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REVIEW ARTICLE

Nanoemulgel: An Innovative Carrier for Drug Delivery of Poorly Water-Soluble Drugs

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Abstract: Recently, the delivery of hydrophobic/ poorly water-soluble drugs has been a difficult task. Various approaches have been developed to counter the former and other main issues, such as solubility, bioavailability, *etc.* However, only a few formulations have successfully addressed the problems and nanoemulgels are a standout among them. The nanoemulgel drug delivery approach combines multiple benefits associated with emulsion and gel technologies to improve active moiety solubility, bioavailability, and longevity. The article discusses the present status of nanoemulgel research and development, including its preparation methods and characterization techniques. Additionally, the possible uses of nanoemulgel in targeted drug delivery and cosmetic/ personal care products are discussed. Overall, nanoemulgel technology has shown significant promise as a novel approach to augment the transport of water-insoluble moieties. With further research as well as development, it is expected to have a substantial impact on the pharmaceutical and cosmetic industries. This inclusive review highlighted the role of nanoemulgels as a promising carrier for drug delivery, with an overview of a few illustrations supporting the cause.

Keywords: Nanoemulgel, topical drug delivery, lipophilic drug, absorption enhancer, permeability.

1. INTRODUCTION

Comprehensive research in developing chemical synthesis techniques has resulted in a large increase in the production of drugs that are not readily soluble in water [1]. According to the latest data, around 70% of novel chemical entities (NCEs) are insoluble in water [2]. A drug delivery system is a multidisciplinary approach to the delivery of therapeutics to the target tissue, which gives new ideas on controlling the pharmacokinetics, pharmacodynamics, immunogenicity, bio-recognition, non-specific toxicity, and efficacy of the drug. These recently created drugs are challenging to administer orally due to their hydrophobic characteristics. Their characteristics include limited ingestion bioavailability, variable assimilation processes, and intra- and intersubjective pharmacokinetic heterogeneity [3]. Researchers have devised numerous techniques to circumvent the restrictions of poor solubility and biological availability. Alternative means of delivery of formulation design and synthetic or physical altering of drug molecules can be employed to resolve the absorption of drug problems. Despite their numerous ways to administer drug methodologies, lipid-based drug delivery has attracted much interest in hydrophobic drug delivery. Its components include macroemulsion, nanoemulsion, niosomes, self-emulsifying formulation, liposomes, solid-lipid nanoparticles, and more. Within various composition alternatives, emulsion-based preparation is a commercially viable way to overcome the constraint of poor absorption [4]. Nanoemulsions can improve dermal drug absorption, enhancing the absorption rate and penetration of hydrophobic drugs, making them a viable alternative for drug delivery approach [5]. Although the oral route increases patient compliance, it has significant downsides, including gastrointestinal irritation, unavoidable adverse effects, extensive poisoning, and first-pass liver metabolism [6]. To circumvent any of such concerns, a soothing, easy, and subtle topical drug delivery method may be an acceptable option. This offers multiple benefits above the ingestion route, including targeted drug distribution resulting in lower systemic adverse reactions, minimal gastrointestinal discomfort, bypass of the first-pass metabolic process, and enhanced drug absorption [7, 8]. Indigenous topical formulations, such as lotions, creams, and ointments, have a viscous nature, durability concerns, limited spreadability, and other limitations that impair patient compliance. Advanced transdermal preparations, such as clear gel, nano gel, and (micro/nano) emulgel, enhance patient compliance and formulation efficiency, durability, and tolerability. Numerous investigations indicate that topically applied medication strategies enhance drug absorption [9, 10]. The usual epidermal approach is approximately three times more effective than ingestion regarding lacidipine bioavailability. This could be because the therapy avoids the metabolic process's first-pass [9].

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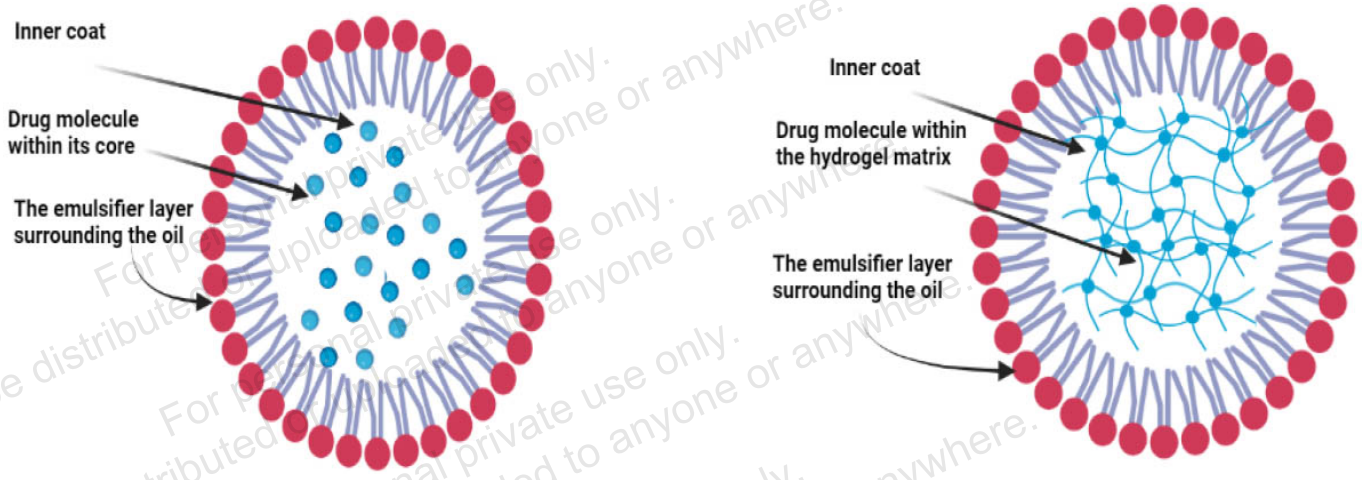

Fig. (1). Structure of nanoemulsion and nanoemulgel. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Bhaskar and colleagues reported in another study that flurbiprofen topical nanoemulsion has 4.4 times the biological efficacy of oral administration [10]. Thus, a topical drug delivery system can boost a lipophilic drug's biological efficacy. Topical application enhances penetration over the skin by enabling the drug to endure in a constant state for an extended period [9].

1.1. Topical Application of an Emulsion-based Nanocarrier

Hydrophobic drug administration poses an essential obstacle with standard transdermal delivery systems due to its limited effectiveness in therapy and low membrane penetration. According to research, nanoscale-sized transdermal preparations may enhance drug penetration by influencing the structure of the skin's double layer of lipids [11] and prolonging the active moiety residence time frame at the targeted spot [12, 13]. Nanoemulsion serves as an envisaged technique for transporting lipophilic pharmaceuticals. It has more mechanical durability and drug-dissolution ability than emulsion and other diffusion methods. The process also has an extended lifespan, requiring minimal external power [14]. A nanoemulsion is a dispersion system developed from nanoscale-sized (20-200 nm width) tiny drops of an agent in a phase consisting of water in addition to oil stabilized by an acceptable emulsifier. As illustrated by Fig. (**1**), the active ingredient gets trapped inside, thereby being associated with a surfactant layer. Permeation enhancers are typically superfluous when utilizing nanoemulsion as a vehicle for the transport of water-phobic pharmaceuticals [15]. It is more stable because it is less prone to phase separation than other widely used emulsions [16]. Some experiments have revealed that nanoemulsion delivery techniques efficiently transfer drugs into the skin more effectively than conventional ointments [17], creams [18], gels [19], and emulsions [20]. The process can disperse all water-resistant and water-loving drugs in its molecular makeup, depending on whether the nanoemulsion is oil mixed with water or water mixed with oil [21].

Despite its multiple advantages, nanoemulsion has a poor spreading coefficient, viscosity, and adhesion to the skin [22]. As an outcome of these issues, topical nanoemulsion's therapeutic use is limited [23]. The challenge was handled by inserting the nanoemulsion into the gel matrix, which transformed it into a nanoemulgel, as illustrated in Fig. (**1**).

1.2. Topical Delivery of Drugs through Nanoemulgel

"nanoemulgel" refers to an amalgamation consisting of nanoemulsion and hydrogel. The two approaches offer drawbacks, including nanoemulsion's poor spreadability and retention and hydrogels' difficulty in integrating lipophilic ingredients [24, 25]. Nanoemulgel is collectively made-up of a variety of polymers, emulsifiers, and oil molecules that are neutral, chemically produced, or man-made in nature, with particle sizes varying between 5- 500 nm [26]. The drawbacks of both approaches can be overcome by using nanoemulgel. A hydrophobic agent becomes dispersed into the oily component of the nanoemulsion, which follows the addition to the water-based gel, resulting in nanoemulgel [27], enabling the hydrophobic active medicament to be absorbed within a water-based gel while additionally enhancing the consistency of the nanoemulsion. The nanoemulgel serves as a drug reserve in topical drug administration. A therapeutic agent will be transferred from the internal to its external stage, eventually reaching the epidermal layer. While the nanoemulgel had been put onto the epidermis, oil-rich drops emerged from its gel matrix, penetrating the epidermal layer *via* the corneum layer and efficiently releasing the active component [23]. The density of crosslinks and the chemical makeup of the web of chain-like polymers determine the underlying drug release process (Fig. **2**) [28, 29].

