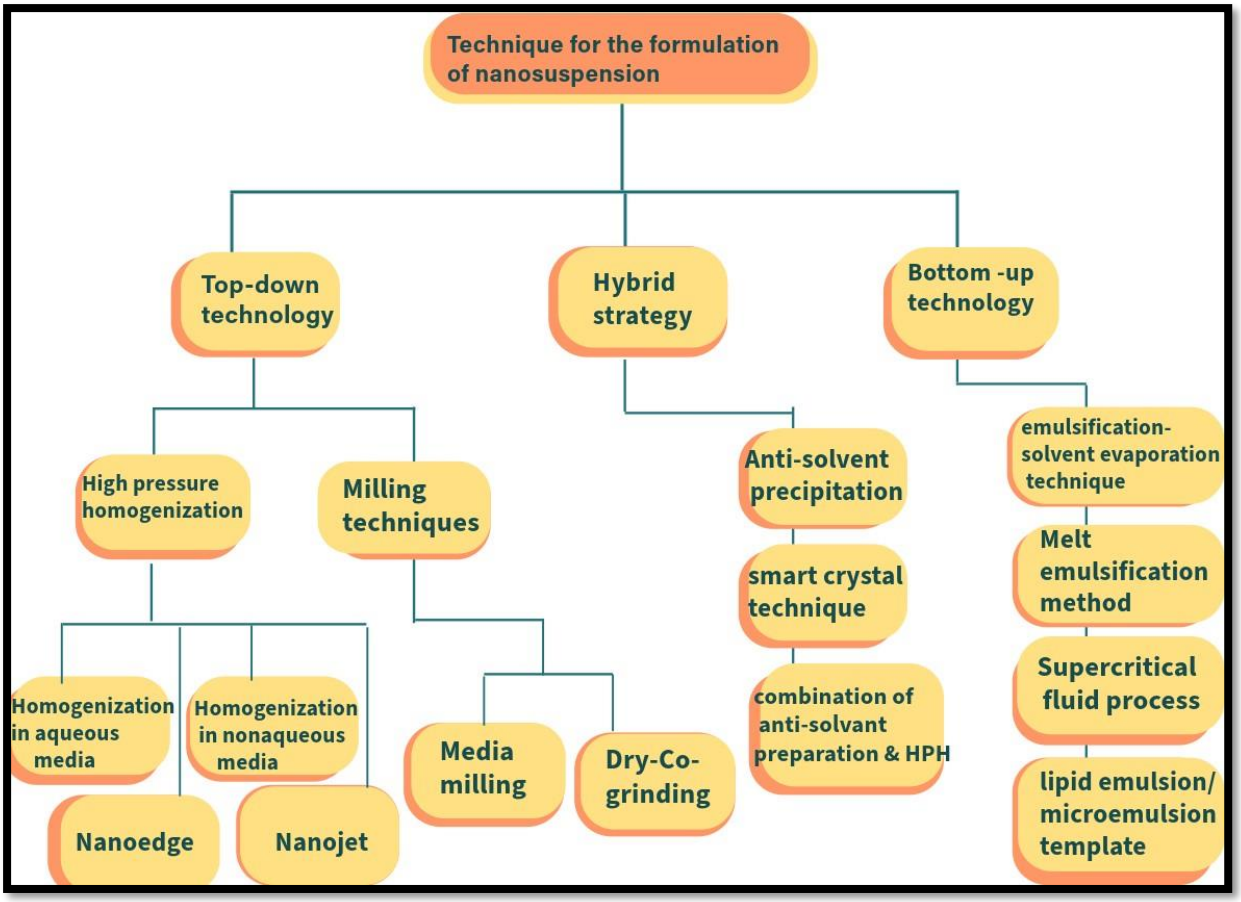

Fig no 01- Flowchart of Nanosuspension Formulation Techniques

1. Top-Down Technology

This approach involves breaking down larger drug particles into nanosized particles using physical or mechanical forces. Key methods include:

- **Wet Milling**: Wet milling is a widely employed technique for producing nanosuspensions of poorly water-soluble drugs. This process involves particle size reduction using grinding media in a liquid medium, typically comprising stabilizers and dispersants. Wet milling is particularly favored for its efficiency, scalability, and ability to achieve uniform and ultra-fine particle sizes, making it an essential tool in pharmaceutical formulation development.

