NIOSOMES USED IN TOPICAL AND TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT –

Modern drug encapsulation technologies, such as niosomes, have revolutionized the medical, pharmaceutical, and cosmetic industries by addressing various formulation problems. Niosomes, also known as non-ionic surfactant vesicles, are composed of non-ionic surfactants, cholesterol, and other lipids. They can encapsulate both hydrophilic and hydrophobic drugs, making them versatile drug delivery systems. There are different types of niosomes based on their size, number of bilayers, or preparation method. The three main types are Multi Lamellar Vesicles (MLV), Large Unilamellar Vesicles (LUV), and Small Unilamellar Vesicles (SUV). The structure of niosomes consists of bi-layered structures formed by non-ionic surfactants. Cholesterol is used to enhance the rigidity and encapsulation efficiency of niosomes. Niosomes offer several advantages, including improved drug stability, sustained release, increased bioavailability, and enhanced drug penetration through the skin. However, they also have some limitations, such as stability issues and potential drug leakage. Various methods are employed for niosome preparation, including thin film hydration, ether injection, dehydration-rehydration vesicles, reverse-phase evaporation, and others. These methods ensure proper encapsulation of drugs and control niosome size. Purification of niosomes can be achieved through centrifugation, gel filtration, and dialysis, ensuring the removal of unentrapped drugs or unwanted chemicals. Niosomal technology finds applications in delivering chemical drugs, proteins, peptides, gene therapy, and vaccine development. They are also explored for in vivo stability, biodistribution, and gene delivery efficiency. Overall, niosomes have the potential to revolutionize drug delivery and address various challenges in the medical and pharmaceutical industries. With ongoing advancements and research, they are likely to become even more effective and widely used in the future.

KEYWORDS-

Niosomes, Topical, Transdermal, Novel, Targeted

INTRODUCTION –

Modern drug encapsulation technologies have had a significant impact on solving development problems in the medical, pharmaceutical and cosmetic industries. These problems include improving the physicochemical properties of the drug in the formulation, such as low bioavailability and solubility, compatibility issues, toxicity, and instability (1). The purpose of

niosomes, a new drug delivery system (NDDS), is to increase bioavailability and transport the active ingredient to the site of disease in a regulated way at a rate determined by the body's needs during the course of treatment (2)

Niosome –

Niosomes are also called as non-ionic surfactant vesicles because of the presence of non-ionic surfactants in their structure. Non-ionic surfactants, such as fatty acids, alkyl esters, amino acids, cholesterol, and other types of lipids, are utilised in niosomal formulations before the formulation is hydrated. The hydrophilic-lipophilic balance of the surfactant is necessary for vesicle formation. Cholesterol may or may not be utilised in the formulation, although utilising cholesterol will raise the rigidity of the bilayered structure and boost the efficacy of the drug's encapsulation. The hydrophobic and hydrophilic medications can both be made into niosomes(3)

Types of niosomes –

Niosomes are classified according to their size (e.g., LUV, SUV), the number of bilayers they include (e.g., SUV, MUV), or the method used to make them (e.g., REV, DRV). Most niosomes fall into one of three kinds. The various niosome kinds are described as follows: Three different forms of uniflagellar vesicles (SUV) include large uniflagellar vesicles (LUV), small uniflagellar vesicles (SUV), and multi flagellar vesicles (MLV) (4)

1) **Multi Lamellar Vesicles (MLV)-**

It consists of many bilayers, each of which isolates the aqueous lipid compartment. The diameter of these vesicles varies from 0.5 to 10 metres. The most often used niosomes are MLV, which are simple to construct and mechanically stable when stored in storage for a long time. The finest pharmaceutical transporter for lipotropic medications is these cells (4)

2) **Large Unilamellar Vesicles (LUV)-**

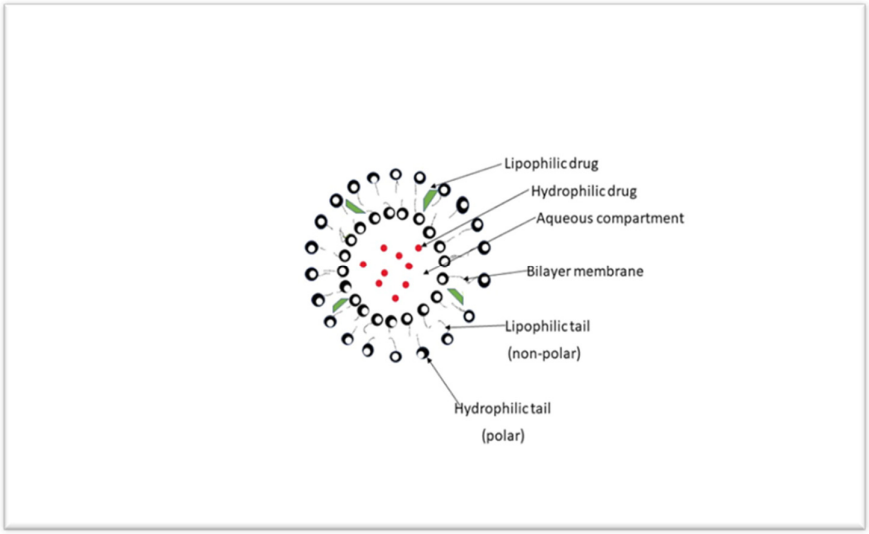
These have a high fluid to lipid partition ratio that allows for extremely effective membrane lipid utilisation while encasing huge amounts of bioactive chemicals. Greater than 0.10 m in size are big unilamellar vesicles (4)