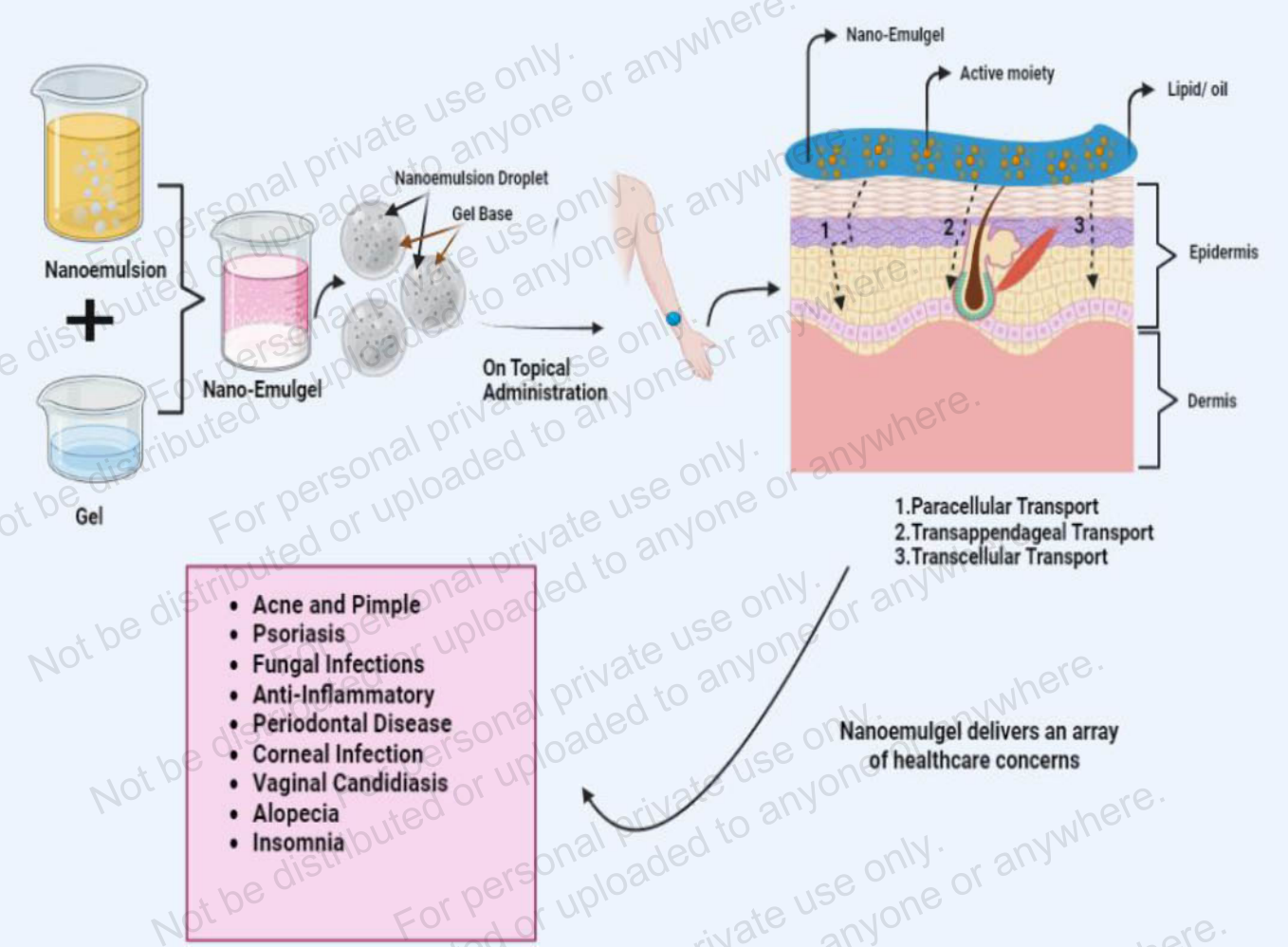

Fig. (2). Mechanistic visualizations of nanoemulgel permeation *via* skin along with its therapeutic benefits. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. THE KEY ELEMENTS OF A NANOEMULGEL

Nanoemulgel is an amalgam of two systems: nanoemulsion and gel system. Water-in-oil or oil-in-water nanoemulsions can be employed as delivery systems for drug vehicles. In both circumstances, it consists of an oil-based component, a water-based component, and a material called an emulsifier, in addition to a cosurfactant [15]. The following section briefly describes the key elements of nanoemulgel formulation that are most typically employed, as illustrated in Fig. (**3**).

2.1. Lipid/ Oil-based Solvents

Lipid has been a key component in developing nanoemulgels; therefore, meticulously chosen, relying on attributes such as dissolution, rigidity, accessibility, and consistency. Due to their limited emulsification characteristics and drug solubility, triglycerides/ edible oils are not commonly employed in nanoemulgel formulations [30-32]. As a result, synthetically altered oils like mono- or diglycerides or medium-chain triglycerides frequently serve as the oil component in nanoemulgel compositions for hydrophobic medication transport [15]. Butenafine nanoemulgel was created by Syamala and his colleagues utilizing Labrafac, a medium-chain triglyceride [33]. Capryol 90 is another oil phase used in nanoemulsion creation that has increased the effectiveness of leflunomide and paclitaxel nanoemulsion formulations [3, 34].

Researchers, alternatively, are working on using natural oil's added value in medicinal effect. Tea tree oil's antibacterial action has been combined with the antifungal drug itraconazole to provide a complementary benefit of nanoemulgel formulation towards candidiasis in the genital tract [35]. Jeengar and colleagues described an additional nanoemulgel of curcumin and emu oil. Emu oil is a pain reliever, abirritant, sedative, antioxidant, and antiallergic, and encourages drug permeability for the therapeutic management of joint synovial sickness [36]. The oils employed by different researchers in manufacturing nanoemulgels are listed in Table **1**.

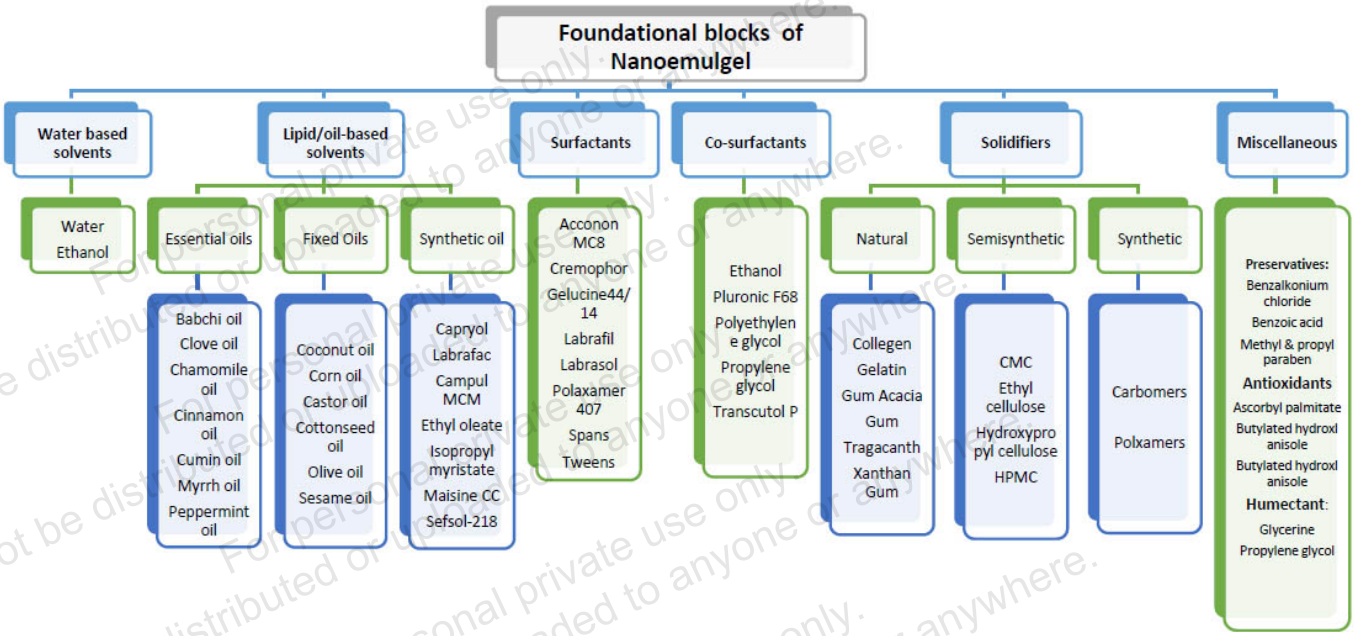

Fig. (3). A framework illustrates the foundational blocks required for developing a nanoemulgel. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.2. Surfactants and Co-surfactants

Surface active agents minimize the tension in the interface amongst the immiscible liquid mixes, thus modifying the dispersion entropy and stabilizing thermodynamically unreliable emulsion systems. The surfactant's security, stability, substantial drug-loading capacity, and strong emulsification capabilities are all variables in choosing an acceptable surfactant for nanoemulgel [32]. Furthermore, the surfactant of choice should be chosen depending on oil soluble content, for instance, Tween-20, initially selected following Capryol 90 and oleic acid solubility [15, 37].

Cosurfactants may interact with surfactants and disrupt the interfacial coating, assisting in emulsification. It could also help with oil solubilization [15]. Depending on their physicochemical qualities, propylene glycol, PEG 400, ethanol, transcutol P, carbopol, and additional cosurfactants have been widely employed for nanoemulsion and nanoemulgel synthesis [36, 37]. According to research, the area that comprises the nanoemulsion on the equilibrium diagram decreases as its level of cosurfactant increases [38, 39].

2.3. Water-based Solvents

In producing an emulsion, water-based solvents act like the phase of water. The most prevalent hydrocarbon solvents around the globe include water as well as ethanol [15].

2.4. Solidifiers

Solidifiers for nanoemulgel include Carbopol 934, Carbopol 940, and hydroxy propyl methyl cellulose (HPMC). Likewise, it strengthened the mix's consistency and might interact to alter the consistency [40]. It is incorporated as part of nanoemulsion formulation to transform the external appearance of the nanoemulsion formulation from liquid to gel, resolving an issue of Nanoemulsions' restricted dispersibility, thickness, and epidermal persistence.

2.5. Absorption Enhancer

The components have been employed to boost the accessibility of the skin temporarily. It infiltrates the skin and engages in its contents [41]. The most prevalent constituents include clove oil, olive oil, sodium lauryl sulfate, palmitate, lecithin [5%], and oleic acid (1%) [42]. Lecithin, oleic acid, urea, menthol, isopropyl myristate, and eucalyptus oil are a few of the sorption enhancers used [41].

2.5.1. Characteristics

These are the following characteristics of absorption enhancers before employing and during the production of nanoemulgel: (a) their actions shouldn't have any therapeutic function in the human system; this implies that they can't interact with any of the receptor sites [43]. (b) In terms of cosmetics, they must be skin-friendly and should not create skin irritation or disruption [44]. (c) No toxicity, low irritation, and unfavorable susceptibility should exist [45]. (d) They should be consistent with the additional drugs and excipients [46]. (e) When withdrawn from the skin, the barrier's effects should be restored soon [47].

2.5.2. Function

The alteration of the corneal layer's integrity [48] or within the cell's attachment to protein molecules [49] initiates the functioning of absorption enhancers. Absorption

Table 1. Components utilized in a variety of nanoemulgel formulations.

