

Recent Advances and Appropriate Use of Niosomes for the Treatment of Skin Cancer

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ABSTRACT

Both melanoma and non-melanoma are the most common types of skin cancers affecting various populations across the globe. Skin malignancy is more prevalent among Caucasian populations. Non-melanoma types of skin cancers are further classified as basal cell and squamous cell carcinomas, respectively. The incidence of non-melanoma type of cancers is relatively higher than melanoma type of skin cancers. Recently published data shows that melanoma of the skin stands as the seventeenth most common type of cancer across the world. Niosome is a drug carrier in a novel drug delivery system wherein the drug is enclosed within the vesicle, which is made up of non-ionic surfactants that are stabilized by the addition of cholesterol. Niosomes help to overcome certain difficulties of skin drug deliveries such as insolubility, instability, low bioavailability, and fast debasement of medications. This review article mainly focuses on the use of niosomes in dermatology particularly aiming at the delivery of drugs via skin. In addition, this review discusses the specific use of niosomal drug delivery systems that may be useful in clinics. The niosomes are gaining popularity in the field of topical drug delivery due to their excellent characteristics like proficiency to carry both hydrophilic and lipophilic drugs, increasing the penetration of drugs, and enhancing drug stability and drug release at sustained levels.

Keywords: Niosomes, Drug carrier, Skin cancer, Penetration enhancer, Dosage form, Drug delivery, Drug therapy, Cancer treatment.

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INTRODUCTION

Cancer was the primary leading cause of approximately 10 million deaths in 2020, or close to one in every six across the globe. The most common structures that are affected by cancers are the lungs and bronchus, colon, prostate, rectum, and urinary bladder in males. However, cancer mostly appears in the thyroid, breast, lung, bronchus, colon, rectum, and uterine corpus in females.¹ In children, the maximum percentage of cancer is blood cancer, brain, and lymph node cancer, respectively.² However,

autosomal dominant inheritance accounts for ~5–10% of melanoma cases.³ In other words, irrespective of gender, offspring of parents with a known genetic mutation have a 50/50 chance of inheriting the susceptibility to cancer. This mainly occurs because of the dysfunction of vital genes that lead to disturbances in the cell cycle, and thereby cause abnormal proliferation, for instance; the absence of tumor suppressor genes that triggers the uncontrolled cell division.⁴ A reduction in DNA methylation

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is one of the characteristic features of cancer cells.⁵ In addition, the cancer cells are characterized by a decrease in the mono-acetylated H4K16 forms that particularly contribute to the majority of histone modifications.⁶

Despite these challenges, there have been various developments in the formulation for the diagnosis and treatment of skin cancer. One of the formulation aspects is niosomes which play an important role in creating advanced interventional therapies. Furthermore, contemporary cancer therapies only focus on treating the symptoms of cancer, not treating the actual cause of it. Therefore, in this review article, we explore the role of a novel drug delivery system and the importance of niosomes in cancer/actinic keratosis treatment. Many formulations are used for the treatment of cancer and several agents are used for enhancing skin penetration. These issues can limit their dose frequency, treatment period, and quantity of doses which may eventually affect cancer therapy as well. Nano-based drug delivery system has the potential to overcome these limitations. Nano-carrier serves as “magic bullets” as they can be functionalized with targeting ligands for site-specific delivery of the drug.⁶

SELECTION OF THE LITERATURE

To search for suitable articles, we used keywords such as “skin cancer”, “niosomes”, novel drug delivery”, nano-carriers“ skin penetration enhancers”, and “melanoma”. All the keywords used to search the articles were used either alone or in combination. Out of the N = 3110 articles published from 2005 to 2022, a total of N = 86 potentially relevant articles were included for final scrutiny. Most of the manuscripts were excluded after reading the title and abstract. We selected manuscripts published in the English language and excluded nonneuropathic pain literature or manuscripts with expert opinions. However, several manuscripts were excluded after reading the full texts. This was mainly due to the lack of a clear description of the type of cancer used in the study or due to the absence of its outcome. Furthermore, the literature that provided conservative treatment techniques and referrals to other studies were also excluded from the current review.

SKIN CANCERS

Melanoma is the most serious type of skin cancer; it arises when unrepaired DNA damage to skin cells results in mutations (genetic flaws), which cause the skin cells to proliferate quickly and develop into cancerous tumors. Malignant tumors are formed because of these mutations, which lead the skin cells to multiply rapidly.

In skin cancer, the growth of abnormal skin cells known as melanocytes is beyond control. The areas of the skin that come in contact with sun rays with UV radiation most often develop skin cancer.⁷ Dermatologists typically follow the mnemonic “ABCDE” termed as asymmetry, borders, color, diameter, and evolution over time to diagnose skin cancer. In addition, if the mole has an irregular shape, varying colors, and size of more than 6 mm should be biopsied to be tested for melanoma.⁸ Sun exposed areas, such as “scalp, face, lips, ears, neck, chest, arms, and hand, and on the legs” in women mostly develop skin cancer. But some regions which are not often come in contact with daylight also result in the development of skin cancers. These areas include “palms, beneath the fingernails or toenails, and genital areas”. The type of skin cancer is only identified where cancer begins. The basal skin cancer may develop in any of the basal cells of the skin of any person.⁸ Various layers of skin are shown in Figure 1.