3) **Small Unilamellar Vesicles (SUV)-**

These kinds of niosomes are typically generated from multilamellar vesicles by homogenization, French press extrusion, or sonication. Small unilamellar vesicles with a diameter of 0.025 to 0.05 m are susceptible to aggregation and fusion due to thermodynamic instability. They are of modest volume and contain only a little amount of an aqueous solute trapped (4).

Structure of noisome –

Understanding the fundamental components of niosomes is crucial because it could affect the chemicals that can create niosomes and the way that medications are loaded into them for delivery (5). Non-ionic surface-active substances have a bi-layered structure called niosomes. These thermodynamically stable bilayered structures can only be created when the right ratio of cholesterol and surfactants is used, and when the temperature is above the gel to liquid transition temperature (6) The opposite of aqueous solutions is an organic solution, while the opposite of hydrophilic heads is an aqueous solution (5)



Components of niosomes –

1) **Cholesterol –**

To strengthen and create niosome formulations, cholesterol, a steroid derivative, is employed (7) It affects the membrane's permeability, rigidity, entrapment effectiveness, ease of rehydrating freeze-dried niosomes, stability, and storage time (8)When the surfactant's HLB value is higher than 6, cholesterol is required to form a bilayer, and it also improves vesicle stability at lower HLB values (9)

2) **Non-ionic surfactants-**

One of the most crucial elements of niosomes are non-ionic surfactants. To produce niosomes, which are utilised to entrap different drugs, different kinds and their combinations are used (8) A non-ionic surface-active substance serves as the fundamental ingredient in the production of niosomes. Non-ionic surface-active molecules have a polar head and a non-polar tail, making them amphiphilic in nature. In compared to anionic, cationic, and amphoteric surfactants, these surfactants are more stable, compatible, and less hazardous because they do not contain any charge (6)

3) **Hydration Medium-**

One of the most crucial ingredients needed for the creation of niosomes is the hydration medium. Phosphate buffer is typically employed as a hydration medium. However, the solubility of the medicine that is encapsulated affects the buffer's pH(8)

4) **Charged molecule-**

Certain charged molecules are provided to niosomes in order to promote their stability by offering electric repulsion to prevent collisions. Two substances that are negatively charged are phosphatidic acid and dicetyl phosphate (DCP). Stearyl pyridinium chloride, a well-known charged substance utilised in niosomal preparations, is similar to stearyl amine in structure(8).

Advantages of niosomes –

- Drugs may be stored in vesicles and then released gradually over time.

- It increases the stability of the drug that has been trapped while being osmotically active and stable.
- They enhance the therapeutic qualities of drug molecules by preventing them from leaving the bloodstream quickly, shielding them from the biological environment, and reducing their contact with target cells.
- The surfactant is biodegradable, biocompatible, and immune-suppressive.
- They increase the oral bioavailability of poorly absorbed medications and boost drug penetration via the skin (7)

Disadvantages of niosomes –

- Although the niosome delivery system has several advantages, stability is an issue because the drug can be hydrolysed in an aqueous suspension of niosomes. There may also be a problem with the drug leaking out of the capture site and clumping the niosomes(6).

Transdermal drug delivery system –

The most common medication administration method is oral, however it has significant drawbacks, such as first pass metabolism, drug breakdown in the gastrointestinal tract due to enzymes, pH, etc. The term "transdermal drug delivery system" (TDDS) describes a method of delivering drugs through the skin to provide local or systemic therapeutic effects. It ranks right behind oral medication and injection as one of the research priorities for third-generation pharmacological preparations(10).The most effective way to deliver chronic and stomach irritant medications is by transdermal drug delivery. Transdermal patches can be simply removed if the need for medication administration is no longer there. Transdermal drug delivery keeps drug levels consistent. Because the majority of medications must be carried via several layers of the skin, their physicochemical qualities prevent most of them from being manufactured as transdermal dosage forms. To be transported through the skin, a medication must have a high lipophilicity. However, in the present day, a number of developments have been made to develop the transdermal delivery of the medicine, including iontophoresis, magnetophoresis, microneedles, etc. To solve these issues, novel drug delivery systems including lipid-based nanovesicles were created. Drug delivery using standard dosage methods was reducing the penetration of the drug as well as the release of the drug (3)