Pharmacological Substance	Lipid/ Oil	Emulsifier	Co-Emulsifiers	Solidifiers	References
Thymol	Caprylic acid, isopropyl myristate, and tea tree oil	Tween 20	PEG 400	Carbopol 940	[52]
Curcumin	Emu oil	Cremophor RH40	Labrafil M2125CS	Carbopol	[36]
Flurbiprofen	Linseed oil, isopropyl myristate, and triacetin	Tween 80	Ethanol + PEG400 + propylene glycol	Carbopol 940	[53]
Ketoconazole	Labrafac™ Lipophile WL1349	Tween 80	PEG 400	Carbopol	[54]
Cyclosporine	Oleic acid	Tween 80	Transcutol P	Guar Gum	[25]
Ferulic acid	Isosteryl Isostearate	Labrasol	Plurolisotearique	Carbopol 940	[55]
Ropinirole	Caproyl 90	Tween 20	Carbitol	Carbopol 934	[16]
Butenafine	Labrafac	Cremophor RH40	Ethanol	Carbopol	[33]
Ketoprofen	Oleic acid	Tween 80	Transcutol-P	Carbopol	[37]
Piroxicam	Oleic acid	Tween 80	Ethanol	Carbopol 934	[40]
Amphotericin B	Sefsol-218	Tween 80	Transcutol-P	Carbopol	[56]
Acelofenac and capsaicin	Olive oil and miglyol	Polysorbate 80	Transcutol	Propylene glycol	[57]
Terbinafine hydrochloride	Liquid paraffin	Polysorbate 80	Glycerin	Carbopol 940	[58]
Glibenclamide	Labrafac and tiacetin	Tween 80	Diethylene glycol monoethyl ether	Carbopol 934	[59]
Carvedilol	Oleic acid	Tween 20	Carbitol	Carbopol 934	[60]
Telmisartan	Labrafil	Acrysol	Carbitol	Carbopol	[61]

enhancers boost the penetration of co-enhancers, co-solvents, or drugs into the superficial corneal layer [50].

2.6. Additional Components of Nanoemulgel

Preservation agents have been employed to safeguard a preparation against contamination by microbes, thus extending its ability to last. Preservation agents frequently employed include methylparaben, benzoic acid, propylparaben, benzalkonium chloride, and others. Antioxidant-rich substances such as butylated hydroxyl toluene, butylated hydroxyl anisole, and ascorbyl palmitate have been utilized to avoid oxidative destruction of formulating ingredients. In contrast, humectants such as glycerine and propylene glycol are used [51]. Thus, as a consequence, nanoemulsion and nanoemulgel formulations developed tend to be more resilient.

Table **1** offers a selection of the most typically reported components associated with nanoemulgel formulations to highlight the key elements of nanoemulgel [29].

3. BENEFITS OF NANOEMULGEL

The Nanoemulgel has multiple benefits, as indicated in Fig. (**4**).

3.1. Enclosure of the Hydrophobic Drug

Because hydrophobic drug components are insoluble in non-aqueous foundations, they exhibit inappropriate drug distribution mechanisms inside the gel. The combination of the water-based gel plus emulsified systems facilitates the inclusion of a hydrophobic medication within the water-soluble base, resulting in improved absorption of the active moiety. Non-polar medications undergo dissolution of the based-on oil portion in the emulsion before they are incorporated into the hydrogel system [62].

3.2. Better Loading Capacity

Nanoemulgel offers a greater loading capacity than other innovative drug delivery approaches. It has more surface area and improved entrapment effectiveness due to its nanoscale size, enabling it to load additional drugs into its web--like system [62].

3.3. Enhanced Pharmacokinetic Profile

The T_{max} and peak plasma concentration of lipophilic drugs are higher in nanoemulgel than in conventional gel or oral formulation. As a result, nanoemulgel preparation improves lipophilic drug bioavailability many times over other lipophilic drug formulations [63].

3.4. Improved Patient Compliance

A rubbing action is essential because of the sticky nature of the transdermal preparation and its low spreading coefficient. Nanoemulgel has improved compliance among

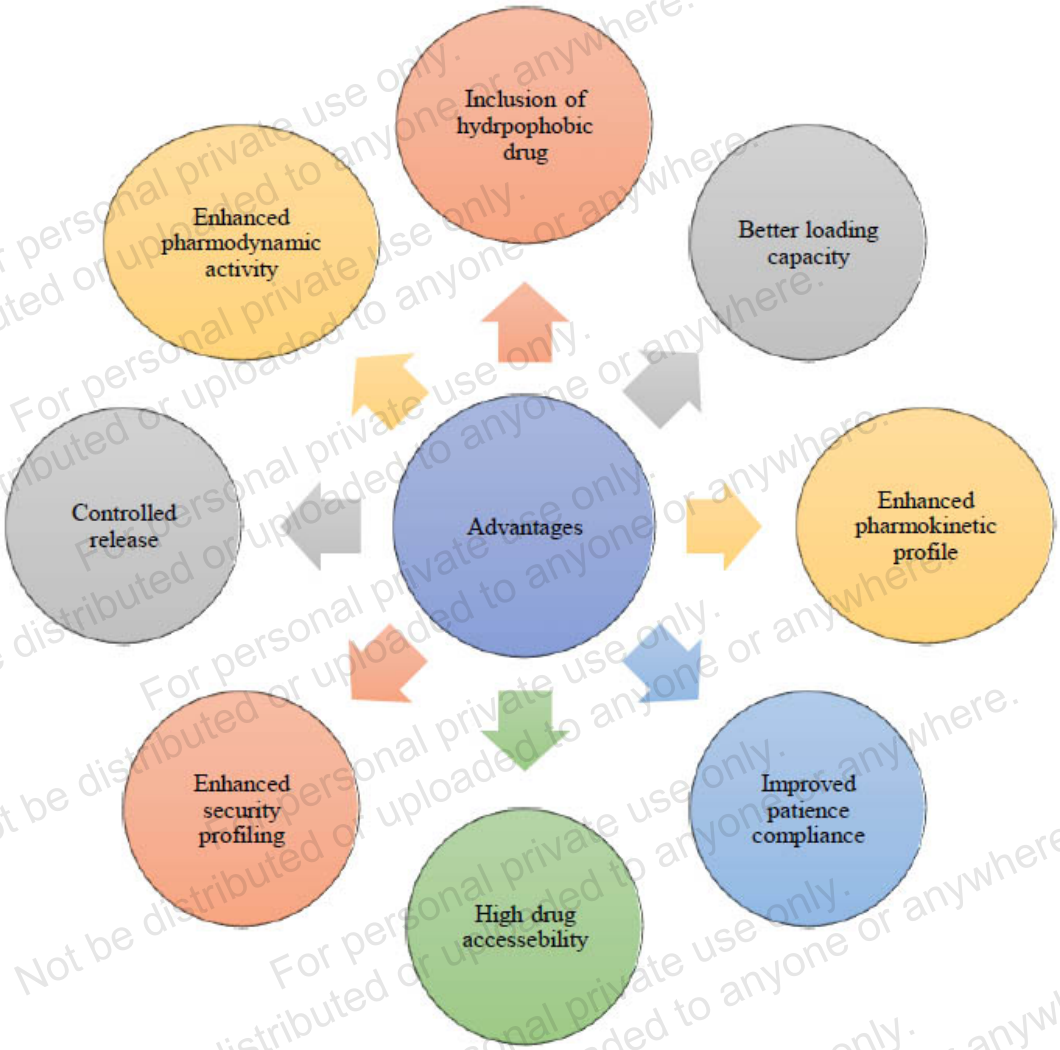

Fig. (4). Benefits of nanoemulgel. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

patients compared to other transdermal preparations as its consistency is sticky-free and easily accessible [28].

3.5. Higher Drug Accessibility into the Surface of the Skin

When juxtaposed with alternative formulations, nanoemulgel demonstrated a substantial rise in the penetration of drugs within the epidermal layer because it may infiltrate the skin layer *via* both paracellular and transcellular routes. However, nanoemulsion only exhibits transcellular infiltration [63].

3.6. An Enhanced Security Profiling

Nanoemulgel prevents metabolism in its first-pass, eliminating its gastrointestinal adverse effect among the active moiety key drawbacks. This produces no cutaneous reactions nor toxic effects when applied [63].

4. DRAWBACKS OF NANOEMULGEL

Furthermore, there are several drawbacks, as indicated in Fig. (**5**), in the formulation of nanoemulgels, such as contact dermatitis causing skin inflammation, allergic responses may occur, several drugs having inadequate skin permeability levels, and drugs with large particle sizes have been challenging to absorb *via* the skin [64, 65].

Table **2** analyses crucial factors such as particle dimension, stability, permeation through the skin, bioavailability, *etc*., in conventional emulgel and nanoemulgel formulations [66].

5. FACTORS INFLUENCING DRUG PENETRATION ACROSS THE SKIN

These are the following factors influencing the penetration of drugs across the skin.

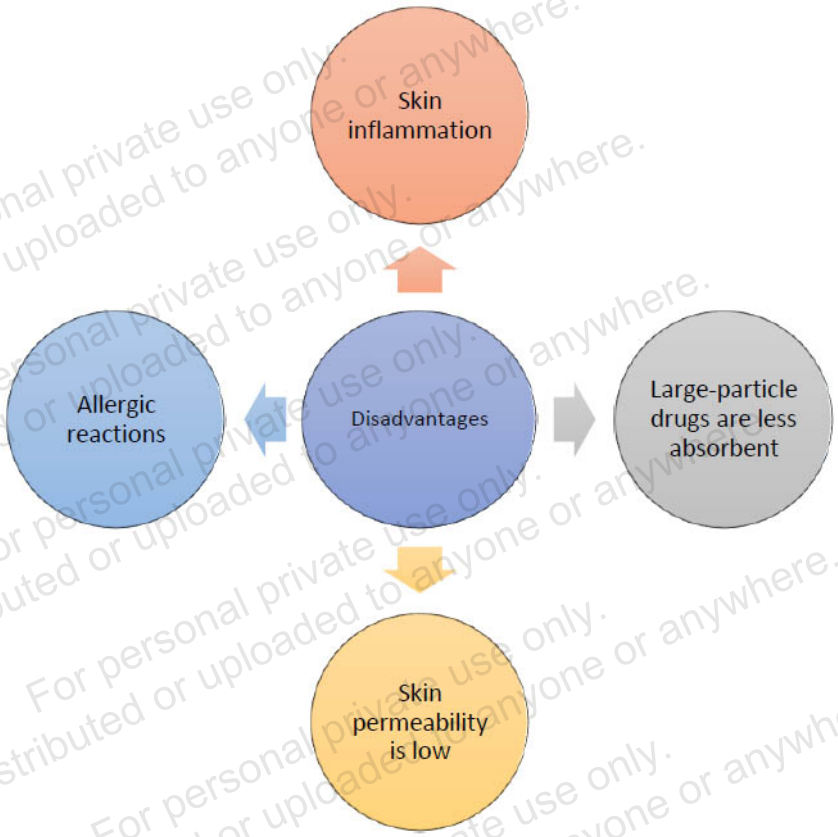

Fig. (5). Drawbacks of nanoemulgel. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. The contrast of conventional emulgel with nanoemulgel.