Basal cell carcinomas (BCCs)

Basal cell carcinomas arise in the outermost layer of skin (epidermis) characterized by abnormal, uncontrolled growth. The areas which are most commonly exposed to the sun rays like “face ears, neck, scalp, shoulders, and back” mainly develop cancer. The UV radiation of the sun with intermittent high exposure or long-term exposure may cause BCCs. Cell carcinomas can be locally destructive if not detected and treated in the early stages. In sporadic cases, they can be fatal, but sometimes these cancers may spread to other sites in the body via metastasis.⁹

Squamous Cell Carcinoma (SCC)

This carcinoma starts from the squamous cells in the outermost layer of the epidermis of the skin with uninhibited growth of abnormal cells. The SCCs are commonly seen in areas of the skin where the sun exposure is maximum and showing the sign of sun damage, with wrinkles or age spots, like the face, ears, scalp, neck, and hands. Mostly SCCs caused by long-lasting exposure to UV radiation from tanning beds and

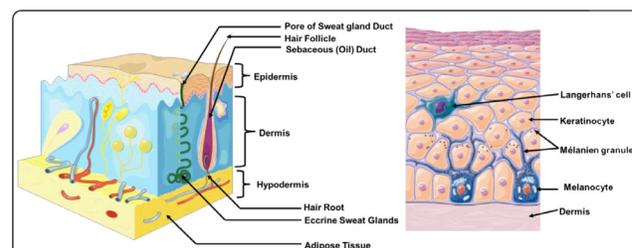


Figure 1: Showing various layers of skin.

the sun. If SCCs are not identified earlier, then they can potentially grow faster and spread to other tissue sites in the body via metastasis.¹⁰

Melanoma

The color of the skin is attributed to a pigment (melanin) that is produced by the melanocytes. Cancer is developed in these cells which are defined as melanoma. Melanomas regularly look like moles and sometimes may arise from them. Though areas of the body which are usually not exposed to the sun having moles may cause the development of melanomas. Intense, intermittent sun exposure which leads to sunburn generally triggers the condition of melanoma. According to reports, using a tanning bed indoors was linked to an elevated risk of melanoma, and using one before the age of 35 increases 75% risk for the development of cancer.¹¹ The use of tanning beds raises melanoma risk as well. Of the three most prevalent types of skin cancers, melanoma is considered to be the most harmful. Melanomas can be cured if detected and treated on time.¹¹ Most basal cell carcinomas are supposed to be caused by long-standing exposure to UV radiation from sunlight. Therefore, it can be considered to be an urbane problem. However, a few medications, like fluorouracil, have been proposed and approved for this use. However, a system must be created to administer this medication so as reach to the deep layer of skin.¹²

NEED FOR A NOVEL DRUG DELIVERY SYSTEM FOR TREATING CANCER

Unadventurous anti-cancer drugs may cause several side effects such as reduced RBC count, loss of hair, and infertility because of the toxic chemical that may kill both healthy and cancerous cells. Also, conventional anti-cancer drugs face critical drug delivery challenges such as low aqueous solubility, and rapid hepatic or renal clearance. The receptor which is responsible for attachment of anti-cancer drug is expressed on an endothelial cell of cancer tissue for active targeting to maximize therapeutic efficacy without causing toxicity to non-cancer cell.^{13,14} In unadventurous chemotherapy, a high dose of drugs must be required because they are extensively metabolized by the liver and clear by the kidney. But by novel drugs, the bioavailability of the drug is enhanced by active or passive mechanism.¹⁵

NIOSOMES

The name “niosomes” derives from the fact that the medication is enclosed in a vesicle consisting of a non-ionic surfactant in niosomes, which are amphiphilic.

Niosomes are like liposomes in that they have a bilayer structure, however, non-ionic surfactants are used in place of the phospholipids in liposomes. In addition to being biodegradable, non-toxic, and immune-suppressive, niosomes must have the advantage over liposomes of delivering both hydrophobic and hydrophilic therapeutic components in their hydrophobic bilayer and watery core, respectively.¹⁶ Despite the paucity of research on the use of niosomes for cutaneous medication delivery, some encouraging findings have been recently been published in the literature that emphasizes the favorable characteristics of niosomes for drug delivery.^{16,17} Commonly, “non-ionic surfactants, cationic polymers, and lipids” serve as the foundation of niosomes. The structure of the niosome is depicted in Figure 2.

CHARACTERISTICS OF NIOSOMES

The main feature of niosomes is that they can trap the solutes particle of the drugs and have an infrastructure containing both hydrophobic and hydrophilic parts of the drug with a wide variety of abilities to disperse and dissolve. Niosome is stable and osmotically active, discharge payload in a controlled manner using its bilayer, therefore niosomes exist as a medication warehouse in the body. Niosomes discharge the medication in a controlled manner utilizing its bilayer. Thus niosomes act as drug delivery cargos in the body. When applied, topically they enhance the skin permeability of drugs. Niosomes are designed according to the desired condition because of flexibility in their structural characteristics. Niosomes can improve drug molecules performance and can increase the stability of the entrapped drug. The availability of the drug can be enhanced at a particular site by protecting the drug from the biological environment.¹⁸ The details of the merits and demerits of niosomes are described in Table 1.

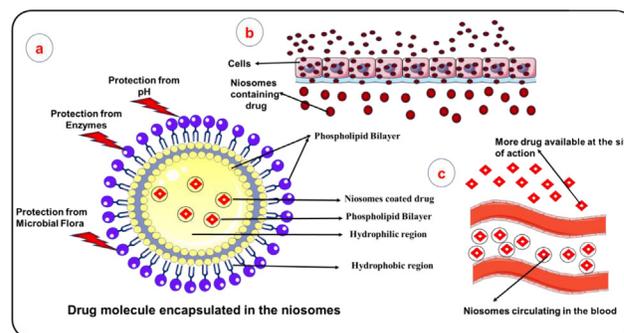


Figure 2: a) Structure and Advantages of niosome, b) Permeability enhancement of drug through niosome and c) Amount of drug at the site of action through niosomes.