❖ **Principles of Wet Milling**

The technique leverages mechanical forces generated by the grinding media within a milling chamber. These forces include:

Shear Forces: Caused by the movement of the grinding media.

Impact Forces: Generated when grinding media collide with drug particles. These forces collectively break down drug particles to nanoscale dimensions. The presence of stabilizers prevents particle agglomeration, ensuring a uniform suspension.

❖ **Process of Wet Milling**

There are multiple step of wet milling process as shown in figure 2:

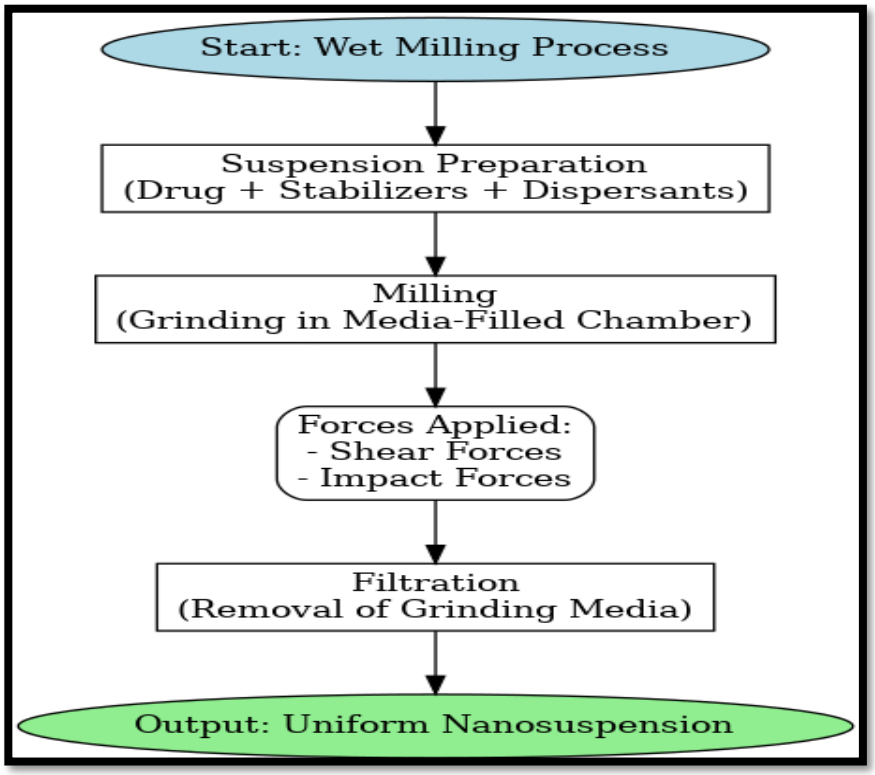

Fig no 02- Flow chart on wet milling process

Preparation of the Suspension: Drug particles are suspended in a liquid medium containing stabilizers and dispersants.

Milling: The suspension is passed through a milling chamber filled with grinding media (e.g., zirconium oxide or glass beads).

Energy Application: Mechanical energy from the milling machine drives the grinding media to break down drug particles.

Filtration: Post-milling, the suspension is filtered to remove grinding media and achieve the desired product.

Types of Wet Milling Techniques

Ball Milling: Uses rotating cylinders partially filled with grinding media and the drug suspension.

Bead Milling: Involves smaller grinding media in a stirred milling chamber, providing high energy for efficient particle size reduction.

Applications of Wet Milling

Production of nanosuspensions for poorly water-soluble drugs.

Improvement of bioavailability and dissolution rates.

Generation of suspensions with narrow particle size distributions for drug delivery systems.

Advantages

Effective Particle Size Reduction: Produces particles in the nanoscale range.

Scalable: Adaptable for small-scale R&D or large-scale production.