Parameter	Conventional Emulgel	Nanoemulgel
Thermodynamic stability	Not stable due to the inherent tendency of coalescence, which results in deposition or creaming [67]	Brownian motion is stable against gravity because of the smaller particle size, preventing sedimentation or creaming [63].
Particle Dimension	> 500 nm [68]	<100 nm [69]
Bioavailability	It is not precisely absorbed as Nanoemulgel [70].	Increased bioavailability due to tiny size and vast surface area [29].
Permeation	Permeation is decreased in comparison [71].	Because of its smaller particle size, it has a high penetration rate [63, 71].
Preparation	High-energy procedures are required [72].	It may be created in two ways or both low and high-energy processes [26].
Systemic absorption	Minimum	Higher because of the particles' tiny size and huge surface area when compared to conventional emulgel [72].
Ability to cross BBB	BBB cannot be crossed [73].	Due to its small particle size, it can cross the BBB [74].

5.1. Biological Factors

These are some biological factors that influence the penetration of drugs across the skin [75].

- Surface/ dermis depth: The level of thickness of the dermis ranges from the skin's outermost layer down to the layer beneath its surface. The depth of the epidermis is around 1-4 mm. The rate of skin dispersion on both the foot and the hand is high.
- Lipid content: It functions as a fluid barricade if the fat content inside the corneal layer is low and cutaneous permeation is high.
- Density of hair follicles: The infundibulum of the hair follicle has a far bigger capacity for storage over the corneal layer.
- A certain number of sweating glands.
- Surface pH: Perspiration and oily acids released by

the sebaceous gland change the pH value within the epidermis surface.
- Circulation of plasma.
- Increases drug absorption through the skin.
- Skin inflammation disturbs the stratum corneum's continuity and promotes permeability.
- Surface temperature: The percentage of skin permeation increases as the surface temperature rises.

5.2. Biophysical/ Thermo-physical Factors

These are some biophysical/ thermo-physical factors that influence the penetration of drugs across the skin.

- N-octanol-water partition ratio (log p): The higher the significance of the n-octanol-water partition ratio, the easier it is for the drug to be absorbed percutaneously.
- Molecular mass (More than 400 Dalton).
- Ionization level (only unionized medicines are well absorbed).
- The Effect of the Vehicle: Hydroalcoholic gel provides an extremely effective absorption through cutaneous tissue [75].

6. FACTORS WHEN SELECTING A SKIN-CARE PREPARATION

These are the following factors when selecting a skin--care preparation that influences the penetration of the drug across the skin.

- The drug should not affect the skin.
- Lotions and cream forms are often more soothing than gel forms regarding irritation or sensitization potential. Stay away from ointments if you are allergic to emulsifiers or preservatives.
- An occlusive vehicle, for instance, promotes active ingredient penetration while also increasing efficacy. The vehicle's qualities could be drying out, chilling, moisturizing, or protecting.
- It should correspond to the kind as part of composition on the specific area (for example, gel state or moisturizer on hair-like areas).
- The treatment should be tailored to the kind of lesions. Avoid oily applications if you're suffering from extreme blubbering allergic reactions, for instance [76-78].

The success of nanoemulgel as an innovative delivery method depends on a few essential characteristics that enable its efficacy and versatility in various applications. The major candidate properties that make nanoemulgel an appealing alternative for medicinal and cosmetic formulations are outlined below in Fig. (**6**) [79, 80].

7. METHODOLOGY OF NANOEMULGEL

Nanoemulgel has been developed through an extreme--pressure homogenizing approach. Nanoemulgel can be produced in three processes, discussed below [71], and represented in a flow diagram in Fig. (**7**).

7.1. Preparation of Nanoemulsion

Emulsifiers tend to dissolve in an oily or aqueous phase of choice. The therapeutic agent is subsequently dissolved within an oily or an aqueous phase based on solubility. After both phases have been heated, they are blended by slowly adding one part to the other while continuously stirring as long as it attains room temperature, together with numerous nanoemulsification processes used for generating nanoemulsion [81].

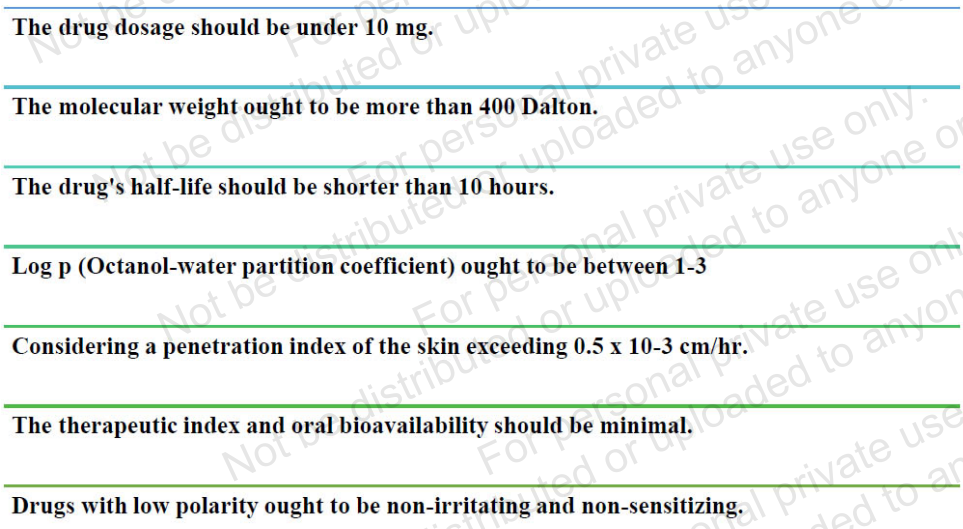

Fig. (6). Ideal drug candidate qualities for formulation in nanoemulgel. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

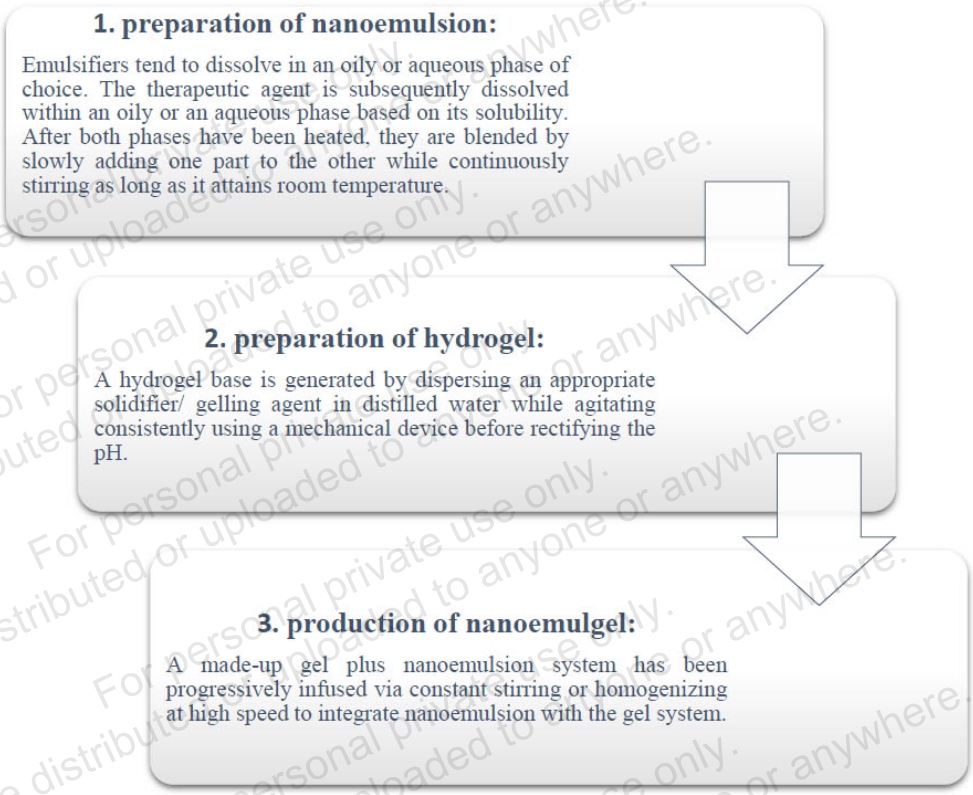

Fig. (7). Flowchart of the methodology of nanoemulgel. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

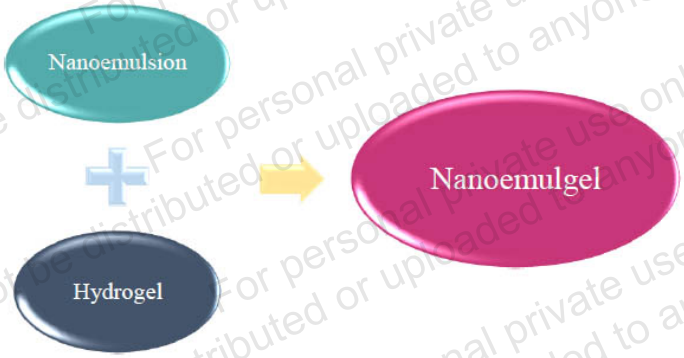

Fig. (8). Process of Formation of nanoemulgel. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

7.2. Preparation of Hydrogel

A hydrogel base is generated by dispersing an appropriate solidifier/ gelling agent in distilled water while agitating consistently using a mechanical device before rectifying the pH.

7.3. Production of nanoemulgel

A made-up gel plus nanoemulsion system has been progressively infused *via* constant stirring or homogenizing at high speed to integrate nanoemulsion with the gel system.