Table 1: Merits and demerits of niosomes.¹⁹⁻²⁴

Merits	Demerits
1. Depending on the need, the vesicle's features, such as size and lamellarity, can be changed	1. Requires sophisticated instrumentation
2. The vesicles act as a depository of the drug from where the drug is released slowly and offer a controlled release	2. Aggregation may occur during preparation
3. Niosomes distribute both hydrophilic and hydrophobic medications in their aqueous inner core and lipid bilayer, and they also shield the drug from unfavorable circumstances	3. Leaking of the entrapped drug
4. Aqueous-based vesicular suspension such as niosomes offers better patient compliance over oil-based systems	4. Physical instability
5. Niosomes are osmotically active	5. Drug hydrolysis confines the shelf life of the dispersion by reducing drug encapsulation
6. The stability of the entrapped drug is increased	6. Time-consuming preparations
7. Improve the skin penetration of drugs when applied topically	-
8. Enhance the therapeutic performance of drugs by shielding them from the biological environment and restrictive their effects on target cells, so lowering the drug's clearance	-

Types of Niosomes

The size of the niosomes (e.g., LUV, SUV), their number of bilayers (e.g., SUV, MUV), or their manufacturing process (e.g., REV, DRV) determines their classification. Niosomes mostly come in three different categories. The following is a description of the several niosome types: Large unilamellar vesicles (LUV), Small unilamellar vesicles (SUV), and Multi lamellar Vesicles (MLV) are three types of vesicles (SUV).²⁵⁻²⁷

Multi Lamellar Vesicles (MLV)

It comprises many bilayers that each individually enclose the aqueous lipid compartment. These vesicles range in diameter from 0.5 to 10 μ m. The most popular niosomes are MLV. that are easy to build and mechanically stable when kept in storage for an extended period. These cells work best as medication transporter for lipotropic drugs.²⁶⁻²⁷

Large Unilamellar Vesicles (LUV)

An elevated fluid to lipid partition proportion is present in these, allowing for very efficient membrane lipid utilization while encasing enormous volumes of bioactive compounds. Large unilamellar vesicles are larger than 0.10 μ m in size.²⁸

Small Unilamellar Vesicles (SUV)

In one of three ways—homogenization, French press extrusion, or sonication—these sorts of niosomes are frequently produced from multilamellar vesicles. Thermodynamic instability makes small unilamellar vesicles that have a diameter of 0.025 to 0.05 μ m prone to aggregation and fusion. The amount of an aqueous

solute that is trapped in them is minimal, and their volume is also small.^{27,29,30}

Other types of Niosomes

Bola surface active agent accommodate niosomes

The surface active agent is constructed of omega-hexadecylbis-(1-aza-18 crown-6) (bolasurfactant), which contains niosomes: cholesterol and span-80 in a 2:3:1 molar ratio.¹⁴

Aspasomes

Aspartate palmitate, cholesterol, and the Aspasomes are vesicles formed by the combination of the highly charged lipid diacetyl phosphate. Niosomes are created by sonicating aspasomes after they have been hydrated with water or another aqueous solution. Drugs can have their transdermal permeability increased by aspasomes. Since aspasomes naturally possess antioxidant properties, they have been employed to alleviate illnesses brought on by reactive oxygen species.³¹

NIOSOMES IN CANCER CHEMOTHERAPY /ACTINIC KERATOSIS

Hydrophobic medications are entrenched into the bilayer itself, whereas hydrophilic drugs are held within the vesicle-like structure of the niosome.¹⁷ Loreal firstly developed Niosome in 1975. Niosomes overcome the disadvantages associated with liposomes¹⁹ (Table 2). The main purpose of developing niosomal formulation is to overcome the problem related to the chemical stability of drugs, biodegradability, biocompatibility, cost-effective production, easy storage and handling, and

Table 2: Differences between liposomes and niosomes.²¹⁻²⁴

Liposomes	Niosomes
Highly expensive	Less expensive
Phospholipids are susceptible to oxidative degradation	Non-ionic surfactants are stable for oxidative degradation
Need for a distinct method for purification, storage, and handling of phospholipid	No unique method is needed
Comparatively more toxic	Less toxic
Size range 10-3000 nm	Size range 10-100 nm

low toxicity. It can be administered in several ways, like orally, parenterally, and topically. Niosomes serve as a delivery system for medications, including synthetic and natural ones, antigens, hormones, and other bioactive substances.²³

Niosomes have a bilayer shape comparable to liposomes, while the phospholipids in liposomes are ideal additions like cholesterol and charge-inducing chemicals. "Alkyl ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, alkyl glyceryl ethers and block copolymers" are the different types of non-ionic surfactants.²⁴ A solid with a white waxy consistency, cholesterol is crucial for the formation of niosomes. It is an amphiphilic molecule that joins with the hydrophilic head of the non-ionic surfactant to generate hydrogen bonds. It significantly contributes to the strength of the niosomal structure by giving vesicles mechanical stiffness, improving encapsulation effectiveness, and reducing leakiness of the vesicular niosomes.²⁴ Additionally, vesicle size is inclined by the level of cholesterol in the body. To supply charge over the surface of the niosomal formulation, charge-inducing chemicals are used. Owing to the electro-repulsive force that prevents niosomes from aggregating and allowing them to stay suspended in the vehicle for a longer period, these charges give vesicles added stability. Depending on the choice of charge-inducing chemicals, these charges can be positive or negative; for instance, "diacetyl phosphate (DCP) and phosphatidic acid" produce negative charges, while "stearylamine (STR) and stearyl pyridinium chloride" are employed to induce positive charges.^{19,24}