Versatility: Can process a wide variety of drugs and formulations.

Disadvantages

Time-Consuming: Requires prolonged processing for certain drugs.

Potential Contamination: Grinding media may introduce impurities.

Heat Generation: Excessive heat can degrade thermolabile drugs.

Stabilizers in Wet Milling

The choice of stabilizers is crucial in preventing particle agglomeration and maintaining nanosuspension stability. Commonly used stabilizers include:

Polymers: Polyvinylpyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC).

Surfactants: Poloxamers, Lecithin.

Case Studies and Commercial Applications

Fenofibrate Nanosuspensions: Improved dissolution and bioavailability using bead milling.

Amphotericin B Nanosuspensions: Enhanced antifungal activity and reduced toxicity.

High-Pressure Homogenization (HPH): **Overview**: Developed by H. Müller in 1999, this technique utilizes a piston-gap high-pressure homogenizer to process drug-surfactant suspensions. The formulation is passed through a nanosized aperture valve under high pressure, leading to particle size reduction.

Principle:

This method is based on the cavitation phenomenon. According to Bernoulli's law, the flow volume of a liquid through a system is constant. As the suspension is forced through a 25 µm aperture from a 3 cm-wide cylinder, dynamic pressure increases, and static pressure falls below the boiling point of water at room

temperature. This causes water to boil, forming gas bubbles. When the suspension exits the gap and pressure normalizes, these bubbles collapse (cavitation), generating forces strong enough to reduce drug microparticles to nanoparticles as shown in figure 3.

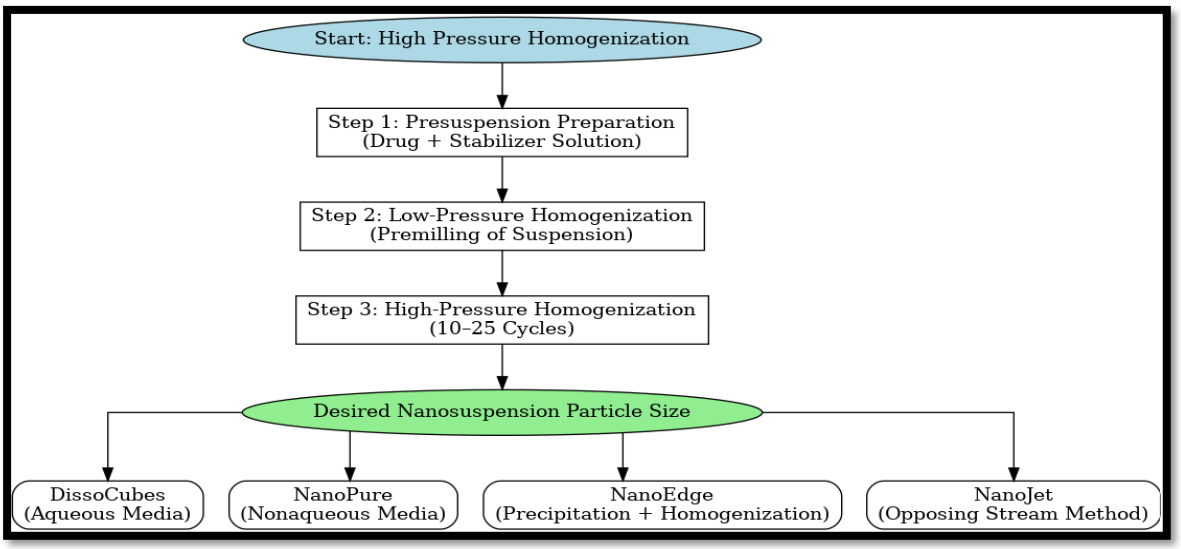

Fig no 03- Flow chart for High-pressure Homogenization.

Advantages:

Does not erode processing materials.

Suitable for drugs poorly soluble in aqueous and organic media.

Disadvantages:

Requires preprocessing (e.g., drug micronization).

Involves costly equipment, increasing formulation costs.