8. FORMULATION OF NANOEMULGEL

Nanoemulsion-based gels have been developed by amalgamating 1g of a gelling ingredient with enough distilled water. A gel-forming solution ` is stored in a dark place for 25 hours to achieve a complete swelling system. A drug-loaded nanoemulsion is slowly introduced while

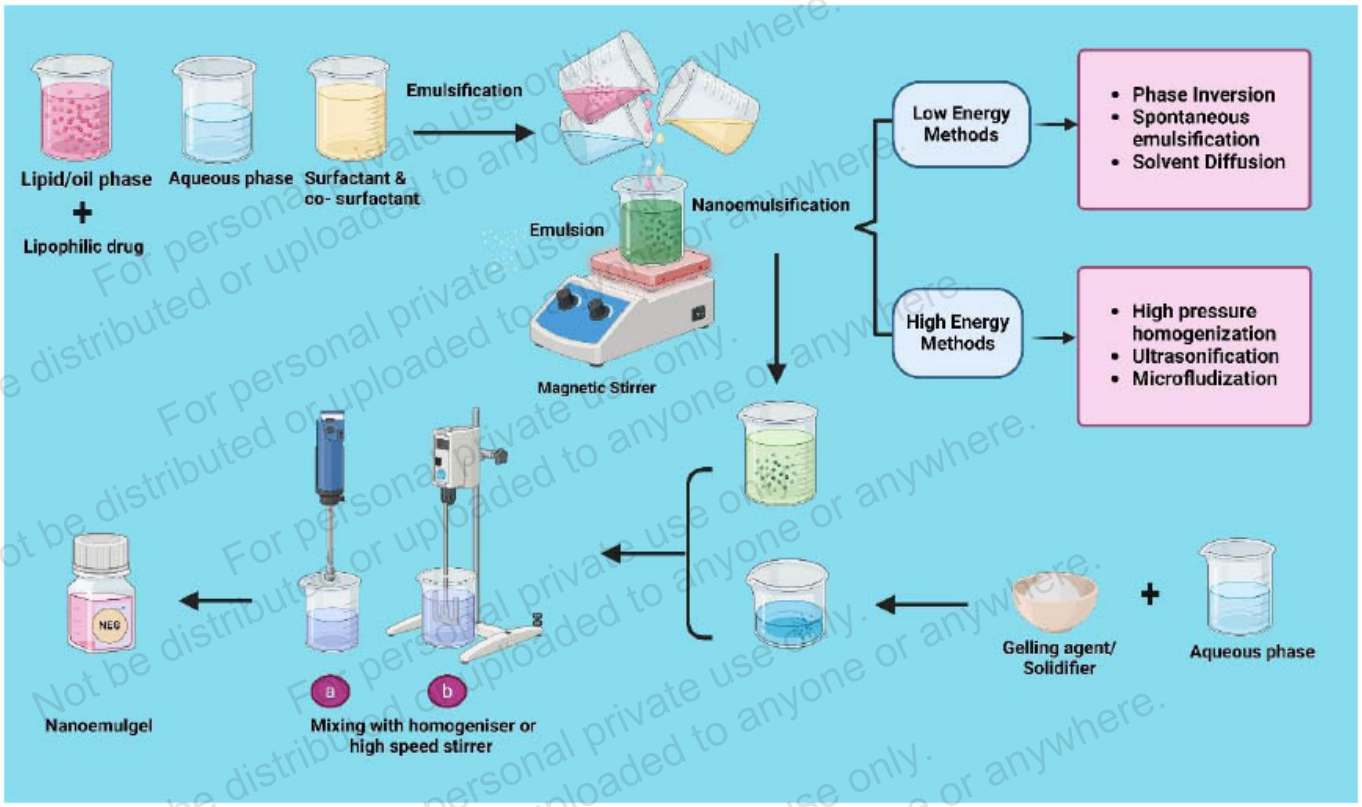

Fig. (9). Schematic representation of the nanoemulgel production process. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

magnetically stirring it into a viscous gel-forming solution, as illustrated in Fig. (**8**) [82].

8.1. Water-based/ Aqueous Phase

The aqueous phase composition predominantly determined the size of droplets and nanoemulsion stability [83]. The physiological environment has pH values between 1.2 (Stomach pH level) -7.4 or above (blood and intestinal pH level). Further, many chemicals inside the body's environment may considerably affect nanoemulsion properties.

8.2. Methods for Preparing Stabilized Nanoemulsions

As shown in Fig. (**9**) for manufacture, adequate procedures must be used to provide transparent and stabilized nanoemulsion compositions [84]. The approaches are required for lowering the size of droplets to the nanoscale.

8.2.1. Homogenization using High-pressure

A high-pressure homogenizer piston has been utilized to create a stabilized nanoemulsion with particles as small as 1 nm by employing multiple forces such as cavitation, *etc*. This method will be carried out again and again up until the ideal nanosize formulation is attained.

8.2.2. Microfluidization

A device called a microfluidizer is used to microfluidize the prepared formulation. High-pressure drives their product through microchannels, which leads to submicron particles. The process was repeated multiple times until the nanoemulsion was stabilized [81].

8.2.3. Ultrasonication

The ultrasonication approach employs ultrasonic vibrations to generate a stabilized nanoemulsion with substantially smaller particles [85]. In this case, the cavitation process is the technique of choice to accomplish the necessary nanosized composition.

8.2.4. Phase Separation Method

The phase inversion approach is utilized to manufacture a stabilized nanoemulsion using chemical energy during phase transition with a steady temperature with the assistance of an emulsion formation process.

9. EVALUATION PARAMETERS FOR NANOEMULGEL

9.1. Appearance

Color, uniformity, consistency throughout, and pH of the

developed nanoemulgel compositions were evaluated visually. An electronic pH meter (Digital pH meter DPH 115 pm) has been employed for determining the pH level of one percent of the water-based solution of the developed Gellified Emulsion.

9.2. Spreadability

A device adapted in the research setting and employed for this research [86] is used to determine spreadability. It is formed with a hardwood block with a pulling system. This approach is used to determine spreadability. A sufficient amount of nanoemulgel (approximately 2 gm) has been placed under examination of the ground slide. Nanoemulgel has been positioned within that slide, accompanied by another glass slide of identical size as the established base slide alongside a clasp for holding it together. A mass of one kilogram was set over the surface of each slide over 5 minutes to eliminate airflow while developing a homogeneous layer of nanoemulgel beneath each slide. Scrape extra nanoemulgel from the edges. The top part of the slide is subsequently removed with an 80-gram pull. A thread length connected to an adjustable loop determines the duration measured in seconds necessary for the upper slide to reach a 7.5 cm area. A briefer time frame signifies increased Spreadability. This equation is utilized to figure out spreadability.

$$S = M.L/T$$

Where,

S = spreadability,

M =Weight is fixed to the upper slide.

L = Glass slide length

T =Time required for separating the slides from one another.

9.3. Rheological Studies

The consistency of the developed jellified nanoemulsion compositions has been assessed by employing the Brookfield viscometer (Brookfield DV-E viscometer). The jellified nanoemulsion was rotated for 10 (min.) and 100 (max.) revolutions in a minute using Spindle 6. An associated dial value upon each rate had a mark of 16. The formulation's consistency was assessed.

9.4. Analysis of Drug Content

A UV-visible spectrophotometer has been employed to analyze the drug amount within nanoemulgel. A predetermined amount of nanoemulgel insolvent (methanol) is sonicated. The formulations' drug content was determined.

9.5. *in-vitro* Diffusion Analysis

During the purpose of drug diffusion analyses, the Franz diffusion cell model (efficient diffusion process, surface area 3.14 cm^2 with cell volume 15.5 ml) has been employed [87]. The surface of the cell membrane of an egg has been liberally coated with nanoemulgel (around 200 mg). The membrane of the egg is pinched amid the donor and the receptor chambers of the diffusion cell. The receptor compartment has been stuffed with a freshly prepared PBS (pH 5.5) mixture to dissolve the pharmaceutical ingredient. An electromagnetic stirrer has been employed to stir the receptor chamber. Specimens (1 mL fraction) have been obtained at regular intervals. After successive dilutions, samples have been examined for the amount of drug using an ultraviolet (UV)-visible spectrophotometer at 226 nm. The aggregate quantity of pharmaceutical ingredients donated after every interval was estimated using progressive adjustments. The total quantity of the pharmaceutical ingredients diffused through the cell membrane of an egg has been estimated over time.

9.6. Dimension and Distribution of Globules in Nanoemulgel

Using the Malvern zeta sizer dimension and dispersion of globules have been figured out. A 1.0-gram specimen has been diluted with distilled water to generate a uniform dispersion. The ingredient has been injected using the zeta sizer photocell. The mean dimension of globules with their dispersion has been determined.

9.7. Scanning Electron Microscopy

SEM, or microscopy with scanning electrons, is frequently utilized to figure out the physical attributes of a nanoemulsion. SEM has been used to image the globules in three dimensions [23, 88]. The samples are inspected at various magnifications at a sufficient increase in the voltage, generally 20 kV. The morphological characteristics of the surface of the dispersed substance in the formulation are functionally analyzed using SEM. To acquire an automated result of the structure and surface morphology, software for image analysis can be employed.

9.8. Stability Studies

The chosen formulations were stored for three months at 4, 25, and 40°C. Viscosity was determined in three monthly batches, while the results were presented as mean ± SD.

9.9. Extrudability Studies (Tube Analysis)

The objective of the examination was to determine the force needed for the extrusion of a substance in a tube. The total amount of nanoemulgel expelled from the lacquer aluminum flexible tube was computed using the mass in grams necessary for dispensing a minimum 0.5 cm swath of nanoemulgel after 10 seconds [89]. The larger the amount of emulgel ejected, the better the extrudability. The extrudability is subsequently established by employing the equation outlined beneath,

Extrudability = Mass of nanoemulgel required for extrusion through a tube (in g)/Area (in cm^2).

9.10. Skin Irritability Analysis (Patch Test)

A formulation has been applied on cleanly shaven rat

skin, and unwanted color and skin morphological alterations must be observed within 24 hours. The evaluation is regarded as acceptable if no irritation develops.

9.11. pH Determination

A pH meter has been used to determine the created formulations' pH. Each formulation was added to a 250 mL beaker; then, the pH meter was placed in the solution to take measurements [90]. The procedure was carried out over three times utilizing alike phrasing.

9.12. Drug Release Kinetic Studies

To study the underlying process of the release of drugs through the topical application of nanoemulgel, release data is inputted in the subsequent equations in order [91, 66, 92]:

Zero-order equation:

$Q=K0t$

Where Q = amount of drug released at time t, and

K0 = zero-order release rate.