Niosomes exhibit some notable advantages over liposomes, including low rate and strong chemical and storage stabilities. Despite the paucity of research on the use of niosomes for cutaneous medication delivery, some encouraging findings have recently been published in the literature that emphasize the favorable characteristics of niosomes for drug delivery.²⁴ "Non-ionic surfactants, cationic polymers, and lipids" are frequently the building blocks of niosomes.³²

Mechanisms of Niosomes Penetration through the Skin

For dermatological disorders, niosomes are challenging drug carriers. Niosomes have been used for the delivery of peptide drugs and in the cosmetics industry as well. The residence interval of the drug in the stratum corneum and epidermis can be increased by topical application of niosomes while minimizing the systemic absorption of drugs. They are believed to enhance the horny layer's characteristics by decreasing transepidermal water loss and by restoring lost skin lipids, which increases smoothness.^{32,33} After the stratum corneum layer of skin, niosomes diffuse as a whole and in the skin new smaller vesicles are formed (re-formation of niosome vesicles).^{34,35} On the surface of the skin, adsorption, and fusion of niosomes leading a high thermodynamic activity gradient at the interface for permeation of lipophilic drugs which works as a driving force.³⁶ The barrier of the stratum corneum overcomes by the effect of vesicles as penetration enhancers. As surfactants are the components of niosomes, they increase transdermal permeation and percutaneous absorption by decreasing surface tension.³⁷ Penetration mechanisms of niosomes are depicted in Figure 3.

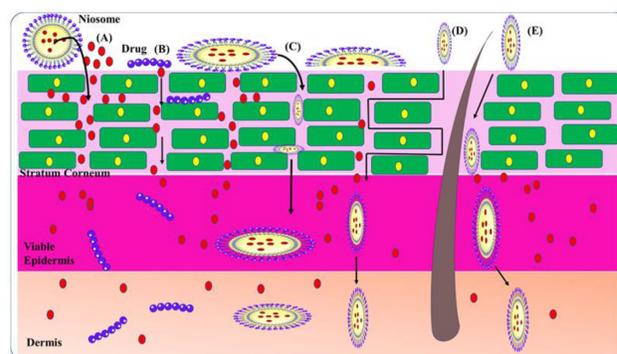


Figure 3: Possible mechanisms of niosomes penetration through skin (a) drug molecules; (b) niosome constituents act as a penetration enhancer; (c) niosome adsorption and fusion with stratum corneum; (d) intact niosome penetration through the intact skin; (e) niosome penetration through hair follicles and pilosebaceous units.

Table 3: Penetration of enhancers for anti-cancer delivery.

Anticancer Drug	Penetration methods	Penetration Enhancer/ Technique used/ Model	Highlights	References
Aminolevulinic acid	Physical Method	Iontophoresis/ <i>In vivo</i> : human	Significantly increased drug penetration	43
5-Aminolevulinic acid (5-ALA) and ALA derivatives	Chemical Method	DMSO and DMSO with EDTA/ Mouse Skin	Increased drug penetration	44
5-Aminolevulinic acid (5-ALA) and ALA derivatives	Chemical Method	Oleic acid/Mouse skin	Increased penetration of ALA in the skin	50
Atenolol	Chemical Method	Iontophoresis/ <i>in vitro</i> : pig ear	The highest permeation was attained when oleic acid was combined with iontophoresis	38
Cisplatin	Chemical Method	Monoolein and propylene Glycol/ <i>In vitro</i> : pig ear	Increased absorbance to the skin	48
Doxorubicin	Chemical Method	Monoolein and propylene Glycol	Improved drug retention in the Skin.	42
Doxorubicin	Physical Method	Iontophoresis/ <i>In vitro</i> : pig ear	Increased drug penetration	47
5-fluorouracil	Chemical Method	Azone, lauryl alcohol and isopropyl myristate Azone/ <i>In vitro</i> : pig ear	It improved drug flux through the Skin.	46
Meso-tetra-(N-methyl pyridinium-4-yl)-porphyrin and meso-tetra-(4-sulfonatophenyl)-porphyrin	Physical Method	Iontophoresis/ <i>In vitro</i> : pig ear	Increased drug skin penetration	41
Metoprolol	Chemical Method	Iontophoresis	Combination of iontophoresis with SLS further enhanced the drug delivery	51
Photosensitizer chlorin and phthalocyanine	Physical Method	Electroporation/ <i>In vitro</i> : pig ear	Increased drug skin penetration	49
Ruthenium Complex	Physical Method	Electroporation/ <i>In vitro</i> : melanoma cell line	Increased drug skin penetration	45
Tretinoin	Chemical Method	Liposomes combined with decylpolyglucosid, 8-glyceride, ethoxydiglycol, caprylocaproyl macrogol and propylene glycol	Improved drug Retention	40
Zinc phthalocyanine tetrasulfonic acid	Physical Method	Iontophoresis/ <i>In vitro</i> : pig ear	Significantly increased drug penetration	39

Methods to improve drug skin penetration

To increase skin permeability, different approaches have been developed. This include; the application of an electric field, for instance; iontophoresis and electroporation, the use of chemical enhancers, and the use of nanocarriers such as liposomes, polymeric, and stable lipid nanoparticles (Table 3). The penetration via stratum corneum and targeting of tumor cells can be improved using this methods.^{36,38}

TECHNIQUES FOR PREPARATION OF NIOSOMES

Niosomes are commonly created by the hydrating nonionic surface active agent using humidify medium. However, they are produced by several approaches, which are all thoroughly discussed here. These techniques include the single-pass technique, the enzymatic method,

“the trans-membrane Ph gradient method, lipid layer hydration, reversed-phase evaporation, EER injection, sonication, the transmembrane pH gradient method, and microfluidization”.