Smart Crystal Technology:

The method leverages the advantages of both wet milling and high-pressure homogenization to achieve:

Effective Particle Size Reduction: Initial size reduction is achieved via wet milling.

Enhanced Uniformity: High-pressure homogenization further reduces particle size and polydispersity, ensuring uniformity.

The dual-step process results in high-quality nanosuspensions with enhanced stability, bioavailability, and suitability for topical applications.

Process of Smart Crystal Technology

1. **Wet Milling Stage**:
   - Drug particles are reduced in size using grinding media in a stabilizer-rich liquid

medium.

- This step ensures an initial reduction to the micron or submicron range.

2. **High-Pressure Homogenization Stage**:

- The pre-milled suspension is subjected to high-pressure homogenization, typically 10–25 cycles.
- Forces like cavitation and shear further refine the particles to the nanoscale range.

Advantages of Smart Crystal Technology

1. **Enhanced Uniformity**: Produces highly uniform nanosuspensions with narrow particle size distributions.
2. **Improved Stability**: Reduced risk of particle aggregation due to synergistic processing.
3. **Topical Suitability**: Ideal for formulations requiring high dispersion stability and skin permeability.

Applications

1. **Topical Drug Delivery**: Enhances drug penetration through the skin, making it highly effective for dermatological applications.
2. **Ocular and Mucosal Delivery**: Smart Crystal Technology improves the stability and bioavailability of drugs for sensitive application sites.
3. **Poorly Soluble Drugs**: Widely applied in the formulation of hydrophobic compounds requiring nanoscale delivery systems.

Melt Emulsification and Emulsification-Solvent Evaporation: Techniques that use emulsions as intermediates to reduce particle size further.

✓ **Melt Emulsification**

Melt emulsification involves melting a hydrophobic drug and dispersing it in a heated aqueous stabilizer solution to form an emulsion. Upon cooling, the emulsion solidifies into nanosized particles.

Process

1. Melting: The drug is melted, typically at temperatures above its melting point.
2. Emulsification: The molten drug is emulsified in an aqueous stabilizer solution using high-shear mixing.
3. Cooling: The emulsion is cooled rapidly, leading to solidification of the drug into

nanosized particles.

Advantages

1. Solvent-Free: Avoids organic solvents, making it eco-friendly.
2. Simple Process: Requires minimal processing steps.

Limitations

1. Temperature Sensitivity: Unsuitable for thermolabile drugs.
2. Limited Drug Load: Effective only for drugs with low melting points.

✓ **Emulsification-Solvent Evaporation**

In this technique, the drug is dissolved in a volatile organic solvent, and an emulsion is formed with an aqueous stabilizer phase. As the solvent evaporates, the drug precipitates into nanosized particles.

Process

1. Preparation of Drug Solution: The drug is dissolved in a volatile solvent like dichloromethane.
2. Emulsion Formation: The drug solution is emulsified into an aqueous phase using high-shear mixers.
3. Solvent Evaporation: The organic solvent is removed by evaporation, leaving behind nanosized drug particles.

Advantages

1. Versatile: Applicable to a wide range of drugs.
2. Controlled Particle Size: Emulsification enables precise control over particle size distribution.

Limitations

1. Use of Organic Solvents: May pose safety and environmental concerns.
2. Residual Solvent: Requires careful removal to ensure drug purity.

Applications of Emulsion-Based Techniques

1. Hydrophobic Drugs: Effective for reducing particle size in poorly water-soluble drugs.
2. Controlled Drug Release: Emulsion techniques allow for encapsulation, aiding sustained-release formulations.
3. Pulmonary and Oral Delivery: Used in nanosuspensions for targeted drug delivery.

Supercritical Fluid Technologies:

Supercritical fluid (SCF) technologies are effective for producing fine particles,

including nanosuspensions, by leveraging the unique properties of supercritical fluids like carbon dioxide (CO_2). These methods use rapid expansion or antisolvent precipitation to achieve nanoscale particle sizes and are valued for their minimal use of harmful solvents.