First-order equation:

$In\ (100-Q) = In\ 100 - K1t$

Where Q = percentage of drug release at time t, and

K1 = first-order release rate constant.

Higuchi's equation:

$Q=K2\sqrt{t}$

Where Q = percentage of drug release at time t, and

K2 = diffusion rate constant.

Korsmeyer-Peppas equation:

$Qt/Qe=Kt^{n}$

Where Qt/Qe = the fraction of drug released from the gel into the receptor media,

K = the device's structural and geometric properties and

n = the drug release mechanism.

The (n) value of 0.5 implies a quasi-Fickian diffusion mechanism, while if (n>0.5), an anomalous or non-Fickian diffusion mechanism exists and if (n=1), a zero-order release mechanism exists.

9.13. Accelerated Stability Studies of Nanoemulgel

The formulations underwent six heating-cooling cycles, each involving refrigeration at 4°C then oven exposure at 40°C for 48 hours at each temperature. The samples had been optically examined for indicators of instability. Resilient samples from the heating-cooling cycle were centrifuged at 3750 rpm for 5 hours. Visual inspection was conducted to identify any cracking or separation, which estimated the gravitational force produced throughout the year [89].

10. APPLICATIONS

Nanoemulgel comprises an amalgam of both a nanoemulsion plus gel that comes with multiple benefits above standard dosage forms, including broadened drug solubility, permeability, plus targeted administration.

10.1. Topical Drug Delivery

Because of its enhanced dissolution of drugs, stability, and skin penetration, nanoemulgel is frequently employed as a topical drug delivery technology method. For example, Nagaraja *et al.* (2021) designed a chrysin-loaded nanoemulgel for the focused, effective dermatological therapy of skin cancer [93].

10.2. Wound Healing

Because of its strong antibacterial activity and improved drug penetration, nanoemulgel has been considered a wound-healing aid. Alyoussef *et al.* (2021) designed a nanoemulgel combining curcumin and resveratrol to recover wounds caused by burns [94].

10.3. Cosmetics

Because of more effective skin penetration and controlled release properties, nanoemulgel is additionally employed in cosmetic companies. Shawahna R (2022), for example, grapeseed oil (*Vitis vinifera* L.) loaded with dermo--cosmetic nanoemulgel owned remarkable cosmetic aspects, offering success in repairing skin flaws [95].

10.4. Sunscreen

Because of its capacity to offer consistent coverage and safeguard against UV rays, nanoemulgel is employed as a sunscreen agent. Created a moringa leaf nanoemulgel sunscreen with a high SPF value [96].

10.5. Ophthalmic Drug Delivery

Because of its enhanced drug penetration and persistence in the eye, nanoemulgel has been considered for ophthalmic drug delivery. For instance, designed a fluconazole-loaded nanoemulgel [97, 98].

Table **3** [29] below conveys a comprehensive list of active moieties, their trade names, and their medical procedures and regimens applications.

11. CURRENT AS WELL AS FUTURE PROSPECTIVE OF NANOEMULGEL

Nanoemulgel is a cutting-edge medication delivery device that combines the benefits of emulsion and gel. The nanosized particle droplets in the emulsion offer a wide surface area over the absorbed drug, while the gel basis promotes consistent and prolonged drug release. Nanoemulgel's existing prospective clients are very optimistic, as it has been found to boost the absorption of drugs, security, and tolerability. Nanoemulgel preparations for a wide range of pharmaceuticals were developed, notably anti-inflammatory substances, analgesics, antifungals, as well as anticancer treat-

Table 3. Available marketed emulgelpreparations.

Product Trade Name	Active Moiety/Drug(s)	Manufacturers	Application
Benzolait AZ emulgel	Benzoyl peroxide	Roydermal	Acne Pimples and skin discoloration
Coolnac Gel emulgel 1%	Diclofenac diethyl amine	Chumchon	Trauma-induced inflammation and discomfort
Diclobar emulgel	Diclofenac diethyl amine	Barakat Pharma	Pain-related inflammation and rheumatic illnesses
Meloxic emulgel	Meloxicam	Laboratories Provet	Management of musculoskeletal pain and inflammation
Miconaz-H- emulgel	Miconazole nitrate, hydrocortisone	Medical Union Pharmaceutics	Candida infection on the skin
Reumadep emulgel	Ashwagandha, myrrh, arnica, rosemary, mint, and cloves	Erbozeta	Trauma-induced inflammation and discomfort
Voltaren emulgel	Diclofenac diethyl ammonium	Novartis Pharma	Joint pain due to osteoarthritis
Voveron emulgel	Diclofenac diethyl amine	Novartis Pharma	Joint pain due to osteoarthritis

ments. The Nanoemulgel technique will undoubtedly have a major role in the forthcoming advancement of novel drug preparations. Experts have been looking at the possibility of using the technology for specialized transportation of active pharmaceutical ingredient delivery, whereby the active moiety might be administered specifically at the position of action, lowering adverse effects and enhancing efficiency. In addition, the usage of nanoemulgel in personal care products and cosmetics is under consideration as it can improve the transport and efficiency of pharmaceutical-grade components such as sunscreen agents and anti-aging substances. Overall, the upcoming potential of nanoemulgel technological advances is extremely positive, and it should significantly impact both the cosmetics and pharmaceutical sectors in the years ahead.

CONCLUSION

The nanoemulgel fabrication combines the positive aspects of both emulsion plus gel technology. The carrier above concept has improved the accessibility and longevity of weakly water-soluble pharmaceuticals, resulting in an attractive drug delivery strategy. The nanosized particles in the emulsion offer an enormous surface area for medication absorption, while the gel framework provides a prolonged release of the medication. Nanoemulgel offers numerous application possibilities involving targeted drug delivery and skin-care products/ personal care products. Following continued advancements in research and development, the nanoemulgel technique is anticipated to eventually serve as a crucial tool in advancing innovative therapeutic formulations, particularly for water-insoluble drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Weissig V, Lizano C, Torchilin VP. Selective DNA release from DQAsome/DNA complexes at mitochondria-like membranes. Drug Deliv 2000; 7(1): 1-5. http://dx.doi.org/10.1080/107175400266722 PMID: 10895413

[2] Beig A, Miller JM, Lindley D, *et al.* Head-to-head comparison of different solubility-enabling formulations of etoposide and their consequent solubility–permeability interplay. J Pharm Sci 2015; 104(9): 2941-7. http://dx.doi.org/10.1002/jps.24496 PMID: 25989509

[3] Kumar P, Pathak D, Singh P. Formulation and evaluation of biodegradable nanoparticles of Glimepiride by ionic gelation method. J Pharm Res 2017; 96-102.

[4] Wadhwa J, Nair A, Kumria R. Emulsion forming drug delivery system for lipophilic drugs. Acta Pol Pharm 2012; 69(2): 179-91. PMID: 22568032

[5] Abolmaali SS, Tamaddon AM, Farvadi FS, Daneshamuz S, Moghimi H. Pharmaceutical nanoemulsions and their potential topical and transdermal applications. Iranian J Pharma Sci 2011; 7(3): 139-50.

[6] Kotta S, Khan AW, Ansari SH, Sharma RK, Ali J. Anti HIV nanoemulsion formulation: Optimization and *in vitro–in vivo* evaluation. Int J Pharm 2014; 462(1-2): 129-34. http://dx.doi.org/10.1016/j.ijpharm.2013.12.038 PMID: 24374067

[7] Iqbal MA, Md S, Sahni JK, Baboota S, Dang S, Ali J. Nanostructured lipid carriers system: Recent advances in drug delivery. J Drug Target 2012; 20(10): 813-30. http://dx.doi.org/10.3109/1061186X.2012.716845 PMID: 22931500

[8] Kaur J, Kaur J, Jaiswal S, Gupta G. Recent advances in topical drug delivery system. Pharm Res 2016; 6(07): 6353-69.

[9] Gannu R, Palem CR, Yamsani VV, Yamsani SK, Yamsani MR. Enhanced bioavailability of lacidipine *via* microemulsion based transdermal gels: Formulation optimization, *ex-vivo* and *in vivo* characterization. Int J Pharm 2010; 388(1-2): 231-41. http://dx.doi.org/10.1016/j.ijpharm.2009.12.050 PMID: 20060457

[10] Bhaskar K, Anbu J, Ravichandiran V, Venkateswarlu V, Rao Y. Lipid nanoparticles for transdermal delivery of flurbiprofen: Formulation, *in vitro*, *ex-vivo* and *in vivo* studies. Lipids Health Dis 2009; 8(1): 6. http://dx.doi.org/10.1186/1476-511X-8-6 PMID: 19243632

[11] Shakeel F, Baboota S, Ahuja A, Ali J, Shafiq S. Skin permeation mechanism and bioavailability enhancement of celecoxib from transdermally applied nanoemulsion. J Nanobiotechnology 2008; 6(1): 8. http://dx.doi.org/10.1186/1477-3155-6-8 PMID: 18613981

[12] Huang X, Peng X, Wang Y, *et al.* A reexamination of active and passive tumor targeting by using rod-shaped gold nanocrystals and covalently conjugated peptide ligands. ACS Nano 2010;