Topical drug delivery system-

The application of topical medications has been practised for a very long time in order to achieve a variety of effects on the skin's surface, epidermis, dermis, and hypodermis. However, the traditional topical treatments have a number of drawbacks, including limited percutaneous penetration (due to the stratum corneum's function as a barrier) and absorption into the bloodstream. A number of approaches, including the delivery of absorption enhancers, are now offered by scientific reports that can carry medications to the skin. Due to its exceptional qualities, such as improving drug penetration, offering a continuous pattern of drug release, and having the capacity to carry both hydrophilic and lipophilic medicines, niosomes are currently enjoying increased popularity in the field of topical drug administration(11,12) Topical medicines deliver their effects just where they are needed. Because it can penetrate the skin more deeply, absorption is improved. There are no benefits of topical administration over traditional dosing forms (11)

Niosomal gel topical therapy encourages drug retention in the skin's most superficial layers, through the SC, where it reaches the viable layers of the epidermis (VE) and, to a lesser extent, the top layer of the dermis. On the other hand, when a transdermal effect is required, it is important to facilitate the penetration of medications that have been encapsulated in niosomal gel so that they can pass through the dermis and epidermis and reach the blood vessels and systemic circulation above the hypodermic tissue. As a result, in addition to the kind and physicochemical properties of the vehicle employed to incorporate them into the final formulation, niosome shape, size, and elasticity are the key factors influencing the efficacy of these therapies. Depending on how they are manufactured, the elements of the niosomal vesicles and the selected vehicle can alter these properties (1)

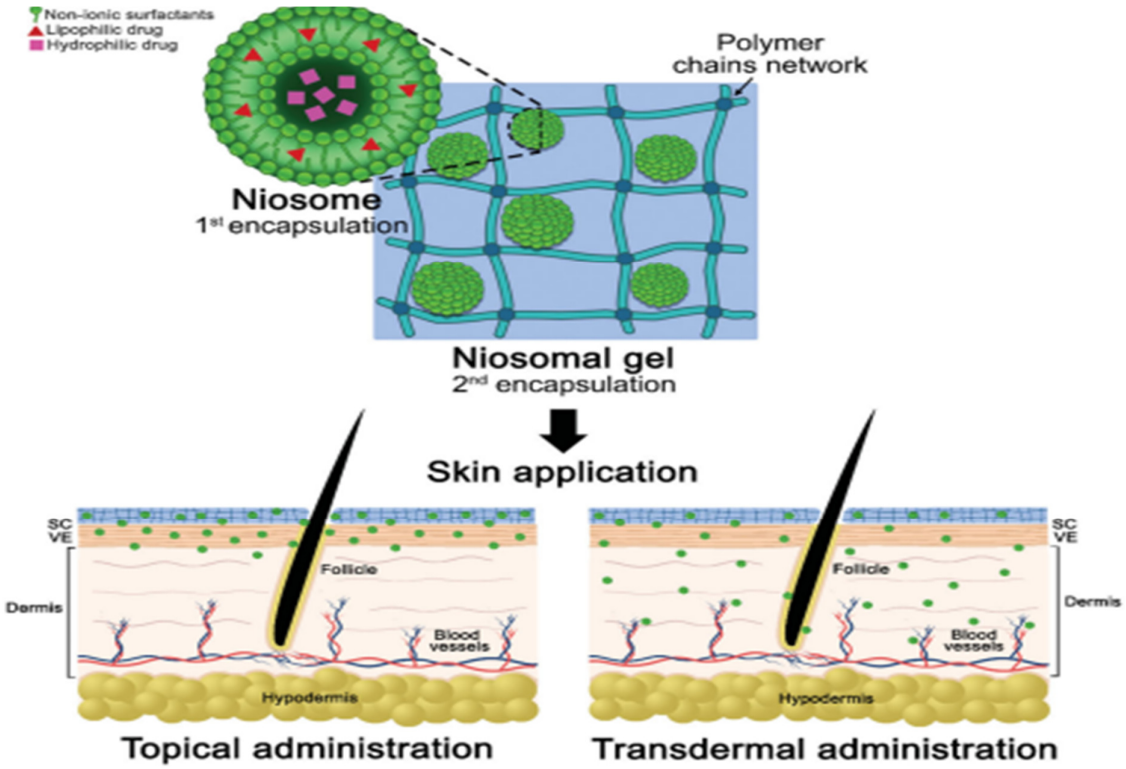


Fig.-Schematic representation of niosomal gel for encapsulation of lipophilic and hydrophilic drugs for skin application. While topical administration promotes the retention of these systems for a local effect, transdermal application improves their permeation for systemic effect. SC: stratum corneum; VE: viable epidermis