Method of trans-membrane pH gradient

A thin lipid layer is created on the inside of a round-bottomed container using surfactant and cholesterol that have been produced in chloroform and vaporize under low compulsion. (To hydrate the resultant lipid coating, an acidic chemical is needed) (usually citric acid). Cycles of freezing and thawing are applied to the prepared multilamellar vesicles.⁵²⁻⁵³ The pH of the specimen is then raised to 7.2. This process can result in niosomes, claim Bhaskaran and Lakshmi⁵⁴ at 87.5 percent entrapment effectiveness (EE).

Hygroscopic lipid layer

The narrow lipid layer on the wall of a vacuum flask is created by evaporating surfactant and cholesterol that have been dissolved in chloroform under low pressure. Under gentle shaking at a temperature just a little bit over the phase conversion temperature of the surfactants, the resulting layer was dripping with a drug-containing fluid blend.⁵⁴⁻⁵⁷ The mass per batch, evaporation angle, the rotation speed of the vacuum rotary elevator, and humidifying process were some of the factors that were validated. To create the latter variable, several solvents (water, phosphate buffer (PB), and PB/drug) and humidity temperatures below and above the gel, conversion temperature was used. Narrow layer dripping was used by Sathali and Rajalakshmi to create terbinafine niosomes, and when those were sonicated, they turned into microscopic unilamellar niosomes.⁵⁴

Reversible phase vanishing

The surface active agents are mixed in an ether and chloroform solution before being added to the aqueous stage to create the medication without creating an emulsion. The organic phase is evaporated after homogenizing the resulting mixture.⁵⁴ To produce spherical, stable, homogeneous vesicles, the lipid or surface active agent first appears as a gel before hydration.^{58,59}

Ether Injection

Before being progressively injected through a yardstick pointer into a fluid phase, diethyl ether is used to dissolve the surfactant, cholesterol, and medicine combination. The ether solution is evaporated over the boiling point of the dissolvent using a rotary evaporator. The massive unilamellar vesicles are exposed to more air after the organic solvent has evaporated to condense and create single-flagellar vesicles.⁵⁸

Nitrogen Effervescence

This process establishes niosomes in a single step without the need for any organic solvents, making it innovative. At pH 7.4 and 70°C, this buffer is used to disperse cholesterol and surfactant. It was most likely a flask with three necks and a spherical bottom. The first two necks are set in water-chilled outflow to manage the temperature. Due to the homogeneity of the material, nitrogen gas was able to enter through the third neck (cholesterol and surfactant). As a result, big unilamellar vesicles were constructed. A steady surge of nitrogen gas bubbles is fed through the disbandment to form tiny unilamellar vesicles.⁶⁰

Sonographic

Baillie *et al.* techniques were used to prepare niosomes for the sonication-mediated approach.⁶¹ The water phase that carries the medication in flax is disseminated with the surfactant cholesterol mixture. For three minutes at 60°C, the mixture is treated to probe sonication or a bath sonicator to induce the development of multilamellar vesicles.⁶²

Enzymatic approach

In this method, niosomes are generated from a mixed micellar solution via an enzymatic approach. Esterase cut the ester bond, resulting in the degradation of substances like polyoxymethylene and cholesterol, which produce multilamellar niosomes. Both polyoxymethylene cholesteryl subacetate diacetate and polyoxymethylene stearyl derivatives⁶³ are the surfactants used in this process.⁶⁴

Single-Pass Technique

A lipid solution or suspension is continuously extruded via a nozzle using this proprietary technique after passing through a porous device. A constrained number of sizes between 50 and 500 nm are made available to niosomes by the combination of homogenization and high-pressure extrusion.⁶⁵

Micro-fluidization

Recently, micro fluidization has been used to give unilamellar vesicles a specified approximate circulation. By connecting two fluidized surges at an extremely high rate in an appropriately recognized minor-scale vehicle inside the interface chamber, this technique—which is based on the submerged jet principle—can be used to join two different types of fluids. The energy transported to the system has been resolved to remain in the region where the niosomes are created due to the thin-liquid sheet impingement near a common front. The outcome was a Niosomes form with a stronger consistency, a more manageable size, and excellent repeatability.⁶⁵

UNENTRAPPED DRUG SEPARATION

Diverse techniques, including centrifugation, gel filtration, and dialysis, were used to remove untrapped solute from the vesicles.