Principle of Supercritical Fluids

A supercritical fluid exists above its critical temperature and pressure, displaying properties of both liquids and gases. These properties allow SCFs to dissolve substances and then rapidly precipitate particles through specific processes.

Techniques in SCF Technologies

1. Rapid Expansion of Supercritical Solutions (RESS)

In RESS, the drug is dissolved in a supercritical fluid, typically CO_2. The solution is then rapidly expanded through a nozzle into a low-pressure environment. This rapid expansion causes a sudden drop in solubility, resulting in precipitation of fine particles.

Steps:

1. Dissolve the drug in supercritical CO_2.
2. Expand the solution rapidly through a nozzle.
3. Collect the precipitated particles.

❖ **Advantages**:

- Solvent-free process.
- Produces uniform particles.

Limitations:

- Limited to drugs soluble in supercritical CO_2.

2. **Supercritical Antisolvent (SAS) Precipitation**

SAS uses a supercritical fluid as an antisolvent. The drug is dissolved in an organic solvent, and the supercritical fluid is introduced. The interaction between the solvent and SCF causes rapid precipitation of the drug.

Steps:

1. Dissolve the drug in a volatile solvent.
2. Introduce SCF as an antisolvent.
3. Collect the precipitated particles.

Advantages:

- Suitable for a variety of drugs.

- Produces stable, nanosized particles.

Limitations:

- Requires careful control of operating conditions.

❖ **Applications**

- Pulmonary Drug Delivery: Produces fine particles suitable for inhalation therapies.
- Poorly Soluble Drugs: Enhances solubility and bioavailability of hydrophobic drugs.
- Sustained Release Systems: Provides controlled release through particle size optimization

2. Bottom-Up Technology

This method builds nanosized drug particles from molecular or atomic levels using precipitation techniques as shown in figure 4. Examples include:

- **Antisolvent Precipitation**: A solvent containing the drug is rapidly mixed with a nonsolvent, causing the drug to precipitate as nanoparticles.
- **Spray Drying**: Converts a solution of the drug into nanoparticles through rapid solvent evaporation.