Mechanisms of niosomes penetration through the Skin-

Niosomes are difficult medication carriers for dermatological conditions. The delivery of peptide medications as well as the cosmetics sector have both exploited niosomes. By applying niosomes topically, it is possible to prolong the time that a medicine stays in the stratum corneum and epidermis while reducing its absorption into the bloodstream. By reducing trans epidermal water loss and replenishing lost skin lipids, which improves smoothness, they are thought to improve the horny layer's features. Following the stratum corneum layer of the skin, the niosomes spread as a whole and form new, smaller vesicles in the skin (re-formation of niosome vesicles). Niosome fusion and adsorption on the skin's surface create an interface with a strong thermodynamic activity gradient that acts as a catalyst for the absorption of medicines with a high lipophilicity. Vesicles' role as penetration enhancers allows them to break through

the stratum corneum's barrier. Considering that surfactants are niosome components, they boost transdermal penetration and percutaneous absorption by lowering surface tension(4)

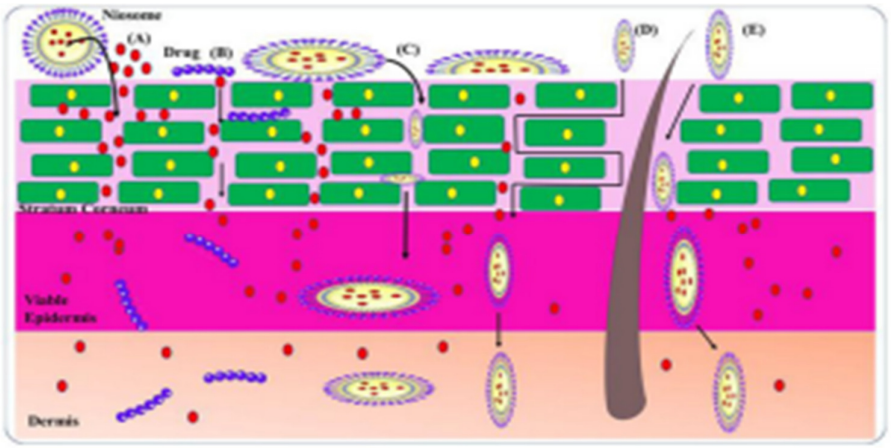


Fig -Possible mechanisms of niosomes penetration through skin (A) drug molecules; (B) niosome constituents act as a penetration enhancer; (C) niosome adsorption and fusion with stratum corneum; (D) intact niosome penetration through the intact skin; (E) niosome penetration through hair follicles and pilosebaceous units.

METHODS OF PREPARATION –

1) Thin film hydration method –

Bangham et al. were the first to present the TFH approach for the preparation of liposomes. The TFH method is one of the best and easiest methods for the preparation of liposomes and can also be used for the preparation of niosomes (13) . This approach is often used to obtain MLVs, which are good models for lipophilic encapsulation due to the presence of multiple bilayer (1).Thin-film hydration (TFH), commonly known as hand-holding, involves antibiotics, cholesterol, and hydrophobic charges in weak organic solvents such as chloroform, diethyl ether, ethanol or methanol (14). The heavy organic was removed without trace by the evaporator area until a film formed and the film dried (3). Thin layers may contain hydrophilic substances (14). The dry surfactant film is hydrated with the corresponding aqueous phase at a temperature higher than the transition temperature (Tc) of the surfactant used (1). The surfactant typically has a glass transition temperature (Tc) of greater than 60 °C. Hydration of the surfactant membrane creates heterogeneous large multilamellar vesicles, while gradual hydration leads to the formation of giant unilamellar vesicles (GUVs) (14).The hydration medium is physiological saline, buffer, 5% glucose, etc. and lipid phase or aqueous phase is added according to the hydrophilicity and lipophilicity of the drug (3). After rehydration is complete, MLV vesicles of various diameters are formed (13). This technique is used in conjunction with sonication to obtain vesicles with narrow size distribution (5).Usually, this size reduction is achieved by sonication using a probe or water bath, leading to the formation of SUVs (14).Probe sonication generates localized heat, which can affect the chemical stability of surfactants and APIs while also increasing the potential for probe contamination. Bath sonication is a good choice because sonication cannot be controlled when producing monodisperse nanocores (14). Another technique for size reduction is continuous extrusion of

formulations from polycarbonate filters. Effective size reduction using this method is related to the extrusion cycle and the pore size of the filter membrane (14). This method is widely used to produce drug-laden vesicles such as insulin, doxorubicin and other extracts (3).The main challenge of TFHs is the limited encapsulation of the aqueous core, often leading to poor encapsulation efficiency of hydrophilic substances. Colchicine, insulin, nevirapine, tenofovir disoproxil fumarate and doxorubicin have been used successfully in this way. This shows that there are many methods (14). Niosome-encapsulated prilocaine and lidocaine were prepared using the thin-film hydration technique (15). Niosomes containing Linezolid were prepared by thin film hydration method using non-ionic surfactants (span 40, 60 and Tween 60, 80) and cholesterol in the ratio (1:1, 1:1.5, 1:2) (16).