4(10): 5887-96.
http://dx.doi.org/10.1021/nn102055s PMID: 20863096
[13] DeLouise LA. Applications of nanotechnology in dermatology. J Invest Dermatol 2012; 132(3): 964-75.
http://dx.doi.org/10.1038/jid.2011.425 PMID: 22217738
[14] Shafiq-un-Nabi S, Shakeel F, Talegaonkar S, *et al.* Formulation development and optimization using nanoemulsion technique: A technical note. AAPS PharmSciTech 2007; 8(2): E12-7.
http://dx.doi.org/10.1208/pt0802028 PMID: 17622106
[15] Azeem A, Rizwan M, Ahmad FJ, *et al.* Nanoemulsion components screening and selection: A technical note. AAPS PharmSciTech 2009; 10(1): 69-76.
http://dx.doi.org/10.1208/s12249-008-9178-x PMID: 19148761
[16] Kim BS, Won M, Yang , Lee KM, Kim CS. *in vitro* permeation studies of nanoemulsions containing ketoprofen as a model drug. Drug Deliv 2008; 15(7): 465-9.
http://dx.doi.org/10.1080/10717540802328599 PMID: 18712624
[17] Fini A, Bergamante V, Ceschel GC, Ronchi C, De Moraes CAF. Control of transdermal permeation of hydrocortisone acetate from hydrophilic and lipophilic formulations. AAPS PharmSciTech 2008; 9(3): 762-8.
http://dx.doi.org/10.1208/s12249-008-9107-z PMID: 18563577
[18] Teichmann A, Heuschkel S, Jacobi U, *et al.* Comparison of stratum corneum penetration and localization of a lipophilic model drug applied in an o/w microemulsion and an amphiphilic cream. Eur J Pharm Biopharm 2007; 67(3): 699-706.
http://dx.doi.org/10.1016/j.ejpb.2007.04.006 PMID: 17537622
[19] Abramović Z, Šuštaršič U, Teskač K, Šentjurc M, Kristl J. Influence of nanosized delivery systems with benzyl nicotinate and penetration enhancers on skin oxygenation. Int J Pharm 2008; 359(1-2): 220-7.
http://dx.doi.org/10.1016/j.ijpharm.2008.03.014 PMID: 18472233
[20] Bolzinger MA, Briançon S, Pelletier J, Fessi H, Chevalier Y. Percutaneous release of caffeine from microemulsion, emulsion and gel dosage forms. Eur J Pharm Biopharm 2008; 68(2): 446-51.
http://dx.doi.org/10.1016/j.ejpb.2007.10.018 PMID: 18191759
[21] Date AA, Desai N, Dixit R, Nagarsenker M. Self-nanoemulsifying drug delivery systems: formulation insights, applications and advances. Nanomedicine 2010; 5(10): 1595-616.
http://dx.doi.org/10.2217/nnm.10.126 PMID: 21143036
[22] Khurana S, Jain NK, Bedi PMS. Nanoemulsion based gel for transdermal delivery of meloxicam: Physico-chemical, mechanistic investigation. Life Sci 2013; 92(6-7): 383-92.
http://dx.doi.org/10.1016/j.lfs.2013.01.005 PMID: 23353874
[23] Mou D, Chen H, Du D, *et al.* Hydrogel-thickened nanoemulsion system for topical delivery of lipophilic drugs. Int J Pharm 2008; 353(1-2): 270-6.
http://dx.doi.org/10.1016/j.ijpharm.2007.11.051 PMID: 18215479
[24] Begur M. Enhanced permeability of cyclosporine from a transdermally applied nanoemulgel. Pharm Sin 2015.
[25] Zhao F, Yao D, Guo R, Deng L, Dong A, Zhang J. Composites of polymer hydrogels and nanoparticulate systems for biomedical and pharmaceutical applications. Nanomaterials 2015; 5(4): 2054-130.
http://dx.doi.org/10.3390/nano5042054 PMID: 28347111
[26] Anand K, Ray S, Rahman M, *et al.* Nano-emulgel: Emerging as a smarter topical lipidic emulsion-based nanocarrier for skin healthcare applications. Recent Patents Anti-Infect Drug Disc 2019; 14(1): 16-35.
http://dx.doi.org/10.2174/1574891X14666190717111531 PMID: 31333141
[27] Eid AM, El-Enshasy HA, Aziz R, Elmarzugi NA. Preparation, characterization, and anti-inflammatory activity of Swietenia macrophyll a nanoemulgel. J Nanomed Nanotechnol 2014; 5(2): 1-0.
http://dx.doi.org/10.4172/2157-7439.1000190
[28] Chellapa P, Mohamed AT, Keleb EI, *et al.* Nanoemulsion and nanoemulgel as a topical formulation. IOSR J Pharm 2015; 5(10): 43-7.
[29] Sultana N, Akhtar J, Khan MI, *et al.* Nanoemulgel: For promising topical and systemic delivery. Drug Development Life Cycle. 2022.
[30] Aithal GC, Narayan R, Nayak UY. Nanoemulgel: A promising phase in drug delivery. Curr Pharm Des 2020; 26(2): 279-91.
http://dx.doi.org/10.2174/1381612826666191226100241 PMID: 31878849
[31] Warisnoicharoen W, Lansley AB, Lawrence MJ. Nonionic oil-in-water microemulsions: The effect of oil type on phase behaviour. Int J Pharm 2000; 198(1): 7-27.
http://dx.doi.org/10.1016/S0378-5173(99)00406-8 PMID: 10722947
[32] Sapra B, Thatai P, Bhandari S, Sood J, Jindal M, Tiwary A. A critical appraisal of microemulsions for drug delivery: part I. Ther Deliv 2013; 4(12): 1547-64.
http://dx.doi.org/10.4155/tde.13.116 PMID: 24304251
[33] Syamala U. Development & optimization of allyl amine antifungal nanoemulgel using 23 factorial design: for the treatment of tinea pedis. Eur Sci J 2013; 4: 597-605.
[34] Pund S, Pawar S, Gangurde S, Divate D. Transcutaneous delivery of leflunomide nanoemulgel: Mechanistic investigation into physicomechanical characteristics, *in vitro* anti-psoriatic and anti-melanoma activity. Int J Pharm 2015; 487(1-2): 148-56.
http://dx.doi.org/10.1016/j.ijpharm.2015.04.015 PMID: 25869452
[35] Mirza MA, Ahmad S, Mallick MN, Manzoor N, Talegaonkar S, Iqbal Z. Development of a novel synergistic thermosensitive gel for vaginal candidiasis: An *in vitro*, *in vivo* evaluation. Colloids Surf B Biointerfaces 2013; 103: 275-82.
http://dx.doi.org/10.1016/j.colsurfb.2012.10.038 PMID: 23201748
[36] Jeengar MK, Rompicharla SVK, Shrivastava S, *et al.* Emu oil based nano-emulgel for topical delivery of curcumin. Int J Pharm 2016; 506(1-2): 222-36.
http://dx.doi.org/10.1016/j.ijpharm.2016.04.052 PMID: 27109049
[37] Arora R, Aggarwal G, Harikumar SL, Kaur K. Nanoemulsion based hydrogel for enhanced transdermal delivery of ketoprofen. Advan Pharma 2014; 2014: 1-12.
http://dx.doi.org/10.1155/2014/468456
[38] Shafiq S, Shakeel F, Talegaonkar S, Ahmad FJ, Khar RK, Ali M. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur J Pharm Biopharm 2007; 66(2): 227-43.
http://dx.doi.org/10.1016/j.ejpb.2006.10.014 PMID: 17127045
[39] Anton N, Vandamme TF. The universality of low-energy nano-emulsification. Int J Pharm 2009; 377(1-2): 142-7.
http://dx.doi.org/10.1016/j.ijpharm.2009.05.014 PMID: 19454306
[40] Aggarwal G, Dhawan B, Harikumar SL. Enhanced transdermal permeability of piroxicam through novel nanoemulgel formulation. Int J Pharm Investig 2014; 4(2): 65-76.
http://dx.doi.org/10.4103/2230-973X.133053 PMID: 25006551
[41] Mortazavi SA. An investigation into the effect of various penetration enhancers on percutaneous absorption of piroxicam. Res Pharm Sci 2012; 7(4): 225-34.
[42] Ashara K, Soniwala M, Shah K. Emulgel: A novel drug delivery system. J Pak Assoc Dermatol 2016; 26(3): 244-9.
[43] Ayub AC, Gomes ADM, Lima MVC, Vianna-Soares CD, Ferreira LAM. Topical delivery of fluconazole: *in vitro* skin penetration and permeation using emulsions as dosage forms. Drug Dev Ind Pharm 2007; 33(3): 273-80.
http://dx.doi.org/10.1080/03639040600829989 PMID: 17454060
[44] Bhowmik D. Recent advances in novel topical drug delivery system. Pharma Innov 2012; 1(9)
[45] Ace LN Jr. Pharmaceutical dosage forms and drug delivery systems. Am J Pharm Educ 2001; 65(1): 104.
[46] Chein YW. Transdermal drug delivery and delivery system. Novel drug delivery system. New York: Marcel Dekker, Inc 1992; 50: pp. 1-381.
[47] Pathan IB, Setty CM. Chemical penetration enhancers for transdermal drug delivery systems. Trop J Pharm Res 2009; 8(2)
http://dx.doi.org/10.4314/tjpr.v8i2.44527
[48] Barry BW. Lipid-protein-partitioning theory of skin penetration enhancement. J Control Release 1991; 15(3): 237-48.
http://dx.doi.org/10.1016/0168-3659(91)90115-T
[49] Pfister WR, Hsieh DS. Permeation enhancers compatible with transdermal drug delivery systems. Part I: selection and formulation considerations. Med Device Technol 1990; 1(5): 48-55.
PMID: 10171148
[50] Arora P, Mukherjee B. Design, development, physicochemical, and *in vitro* and *in vivo* evaluation of transdermal patches contain-

ing diclofenac diethylammonium salt. J Pharm Sci 2002; 91(9): 2076-89.
http://dx.doi.org/10.1002/jps.10200 PMID: 12210054

[51] Dev A, Chodankar R, Shelke O. Emulgels: A novel topical drug delivery system. Pharma biol eval 2015; 2(4): 64-75.

[52] Ahmad J, Gautam A, Komath S, Bano M, Garg A, Jain K. Topical nano-emulgel for skin disorders: Formulation approach and characterization. Recent Patents Anti-Infect Drug Disc 2019; 14(1): 36-48.
http://dx.doi.org/10.2174/1574891X14666181129115213 PMID: 30488798

[53] Radhika PR, Guruprasad S. Nanoemulsion based emulgel formulation of lipophilic drug for topical delivery. Int J Pharm Tech Res 2016; 9(6): 210-3.