Dialysis

The primary method for removing the untrapped medication from vesicles is dialysis. In dialysis tubing, the aqueous niosomal dispersion was compared to phosphate buffer, normal saline, or glucose mixture.⁶⁰

Gel filtering

Untrapped drug is unaffected by niosomal dispersion gel filtering via a Sephadex-G-50 column and percolation with phosphate-buffered saline or normal saline.⁶⁰

Centrifugation

The above phase was eliminated after centrifuging niosomal suspension. To produce a niosomal suspension devoid of untrapped drugs, the pellet was resuspended.^{66,67}

CHARACTERIZATION OF NIOSOMES

In general, characterization of niosomes is similar to that of other nanocarriers.⁶⁸

Size

The beam slant scattering method might be used to calculate the mean diameter of niosome vesicles, which are thought to be spherical in shape.⁶⁹ To assess the diameter of these vesicles, optical and electron microscopy, ultracentrifugation, molecular sieve chromatography, freeze-fracture electron microscopy, photon correlation microscopy, and molecular and photon microscopy may all be used.^{70,71} The increase in vesicle width caused by niosome freeze-thawing might be due to vesicle fusion occurring during the cycle.

Bilayer formation

An X-cross formation is indicative of the gathering of non-ionized surfactants into a bilayer's vesicle under light polarisation microscopy.⁷²

Number of lamellae

Small angle X-ray scattering, electron microscopy, and nuclear magnetic resonance (NMR) spectroscopy are used to ascertain.⁷⁰

Membrane rigidity

Membrane stiffness may be estimated by following the vigor of a fluorescence probe as a role of temperature.⁷²

Entrapment efficiency

The untrapped medicament is removed after niosomal dispersion is prepared, and the drug that is still entrapped in niosomes is identified by completely disrupting the vesicles with 50% n-propanol or 0.1 percent Triton X-100 and analyzing the resulting mixture using the correct trail method for the drug.⁷³ It is illustrative of: Entrapment efficiency (EE) = (Amount entrapped / total amount) × 100.

In vitro release study

The use of dialysis tubing was described as a technique for *in vitro* release rate analysis.⁷⁴ A dialysis bag has been cleaned and put in distilled water to soak. The tubing-based bag was sealed after the vesicle suspension was pipetted inside of it. The vesicle-containing bag was next placed in a 250 ml beaker containing 200 ml of buffer solution, which was constantly shaken at either 25°C or 37°C. The buffer was subjected to periodic medicament content analysis using the proper trail technique. Another method utilized gel filtration on Sephadex G-50 powder that was kept in double-distilled water for 48 hr to allow the isoniazid-encapsulated niosomes to enlarge.⁷⁵ The top of the column was first filled with 1 ml of the ready-to-use niosome solution, and the elution was performed using ordinary saline. When isoniazid is released from niosomes, it initially appears as a somewhat thick, white opalescent solution and later as a free drug. Niosomes were isolated and placed into a partition tube with a sigma partition sac connected to one end. The dialysis tube was placed in a pH 7.4 phosphate buffer solution and stirred with a magnetic stirrer. High-performance liquid chromatography (HPLC) was used to extract samples and analyze them at predefined intervals.⁷⁶

In vivo Study

This study made use of albino rats. Groups were used to divide up these rats. Niosomal suspension was administered intravenously (via the tail vein) using the proper disposal syringe for the *in vivo* investigation.

FACTORS AFFECTING PHYSIO-CHEMICAL PROPERTIES OF NIOSOMES

Further discussion is given on several variables that impact the physio-chemical characteristics of niosomes.

Choice of surfactants and main additives

To make niosomes, a surface active agent has to have a hydrotropic head and an aquaphobic tail. The aquaphobic tail can be composed of one, two, or even more steroidal, perfluoroalkyl, or alkyl groups.⁷⁶ Ether-type surfactants are more dangerous than dialkyl-type surfactants due to their single-chain alkyl tail. Since esterases *in vivo* break down ester-linked surfactants into triglycerides and fatty acids, they are less toxic and chemically less stable than ether-type detergent.⁷⁷ Surfactants having alkyl chains spanning from C12 to C18 are ideal for the production of niosome. Vesicles can be produced by Span series surfactants with an HLB value of 4 to 8 value.⁷⁸ Stable niosomes can be produced by combining several chemicals with detergent and medicament. The niosomes that are created have a

range of morphologies, and by altering the features of the membrane with various additives, one may vary the permeability and stability characteristics of the niosomes. Polyhedral niosomes composed of C16G2 react when a little quantity of solulan C24 (cholesteryl poly-24-oxyethylene ether) is introduced. Surfactants in the Span series with an HLB number of 4 to 8 can generate vesicles.⁷⁸ The steric barrier that would otherwise cause aggregation does not change the structure of the polyhedral niosomes. But when C16G2:cholesterol:solulan (49:49:2) is added, spherical niosomes are produced.^{79,80} Membrane composition affects niosomes average size. The niosomal system becomes stiff when a cholesterol molecule is added, which limits medication leakage from the noisy system.⁸¹

Temperature of hydration

The humidified temperature affects the niosomes shape and size. For best results, it must be higher than the temperature at which the system transitions from the gel to the liquid phase.

The niosomal system's fluctuating temperature affects the assembly of surfactants into vesicles and alters vesicle shape.^{76,80}

At 48°C, a polyhedral vesicle formed of C16G2:solulan C24 (91:9) becomes a spherical vesicle after heating. However, after being cooled from 55°C, the vesicle initially forms a collection of small, spherical niosomes at 49°C, and then, at 35°C, it changes into polyhedral structures. While being heated or cooled, the vesicle formed by C16G2:cholesterol:solulan C24 (49:49:2) remains the same.⁶⁸ The volume of the humidify medium and the duration of the niosomes humidify are additional crucial criteria in addition to those already discussed. The construction of weak niosomes or the development of drug leakage issues could occur from the improper selection of these components.