2) Ether Injection Method –

The ether injection method involves slowly injecting niosome fractions in ether, ethanol or isopropanol at a rate of about 0.25 mL/min through a 14 gauge needle into a pre-diluted phase held at 60°C. Slow evaporation of the solvent causes the ether gradient to extend towards the water-anhydrous liquid interface, which may be responsible for the formation of the bilayer structure (14) and yields fast efficiency phase for the fluid and hence the hydrophilic solution (1) Ether injection can also be used to prepare LUVs and SUVs (1). In some cases, ethanol forms an azeotrope with water; The disadvantage of this method is the disadvantage of this method with the effect of temperature compensation (14)Kakkar and Kaur used this method to prepare elastic blisters containing 60 to tween 80 to encapsulate the lipophilic drug ketoconazole. They used ethanol as a solvent for Span 60 and ketoconazole and injected their solution into an aqueous phase containing Tween 80(13)

3) Dehydration–Rehydration Vesicles (DRV) Method-

This approach was first explained in 1984 by Kirby and Gregoriadis. These vesicles were originally made using a thin-film hydration process, after which they were frozen in liquid nitrogen and then freeze-dried for an extended period of time. Powder niosomes were heated at 60 °C and hydrated with phosphate buffered saline (pH - 7.4). This process was used by Abdelkader et al. to create naltrexone niosomes for ocular administration. The effectiveness of trapping of niosomes produced by various processes was compared. They discovered that, when compared to niosomes made using the reverse-phase evaporation technique, thin-film hydration technique, freeze and thaw method, and dehydration and rehydration method, entrapment efficiency of niosomes made using the latter two methods was superior (6)

4) Reverse phase evaporation method-

In order to use the reverse phase evaporation technique, the non-ionic surfactant and other ingredients must be dissolved in an organic solvent (13)The loaded medication is mixed with the organic phase to create an emulsion, which is then sonicated, after being dissolved in an aqueous solution like water or PBS. A rotary vacuum evaporator operating at 40–60 °C removes the organic solvent to create the niosomes (5)The lipoid or surface-active ingredient initially appears as a gel before hydration, producing spherical, stable, homogeneous vesicles(4) With the help of this preparation technique, it is possible to prevent the aggregation, fusion, and leakage of niosomes that may take place over time (1).In contrast to the TFH approach, the REV method could produce vesicles that contained nanoparticles of homogeneous size and unilamellar or oligolamellar structures (5)

5) The bubble method –

Niosomes are created using the bubble method without the need of organic solvents. The surfactants and additives are combined in an aqueous phase, such as PBS, and then the solution is transferred to a three-neck round-bottom flask. The three-neck flask is then placed within a water bath to regulate the temperature (13)A thermometer is placed in one neck of the system, nitrogen is passed through a second neck, and a water-cooled reflux is coupled to the final neck. Following a 15-second homogenization period at 70 °C during which the components are evenly distributed, nitrogen gas is then added to the mixture. This results in the production of enormous, unilamellar vesicles. It needs to go through more size reduction in order to produce tiny unilamellar vesicles (6).

6) Proniosome Method –

Proniosome has been used as a reliable precursor in the manufacture of niosomes for use in drug delivery systems (13) Proniosomes, also known as dry niosomes, are non-ionic surfactant vesicles in dry form that, when hydrated, quickly transform into niosomes. As a result of their excellent durability, they are now frequently utilised in the formulation of niosomes (5) A water-soluble molecule (carrier), such as sorbitol, maltodextrin, or mannitol, is covered with non-ionic surfactants to create a proniosome. This technique produces thin surfactant films deposited onto the carriers in dry, free-flowing compositions. In order to create proniosome-derived niosomes, proniosome powder is rehydrated in hot water while being stirred. Several benefits of the approach include its appropriateness for scaling up, ease of transportation, and superior chemical and physical stability for long-term storage (13) Additionally, this method might make it possible to further synthesise niosomes in various forms, such as tablets and gel. Proniosomes have been successfully applied in the application of drug administration through a variety of channels, including oral, parenteral, dermal, transdermal, and ocular. This may offer a method for long-term storage as it is the greatest technique to reduce the water content of niosomes to increase their stability(5).

7) Sonication method –

Bansal et al. prepared cefdinir niosomes using the sonication technique (6) The blend of surfactant and cholesterol disperses the aqueous phase that contains the drug in flax. The mixture is subjected to probe sonication or a bath sonicator for three minutes at 60°C to encourage the growth of multilamellar vesicles (4) sonication is done for more than 20 minutes and at temperatures higher than the phase transition temperature(14).