[54] Mahtab A, Anwar M, Mallick N, Naz Z, Jain GK, Ahmad FJ. Transungual delivery of ketoconazole nanoemulgel for the effective management of onychomycosis. AAPS PharmSciTech 2016; 17(6): 1477-90.
http://dx.doi.org/10.1208/s12249-016-0488-0 PMID: 26857516

[55] Harwansh RK, Mukherjee PK, Bahadur S, Biswas R. Enhanced permeability of ferulic acid loaded nanoemulsion based gel through skin against UVA mediated oxidative stress. Life Sci 2015; 141: 202-11.
http://dx.doi.org/10.1016/j.lfs.2015.10.001 PMID: 26437269

[56] Hussain A, Samad A, Singh SK, *et al.* Nanoemulsion gel-based topical delivery of an antifungal drug: *in vitro* activity and *in vivo* evaluation. Drug Deliv 2016; 23(2): 642-57.
http://dx.doi.org/10.3109/10717544.2014.933284 PMID: 25013957

[57] Somagoni J, Boakye CHA, Godugu C, *et al.* Nanomiemgel: A novel drug delivery system for topical application *in vitro* and *in vivo* evaluation. PLoS One 2014; 9(12): e115952.
http://dx.doi.org/10.1371/journal.pone.0115952 PMID: 25546392

[58] Karri VVSNR, Raman SK, Kuppusamy G, Mulukutla S, Ramaswamy S, Malayandi R. Terbinafine hydrochloride loaded nanoemulsion based gel for topical application. J Pharm Investig 2015; 45(1): 79-89.
http://dx.doi.org/10.1007/s40005-014-0149-9

[59] Wais M, Samad AB, Nazish I, Khale AN, Aqil MO, Khan M. Formulation development *ex-vivo* and *in-vivo* evaluation of nanoemulsion for transdermal delivery of glibenclamide. Int J Pharm Pharm Sci 2013; 5(4)

[60] Pratap SB, Brajesh K, Jain SK, Kausar S. Development and characterization of a nanoemulsion gel formulation for transdermal delivery of carvedilol. Int J Drug Dev Res 2012; 4(1): 151-61.

[61] Aparna C, Srinivas P, Patnaik KS. Enhanced transdermal permeability of telmisartan by a novel nanoemulsion gel. Int J Pharm Pharm Sci 2015; 7(4): 335-42.

[62] Singh P, Kumar P. A review on recent advancements in the method of preparation of nanoparticles for the antimicrobial broad spectrum. World J Pharm Pharm Sci 2016; 5(7): 351-74.

[63] Sengupta P, Chatterjee B. Potential and future scope of nanoemulgel formulation for topical delivery of lipophilic drugs. Int J Pharm 2017; 526(1-2): 353-65.
http://dx.doi.org/10.1016/j.ijpharm.2017.04.068 PMID: 28461261

[64] Jain NK, Ed. Controlled and novel drug delivery. CBS publishers & distributors 1997.

[65] Kumari P, Shankar C, Mishra B. The Indian pharmacist. J Magazine 2004; (24): 7-16.

[66] Donthi MR, Munnangi SR, Krishna KV, Saha RN, Singhvi G, Dubey SK. Nanoemulgel: A novel nano carrier as a tool for topical drug delivery. Pharmaceutics 2023; 15(1): 164.
http://dx.doi.org/10.3390/pharmaceutics15010164 PMID: 36678794

[67] Tesch S, Gerhards C, Schubert H. Stabilization of emulsions by OSA starches. J Food Eng 2002; 54(2): 167-74.
http://dx.doi.org/10.1016/S0260-8774(01)00206-0

[68] Nastiti C, Ponto T, Abd E, Grice J, Benson H, Roberts M. Topical nano and microemulsions for skin delivery. Pharmaceutics 2017; 9(4): 37.
http://dx.doi.org/10.3390/pharmaceutics9040037 PMID: 28934172

[69] Ingle AP, Shende S, Gupta I, Rai M. Recent trends in the development of nano-bioactive compounds and delivery systems. In Biotechnological production of bioactive compounds. Elsevier 2020; pp. 409-31.
http://dx.doi.org/10.1016/B978-0-444-64323-0.00014-X

[70] Ashara KC. Microemulgel an overwhelming approach to improve therapeutic action of drug moiety. Saudi Pharm J 2016; 24(4): 452-7.
http://dx.doi.org/10.1016/j.jsps.2014.08.002

[71] Zhou H, Yue Y, Liu G, *et al.* Preparation and characterization of a lecithin nanoemulsion as a topical delivery system. Nanoscale Res Lett 2010; 5(1): 224-30.
http://dx.doi.org/10.1007/s11671-009-9469-5 PMID: 20652152

[72] Li P, Nielsen HM, Müllertz A. Oral delivery of peptides and proteins using lipid-based drug delivery systems. Expert Opin Drug Deliv 2012; 9(10): 1289-304.
http://dx.doi.org/10.1517/17425247.2012.717068 PMID: 22897647

[73] Bahadur S, Pardhi DM, Rautio J, Rosenholm JM, Pathak K. Intranasal nanoemulsions for direct nose-to-brain delivery of actives for CNS disorders. Pharmaceutics 2020; 12(12): 1230.
http://dx.doi.org/10.3390/pharmaceutics12121230 PMID: 33352959

[74] Chatterjee B, Gorain B, Mohananaidu K, Sengupta P, Mandal UK, Choudhury H. Targeted drug delivery to the brain *via* intranasal nanoemulsion: Available proof of concept and existing challenges. Int J Pharm 2019; 565: 258-68.
http://dx.doi.org/10.1016/j.ijpharm.2019.05.032 PMID: 31095983

[75] Tanaji DN. Emulgel: A comprehensive review for topical delivery of hydrophobic drugs. Asian J Pharm 2018; 12(02)

[76] Pant S, Badola A, Baluni S, Pant W. A review on emulgel novel approach for topical drug delivery system. World J Pharm Pharm Sci 2015; 4(10): 1728-43.

[77] Sonaje S, Gondkar S, Saudagar R. Gellified emulsion: A new born formulation for topical delivery of hydrophobic drugs. World J Pharm Pharm Sci 2013; 3: 233-51.

[78] Yadav SK, Mishra MK, Tiwari A, Shukla A. Emulgel: A new approach for enhanced topical drug delivery. Int J Curr Pharm Res 2016; 9(1): 15-9.
http://dx.doi.org/10.22159/ijcpr.2017v9i1.16628

[79] Shingade GM. Review on: Recent trend on transdermal drug delivery system. J Drug Deliv Ther 2012; 2(1)
http://dx.doi.org/10.22270/jddt.v2i1.74

[80] Kshirsagar NA. Drug delivery systems. Indian J Pharmacol 2000; 32(4): 54.

[81] Kumar D, Singh J, Antil M, Kumar V. Emulgel-novel topical drug delivery system-a comprehensive review. Int J Pharm Sci Res 2016; 7(12): 4733.

[82] Harshitha V, Swamy MV, Kumar DP, Rani KS, Trinath A. Nanoemulgel: A process promising in drug delivery system. Res J Pharm Dos Forms Technol 2020; 12(2): 125-30.
http://dx.doi.org/10.5958/0975-4377.2020.00022.1

[83] Mitkari BV, Korde SA, Mahadik KR, Kokare CR. Formulation and evaluation of topical liposomal gel for fluconazole. Indian J Pharm Educ Res 2010; 44(4): 324-33.

[84] Kumar P, Verma N. An overview on niosomes: As an auspesious drug delivery system on the bases of application. Res J Pharma Technol 2021; 14(5): 2896-902.

[85] Rashmi M. Topical gel: A review. Pharma Rev 2008.

[86] Kong M, Chen XG, Kweon DK, Park HJ. Investigations on skin permeation of hyaluronic acid based nanoemulsion as transdermal carrier. Carbohydr Polym 2011; 86(2): 837-43.
http://dx.doi.org/10.1016/j.carbpol.2011.05.027

[87] Kumar P, Verma N. To investigate the effect of span 60 and span 80 polymer on release rate of simvastatin noisome in comparison with pure simvastatin. Int J Pharm Sci Res 2021; 12(7): 3799-04.

[88] Kumar P, Pathak D, Singh P. Formulation and evaluation of the gliempride nanoparticle by complex coacervation method. Science 2016; 5(5): 1852-60.

[89] Alhasso B, Ghori MU, Conway BR. Development of a nanoemulgel for the topical application of mupirocin. Pharmaceutics 2023; 15(10): 2387.
http://dx.doi.org/10.3390/pharmaceutics15102387 PMID: 37896147

[90] Bhattacharya S, Prajapati BG. Formulation and optimization of celecoxib nanoemulgel. Asian J Pharm Clin Res 2017; 10(8): 353-65. http://dx.doi.org/10.22159/ajpcr.2017.v10i8.19510

[91] Shah VP, Simona Miron D, Ștefan Rădulescu F, Cardot JM, Maibach HI. *in vitro* release test (IVRT): Principles and applications. Int J Pharm 2022; 626: 122159. http://dx.doi.org/10.1016/j.ijpharm.2022.122159 PMID: 36067919

[92] Chavda VP, Shah D. A review on novel emulsification technique: A nanoemulsion. Res Rev J Pharmacol Toxicol Stud 2017; 5(1): 29-38.

[93] Nagaraja S, Basavarajappa GM, Attimarad M, Pund S. Topical nanoemulgel for the treatment of skin cancer: Proof-of-technology. Pharmaceutics 2021; 13(6): 902. http://dx.doi.org/10.3390/pharmaceutics13060902 PMID: 34207014

[94] Alyoussef A, El-Gogary RI, Ahmed RF, Ahmed Farid OAH, Bakeer RM, Nasr M. The beneficial activity of curcumin and resveratrol loaded in nanoemulgel for healing of burn-induced wounds. J Drug Deliv Sci Technol 2021; 62: 102360. http://dx.doi.org/10.1016/j.jddst.2021.102360

[95] Shawahna R. Effects of a grapeseed oil (*Vitis vinifera* L.) loaded dermocosmetic nanoemulgel on biophysical parameters of facial skin: A split-face, blinded, placebo-controlled study. J Cosmet Dermatol 2022; 21(11): 5730-8. http://dx.doi.org/10.1111/jocd.15161 PMID: 35713012

[96] Indrayani AW, Artini IGA, Widhiarthini IAA, Tianing NW, Jawi IM. The potential of sunscreen preparation containing ethanol extract of Moringa oliefera leaves in nanoemulgel formulation. Bali Medical Journal 2020; 9(3): 893-903. http://dx.doi.org/10.15562/bmj.v9i3.2081

[97] Pathak MK, Chhabra G, Pathak K. Design and development of a novel pH triggered nanoemulsified *in-situ* ophthalmic gel of fluconazole: *Ex-vivo* transcorneal permeation, corneal toxicity and irritation testing. Drug Dev Ind Pharm 2013; 39(5): 780-90. http://dx.doi.org/10.3109/03639045.2012.707203 PMID: 22873799

[98] Gaikwad SS, Jadhav SV, Salunkhe KS. Nanogel development and its importance in ophthalmic drug delivery system. Curr Nanomed 2022; 12(3): 204-16. http://dx.doi.org/10.2174/2468187312666220915150636