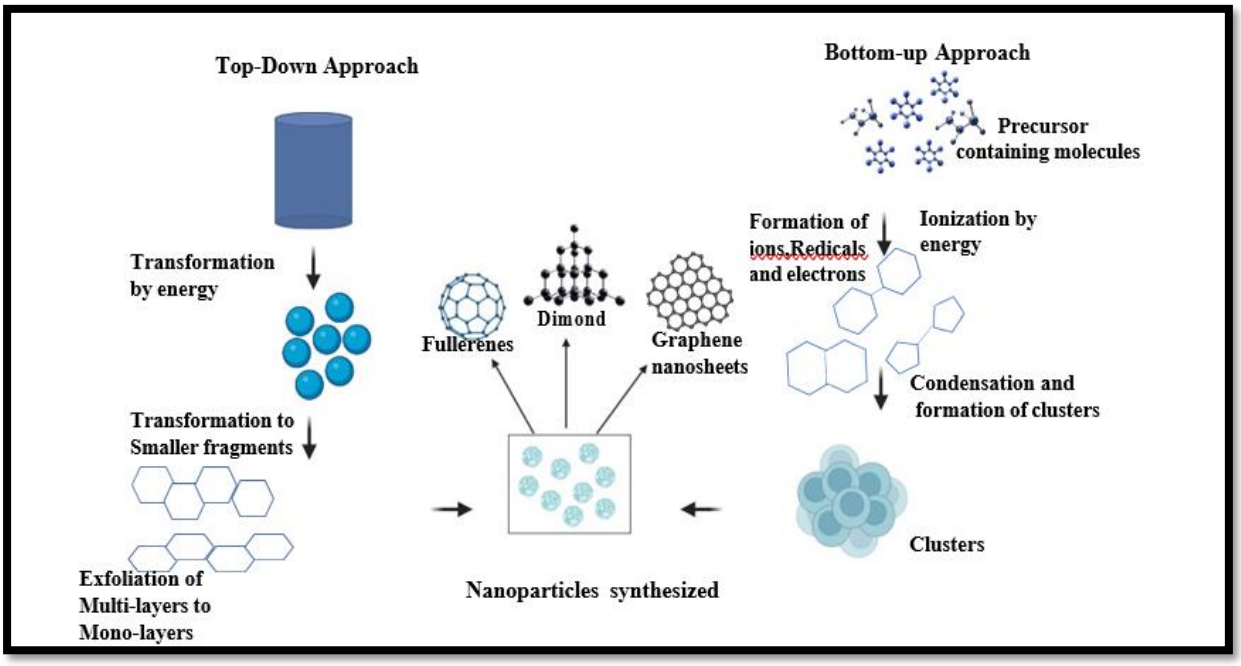

Fig no 04- Nanoparticle synthesis by top-down approach and bottom-up approach

3. Hybrid Strategies

Hybrid approaches combine aspects of top-down and bottom-up technologies to maximize efficiency and stability. For instance:

- **HPH with Antisolvent Precipitation**: Precipitated drug particles are further processed through homogenization for better particle size control and stabilization.

These versatile techniques allow the formulation of nanosuspensions tailored for various routes of administration, including oral, injectable, topical, and pulmonary. The choice of method depends on the physicochemical properties of the drug and the intended therapeutic application, making nanosuspensions a critical tool in modern pharmaceutical formulation.

Evaluation:

Evaluating the effectiveness of nanosuspension techniques requires a systematic approach to assess key parameters, ensuring the final product meets pharmaceutical quality standards. Below is a detailed evaluation framework with corresponding specifications for critical parameters:

1. Particle Size and Size Distribution

- **Specification**:

Mean particle size: < 500 nm for nanosuspensions.

Polydispersity index (PDI): ≤ 0.2 for uniform distribution.

Evaluation Method:

Dynamic Light Scattering (DLS): Measures size and PDI.

Electron Microscopy (SEM/TEM): Confirms morphology and nanoscale size.

2. Zeta Potential

Specification:

Zeta potential: ≥ ±30 mV for stable suspensions (to ensure repulsion between particles and prevent aggregation).

Evaluation Method:

Electrophoretic Light Scattering: Measures surface charge of nanoparticles.

3. Crystallinity and Polymorphism

Specification:

Drug should retain its crystalline or amorphous state, depending on formulation goals.

Evaluation Method:

X-Ray Diffraction (XRD): Analyzes crystalline structure.

Differential Scanning Calorimetry (DSC): Determines melting point and phase

transitions.

4. Saturation Solubility

Specification:

Enhanced solubility compared to bulk drug by ≥ 2- to 5-fold.

Evaluation Method:

Equilibrium Solubility Testing: Measures solubility in aqueous and nonaqueous media.

Drug Content and Encapsulation Efficiency

Specification:

Drug content: ≥ 90% of labeled claim.

Encapsulation efficiency: > 80% for successful formulations.

Evaluation Method:

HPLC/UV Spectroscopy: Quantifies drug concentration.

6. Stability

Specification:

No significant change in particle size, PDI, or zeta potential over 3–6 months.

Chemical stability: No degradation of the drug.

Evaluation Method:

Accelerated Stability Testing: Storage under stress conditions (e.g., 40°C ± 2°C, 75% RH).

Freeze-Thaw Cycles: Evaluates resistance to temperature fluctuations.

7. Dissolution Rate

Specification:

Enhanced dissolution rate compared to bulk drug.

At least 80% drug release within 30 minutes.

Evaluation Method:

USP Dissolution Apparatus: Monitors drug release profiles.

8. Morphology and Surface Properties

Specification:

Uniform, spherical particles with no visible aggregates.

Evaluation Method:

SEM/TEM Imaging: Visual inspection of particle shape and surface characteristics.

9. In Vitro and In Vivo Performance

Specification:

Enhanced bioavailability compared to conventional drug forms.

Consistent pharmacokinetic profiles.

Evaluation Method:

In Vitro Studies: Drug permeability and cellular uptake tests.

In Vivo Studies: Pharmacokinetic evaluations in animal models.

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