8) Microfluidization method –

Micro fluidization is a revolutionary technique for creating niosomes that relies on the jet principle to combine two different fluids, such water and alcohol, in tiny channels. By adjusting several factors, such as the mixing conditions, surfactants, and other components, niosome formulations can be made with the desired particle sizes and size distribution(5)This method regulates material flow by using microchannels with a diameter of 5–500 m. In an interaction chamber, the fluidized stream of lipids in ethanol or isopropanol travels via precisely planned microchannels and engages in ultra-high-velocity interactions with an aqueous stream. Continuous axial mixing of the two phases results in the formation of niosomes through local surfactant molecule diffusion that self-assembles in contact with the aqueous phase(14) Since micro fluidization techniques have the benefit of producing niosomes with smaller sizes, higher reproducibility, and ease of formulation, they have been popular in recent years. And this approach is thought to be a promising one for the commercialization of niosomes (5).

9) Transmembrane pH gradient drug uptake –

For hydrophobic payload that is ionizable, this method is quite practical. This method involves dissolving cholesterol, a surfactant, and a hydrophobic payload in chloroform. A thin layer is then produced on the wall of a round-bottom flask by the solvent's evaporation under reduced pressure. A vortex mixer is then used to hydrate the film with 300 mM citric acid at pH 4.0. The resulting multilamellar vesicles are then subjected to three cycles of freezing and thawing, followed by sonication. The drug-containing aqueous solution is then added to the niosome suspension and vortexed. After adding a 1 M disodium phosphate solution to the sample to elevate the pH to between 7.0 and 7.2, the mixture is heated at 60 °C for 10 minutes to form multilamellar vesicles. Both protonated and unprotonated forms of the payload can be found inside the vesicles due to their neutral exterior. The payload's unprotonated form can pass through the niosome membrane since it is permeable. As a result, the API is protonated in the vesicle's acidic contents and is kept there. Diffusion proceeds until the API concentration on the inside and outside of the vesicle membrane are equal (14). According to Bhaskaran and Lakshmi, this procedure can produce niosomes with an entrapment effectiveness (EE) of 87.5 percent (4).

METHODS OF PURIFICATION-

In general, a significant amount of the drug is not absorbed during hydration. For this reason, over-the-counter drugs should be removed. Some techniques for removing unwanted chemicals are: centrifugation, gel filtration and dialysis ((4,6).

1) Centrifugation-

According to recent research, it is the most widely used method for niosome purification. This technique is particularly useful for extracting vesicle bodies from unembedded genetic material by gradient rapid centrifugation. Many authors have combined this technique with Sephadex-based gel filtration chromatography. The procedure produced 92-100% vesicle healing without dilution. Centrifuge 1 at 15,000 g using an ultracentrifuge. Bayindir and Yuksel were able to remove uncontaminated paclitaxel for 5 hours at 4°C. To remove the illicit drug, Gyanendra et al. Centrifuge the dispersion at 14,000 rpm in the refrigerator at 4°C for one hour. To classify illicit drugs, Patel et al. Centrifuge the preparation at 4000 rpm for 15 minutes at 4 °C. The preparation was centrifuged by Agarwal et al. 30 minutes. At 8000 rpm, at least 3 cycles. Manosroi et al. The papain-laden vesicles were centrifuged at 43,400 g for 10 min at 4 °C and resuspended in distilled water. With centrifugation at 13000 rpm-1, De et al. remove unused medicine (6).

2) Gel filteration –

To get the pure dispersion of niosomes, a gel filtering process is used. By employing Sephadex G75, G50, or G25 8, the unentrapped drug can be eliminated. Gel filtration chromatography was used by Rinaldi et al. to clean the unilamellar niosome suspension. With HEPES buffer as the eluent, they employed Sephadex G75, a glass column with a 50 1.2 cm dimension(6)

3) Dialysis –

Diffusion and osmosis-based process that relies on solvent and solute travelling across semi-permeable membrane. Niosomes are administered in a dialysis bag, and phosphate buffer is used to dialyze the free medication. This technique was used by Mohamed Firthouse et al. to free the medication (miconazole) from the niosome. He placed the niosomal suspension in a

dialysis bag measuring 3 cm by 8 cm and having a cutoff molecular weight of 12,000. The procedure was completed over the course of 24 hours by maintaining this in a beaker containing phosphate buffer, which was changed out every 3 hours for brand-new buffer (6)

RECENT STUDIES ON NIOSOMES –

Sr no.	Type of drug	Name of drug	Composition	Dosage form	Conclusion	Year	References
1	NSAID	Diclofenac sodium	Span 80, cholesterol, ethanol 96% (v/v)	Hydrogel	Compared to the commercial medicine, there was an improvement in the quantity and speed of Diclofenac sodium transport via the skin as well as an increase in drug concentration in the muscle.	2020	(17)
2	Anti-inflammatory, anti-radiation, and anti-aging	Salidroside	Span 40, cholesterol, and sodium dodecyl sulfate (SDS)	Niosome	SDS is a potentially useful stabiliser for transdermal delivery of nanomedicines, such as niosomes.	2020	(18)
3	HMG-CoA reductase inhibitors (statins)	Simvastatin	Span60, Tween 80, and Cremophor RH 40, cholesterol	Gel	A possible novel nanocarrier for transdermal SIM administration into the systemic circulation is niosomal gel filled with SIM.	2021	(19)
4	Anaesthetic	Propofol	Cholesterol, and Span 80	Gel	A possible non-invasive substitute method for administering propofol for procedural sedation, particularly in the context of children.	2021	(20)