Nature of encapsulated drug

The physio-chemical effects of the medicament that is encapsulated affect the charge and stiffness of the niosome bilayers. The medicament is interconnected with surfactant head groups and produces the charge that induces mutual repulsion between surfactant bilayers to enhance vesicle size.⁷⁰ Vesicle aggregation is prevented by the bilayer's charge production.

Factors that affect vesicles size, entrapment efficiency, and release characteristics

Drug

When a medicament is trapped in niosomes, the interconnection of the solute with the head groups of

the surfactant boosts the charge and mutual revulsion of the surface active agents bilayers, increasing the size of the vesicle. The polyoxymethylene glycol (PEG)-coated vesicles' long PEG chains enclose the drugs, reducing their propensity to enlarge. The hydrophilic-lipophilic equilibrium of the medication influence the level of involvement.⁸¹

Amount and type of surfactant

Depending on the temperature, the kind of lipid or surfactant, and the presence of other elements like cholesterol, the bilayers of the vesicles can either be in the so-called liquid state or the gel state. While the structure of the bilayers is more disorganized in the liquid state, it is present in the gel state in a well-ordered form. The mean size of niosomes rises as the HLB of surfactants such as Span 85 (HLB 1.8) to Span 20 (HLB 8.6) increases because the surface free energy decreases as the hydrophobicity of surfactants increases.⁸² The surfactants and lipids are described by the temperature at which the gel-liquid phase transition takes place (TC).

Cholesterol content and charge

Cholesterol improves the hydrodynamic diameter and trapping effectiveness of niosomes. In general, cholesterol has two effects. Cholesterol both raises the chain order of bilayers in the fluid state and decreases the chain order of bilayers in the gel state. When cholesterol levels are high, the gel state changes to a liquid-ordered phase. The bilayers' stiffness increased with increasing cholesterol content because it reduced the rate at which material was released from its encapsulation. The presence of charge tends to expand the interflagellar space between consecutive bilayers in multilamellar vesicle formations, resulting in a larger total entrapped volume.⁸²

Resistance to osmotic stress

When a hypertonic salt mixture is introduced to a suspension of niosomes, the diameter of the niosomes decreases. In a hypotonic salt mixture, there is a delayed release with little vesicle bump that is brought on by the inhibition of fluid elution from vesicles, followed by a rapid release that could be brought on by the mechanical detach of vesicle structure under osmotic stress.⁸³

APPLICATION OF NIOSOMES

In the cosmetic industry, niosomes have been used since 1975, for dermatological purposes. An anti-aging formulation launched by Lancome was the first niosomal product. The major limitation of slow penetration of

drug delivery by the transdermal route can be overcome when drugs are incorporated in niosomes and delivered by the transdermal route, due to which penetration in the skin is increased. Niosomal drug delivery is effective for various pharmacological agents that are used to treat various diseases.⁴⁵ For instance; iobitridol which is a diagnostic agent used for X-ray imaging uses niosomes as carriers. Topical niosomes may serve as a penetration enhancer, solubilization matrix, rate-limiting membrane barrier, or as a local depot for sustained release of dermally active compounds for the modulation of systemic absorption of drugs.⁴⁶

To fight a variety of diseases, several pharmacological substances may be able to use niosomal drug delivery. Following is a discussion of some of their therapeutic applications.

Niosomes as a drug carrier

Iobitridol, a medication used for X-ray imaging, has also been transported by niosomes. Topical niosomes can work as a solubilization matrix, a local depot for the prolonged release of substances with dermal activity, penetration enhancers, or a membrane barrier that limits the pace at which medications are absorbed into the body.

Drug targeting

Niosomes' capacity to target medications is one of their most advantageous features. Drugs can be directed to the reticuloendothelial system using niosomes. Niosome vesicles are occupied preferentially by the reticuloendothelial system (RES). Opsonins, molecules found in the circulating serum, regulate the uptake of niosomes. These opsonins identify the niosome for removal. Animal cancers that are familiar to spread to the liver and spleen are treated with this type of localized medicine. The liver parasite infections can be treated with this medicine localization. Niosomes can be utilized to guide drugs away from the RES and toward other organs. Niosomes can be targeted to certain organs by joining them to a carrier system (like antibodies), as immunoglobulins readily bind to the lipid surface of niosomes.⁸⁴

Antineoplastic

The major part of anti-cancer medications have significant adverse effects. Niosomes can change a drug's metabolism, prolong its half-life, and increase circulation, all of which reduce its negative effects. Niosomes limit the pace of tumor proliferation and increase plasma levels while delaying elimination.⁸⁵

Delivery of peptide drugs

It has long been difficult to avoid the enzymes that would break down peptides used in oral medication administration. Niosomes are being studied to see if they may be effectively protect peptides against gastrointestinal peptide breakdown. An *in-vitro* experiment employing an oral delivery of a vasopressin derivative trapped in niosomes showed that drug involvement significantly increased the stability of the peptide.

Use in studying immune response

Niosomes are employed to research the nature of the immune response to antigens because of their immunological selectivity, low toxicity, and enhanced stability. Non-ionic surfactant vesicles' ability to serve as adjuvants after parenteral administration of a variety of various antigens and peptides is well known.²⁶

Niosomes as carriers of hemoglobin

Haemoglobin is perhaps carried through the blood by niosomes. Niosomal vesicles can transport hemoglobin in anemic people because they are permeable to oxygen.