5	calcineurin inhibitors	cyclosporine	Cholesterol, Span 60	Gel	Niosome use as a possible carrier to enhance cyclosporine penetration and deposition for psoriasis therapy	2021	(21)
6	NSAID	Diclofenac sodium	Cholesterol, Tween 20, and Span 20	Gel	Niosomal compositions can enhance the therapeutic effects of drugs by boosting drug delivery to particular locations.	2021	(22)
7	Peptide hormone	Human growth hormone	Cholesterol, surfactant	Gel	The potential of niosomal gel to replace conventional subcutaneous injections as an efficient long-term sustained release technique for hGH delivery.	2022	(23)
8	Polyphenolic antioxidant	Hydroxytyrosol	Span 60, cholesterol	Gel	Noisome gel offers a more effective and prolonged form of HT delivery than oral administration.	2022	(24)
9	Anti-fungal	Terbinafine	Cholesterol, surfactants	Gel	Terbinasomes may be administered as nano-vesicles for TER medication delivery, creating new avenues for the management of skin infections.	2022	(25)
10	Anti-histaminic drug	Cetirizine hydrochloride	Cholesterol, Brij 35, Span and Tween	Gel	A possible vehicle for the topical treatment of alopecia using	2023	(26)

					cetirizine delivered topically.		
11	Calcium channel blocker of the dihydropyridine class	Lacidipine	Span 60, cholesterol	Gel	Niosomal lacidipine vesicles could offer this medication's current delivery method an alternative.	2023	(27)
12	Natural bioactive	Apigenin	Cholesterol (CHO), span-60	Gel	Gel loaded with niosomes is an effective medication carrier that enhances transdermal distribution and therapeutic efficiency.	2023	(28)
13	Tricyclic antidepressants	Nortriptyline HCl	Cholesterol, surfactant	Gel	By facilitating better medication transport to the intended location, niosomes may increase the efficacy of NOR as an antinociceptive and anti-inflammatory agent.	2023	(29)
14	Antiepileptic	Lamotrigine	Cholesterol, surfactants, PVP, PVA	Patch	Niosomal transdermal patches are a useful replacement for the maintenance medications now in use to manage epileptic episodes.	2024	(30)
15	Anti-rheumatic	Tenoxicam	Span-60	Gel	This study offers a commercially viable method for creating unique niosomal TN-loaded gels.	2024	(31)

NIOSOMAL ADVANCEMENT –

An oral dose form is the sole way to buy the BCS class 2 antifungal medication griseofulvin at the moment. However, as a fungal infection primarily affects the top layer of skin. The formulation of griseofulvin as a topical drug was the aim of this investigation. Furthermore, the medication has a limited solubility due to its BCS class 2 status. In order the development of lipid vesicles increased griseofulvin's solubility. Here, the drug's overall effectiveness was increased by the inclusion of chitosan as a biopolymer for the film formulation because chitosan also displayed anti-fungal action. The purpose of this work was to develop and characterise a chitosan film formulation that incorporates niosomes loaded with griseofulvin for topical delivery. to have a dosage form that addresses the issue of instability and makes it possible to use a topical medication for almost a lengthy period of time. According to the results of this study, chitosan film formulations incorporating griseofulvin-loaded niosomes for dermal (topical) delivery improved the drug's solubility, avoided first-pass metabolism, and avoided side effects related to the commercially available formulation intended for oral administration. finally increasing the drug's effectiveness. enhanced patient compliance and produced a high-quality medication product(32).

As for the use of cosmetics for acne treatment, Wang et al. attempted to develop a 3D-printed liposomal hydrogel (3DP-NH) containing CPT. Reverse-phase evaporation was used to prepare camptothecin-loaded liposomes only, and response surface techniques were used to refine the samples. Based on in vitro analysis, optimized camptothecin loaded vesicles have a size below 150 nm and an encapsulation efficiency of 67% and 71%. Insert CPT-loaded liposomes once into the hydrogel to form CPT-loaded liposome hydrogels (CPT-NH). Permeation and deposition tests showed higher transdermal flux, Q24 and CPT deposition rate ($p < 0.05$) compared to the 3D-printed CPT loaded conventional hydrogel without liposomes (3DP-CPT-CH). Based on in vivo anti-acne activity using a mouse model of acne, 3DPCPT-NH showed potent anti-acne properties, improved skin hydration and no skin irritation (35). The first line of acne treatment is usually benzoyl peroxide (BPO). Drug administration requires multiple injections to achieve the desired results, resulting in larger batches due to low water solubility and limited access to the skin, resulting in skin irritation (33)