Leishmaniasis

A parasite from the genus *Leishmania* infects the liver and spleen cells to cause leishmaniasis, a disease. When treating illnesses where the infectious agent is found in a reticuloendothelial system organ, niosomes can be employed to target the medicine (RES). Antimonials, which are routinely prescribed medications and are related to arsenic, harm the heart, liver, and kidney at high concentrations. According to reports, two dosages administered on consecutive days had an additive impact and improved the niosomal formulation's ability to dissolve sodium stibogluconate. According to Pawar SD *et al.*, the introduction of niosomes allowed for the administration of higher doses of the medication without inducing side effects, increasing treatment effectiveness.⁸⁶

Transdermal drug delivery

Slow drug absorption through the skin is a key problem of transdermal drug administration; nevertheless, transdermal distribution of drugs contained in niosomes has increased the rate of absorption.

Cosmetic delivery

Non-ionic surfactant vesicles were initially used in cosmetics by L'Oreal. Niosomes were created and patented by L'Oreal in the 1970s and 1980s. Niosome, Lancôme's debut product, was launched in 1987 called Niosome.^{26,29} Niosomes have several benefits, including

the capacity to boost the stability of medications that are entrapped in them, improve the bioavailability of components that aren't well absorbed, and improve skin penetration.

Hormone delivery

It was investigated how well the human stratum corneum absorbed estradiol from vesicular formulations *in vitro*. The vesicles were collected with non-ionic n-alkyl polyoxyethylene ether surfactants (CnEOM). Two processes are hypothesized to play a key part in vesicle-skin interlinkage; the stabbing-enhancing effect of surfactant molecules and the influence of the vesicular structures brought about by their adsorption at the stratum corneum suspension interface.⁸⁶

Neoplasia

The anthracycline antibiotic doxorubicin, which has wide-spectrum anti-tumor action, exhibits an irreversible, dose-dependent cardiotoxic impact. This drug's niosomal administration to mice with the S-180 tumor lengthened their lives and slowed the growth of the tumor. The drug's half-life was lengthened, its circulation was prolonged, and its metabolism was changed via niosomal entrapment. Mice bearing the S-180 tumor experienced complete tumor regression after intravenous treatment of methotrexate entrapped in niosomes, as well as increased plasma levels and deliberate clearance.

Vaccine Delivery

An intriguing class of vaccine carrier systems is made up of formulations located on non-ionic surfactant vesicles (niosomes), which are those only seldom immunogenic. Niosomes are getting a lot of interest as an oral vaccine delivery system and for topical immunization. Surfactant, cholesterol, and diacetyl phosphate concentrations were studied for their impact

on niosome shape, particle size, entrapment efficiency, and *in vitro* antigen release. Investigating the immune-stimulating action, it was shown that topical niosomes generated equivalent amounts of endogenous cytokines and serum antibody titers to intramuscular recombinant HBsAg and topical liposomes.⁸⁶

Diagnostic imaging with niosomes

The X-ray imaging diagnostic agent iobitridol is thought to be transported through niosomes. The film hydration process was used to prepare the niosomes, which were then sonicated. A method was used to carry out the increasing encapsulation and stability of vesicles.⁸⁶

Other Applications

Sustained Release

Because they might be kept in circulation by niosomal encapsulation, medicines with low therapeutic index and low water solubility can benefit from the go-through release action of niosomes.⁸⁵

Localized drug action

Drug delivery utilizing niosomes is one way to create localized drug activity since their size and limited porosity between connective tissue and epithelium maintain the medication isolated at the site of administration.⁸⁰ Recently developed topical formulations of niosomes are mentioned in Table 4.

CONCLUSION

Niosomal vesicular drug delivery system possesses good drug penetration capacity via the skin, and therefore it is considered to be a potential dermal drug delivery technique. Drug localization that is relatively stable and non-toxic is also successful. They also offer targeted and sustained drug delivery since they can carry both hydrophilic and hydrophobic medications. High doses

Table 4: Niosomes as a drug carrier for skin cancer treatment using different methods with their results.

Drug	Final Dosage Form	Result	Ref.
Cyclophosphamide	Niosomal gel	Good formulation approach design was achieved for Melanoma treatment	86
Fluorouracil	Niosomes	Affect the permeation of the drug into the Skin	82
5-Fluorouracil	Niosomes	Increased drug penetration of 8- and 4- folds	85
5-Fluorouracil	Niosomal gel	Better permeation parameters	81
5-Fluorouracil	PEG-coated Niosomes	More effective antitumoral activity of the PEGylated niosomal 5-FU	84
Paclitaxel	Niosomes	An entrapment Efficiency of about 80.5% was achieved proving that the drug-loaded niosomes have excellent pharmacokinetics	80
Withania somnifera	Niosomal gel	Withaferin A and withanolide A released from the niosome which enhances topical administration	83

of anticancer medications cannot be delivered into tumor cells because of the keratinized stratum corneum that prevents pharmaceuticals from penetrating the skin. The utilization of physical and chemical techniques as well as the creation of drug delivery systems based on nanoparticles are crucial methods for enhancing the ability of medications to permeate the skin. These formulations frequently improve anticancer medication penetration through the skin, which is a crucial advantage. In addition, they provide various benefits, such as reduced skin sensitivity and improved protection for encapsulated drugs, and thereby nanocarriers act as promising solutions for drug delivery.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BCCs: Basal cell carcinomas; **SCC:** Squamous cell carcinoma; **MLV:** Multi Lamellar Vesicles; **LUV:** Large Unilamellar Vesicles; **SUV:** Small Unilamellar Vesicles; **EE:** Entrapment efficiency; **NMR:** Nuclear Magnetic Resonance.

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