The main components of transferosomes are phospholipids (phosphatidylcholine), 10–25% surfactants/EA (sodium cholate, sodium deoxycholate, dipotassium glycyrrhizinate, Tweens®, Spans®, etc.), 3–10% penetration enhancers (ethanol or methanol), and the hydrating medium (water or a saline phosphate buffer with pH 6. In the process of optimisation, variables such phospholipids: EA, kind of EA, solvent, and pH of the hydration medium employed in manufacturing play crucial roles. These elements have an impact on the PDI, EE, elasticity (phospholipids: EA and type of EA), penetration over the stratum corneum (solvent, type and concentration of EA, carbon chain length and transition temperature of EA), and ionisation of the medication (pH of the hydration medium). Transferosomes have undergone extensive research for their potential use in the transdermal delivery of a variety of therapeutic agents, including vitamins, supplements, corticosteroids, local anaesthetics, anti-inflammatories, antifungals, antioxidants, antineoplastics, antipsychotics, antihypertensives, antihistamines, antibiotics, anti-amoebics and anti-diabetics; macromolecules such as interleukin-2 Studies involving these substances revealed the potential of transferosomes for raised permeability,

sustained drug release prolonging therapeutic efficacy, improved transdermal flux, decreased blood clearance, and improved pharmacokinetic profile(14)

Deformable vesicles are more effective for transdermal medication administration than niosomes and liposomes because they have different penetration processes and have a tendency to settle in the layers of skin tissues that are moister (14)

Current research efforts are focused on process optimisation, innovative compositions, and final formulations. Recent investigations on transdermal medication administration from niosomes in diverse disease models have been undertaken. Given that vesicles' elastic characteristics are provided by edge activators like ethanol. Elastic vesicles are a type of novel, very flexible niosome that are effective at transporting molecules through the skin. They allow them to more readily enter into the deeper layers of the skin. Niosomes have another significant downside in the form of their liquid preparation, which can leak from the application site when used. This challenge can be overcome by including niosomes in an appropriate medium, which is achieved by adding gelling agents to niosomal dispersions to generate a niosomal gel. Niosomal gels have been found to enhance the skin's capacity to hold onto medications and to provide high and persistent medication levels in the skin. Niosomes have evolved into additional structures called proteiosomes, or "dry niosomes," which have been postulated as niosomal formulations. An aqueous niosomal dispersion is produced by hydrating these formulations before to usage. Proniosomes, when applied to the skin, lessen aggregation because they are hydrated with water from the skin under occlusion provide a versatile transdermal drug delivery technology and address the leakage and fusion problems associated with traditional niosomes. A summary of the findings from seven years' worth of research on transdermal niosomal medication delivery systems.(34)

LIMITATIONS –

Niosomal technology has limitations in terms of the types of payloads they may encapsulate, the methods via which they can be administered, and their capacity to maintain the systematic release of payload(14)

The use of a sterilisation method is the fundamental issue with the production of niosomal formulations. Dry heat and steam sterilisation are ineffective methods of heat sterilisation because they can damage formulations based on lipids or surfactants whose Tc is lower than the temperature utilised for sterilisation. Therefore, the employment of these approaches would lead to severe drug leakage as a result of bilayer breakdown(14)

In one study, the effects of surfactants and cholesterol content, in particular, were examined in relation to how different niosomal formulations inhibited the proliferation of human keratinocyte cells(14)

APPLICATIONS –

1) Chemical drug-

Niosomes can be utilised as a substitute for liposomes and polymersomes in nano-vesicle-based delivery systems for chemical drugs. They are useful for chemical drug loading because they have a hydrophilic cavity and a hydrophobic shell. In order to accomplish the required therapeutic effects, they can also offer a means for the simultaneous administration of two various medication classes(5).

2) Protein and Peptide-

Drugs Important therapeutic substances for the treatment of diseases may be found in proteins and peptides like insulin and bacitracin. But because of their low bioavailability, instability during storage and after administration, as well as some side effects, their clinical application is hampered. Niosomes may be used as effective drug delivery systems for a variety of proteins and peptides to address these issues. They also perform well in the development and administration of vaccines(5).

3) Gene Delivery-

Gene therapy, a novel approach to treating diseases, has become a potent tool in recent years. For clinical applications, delivery is still a challenge. Two methods are used for the transport of gene materials: non-viral gene carriers that primarily rely on polymers and lipids. Unspecific adhesion and toxicity during circulation in vivo are potential side effects of the commonly used gene delivery agent lipoplex(5).

4) The In Vivo Stability, Biodistribution and Formation of Protein Corona of Niosomes-

The effectiveness of their delivery is significantly influenced by the nano-carrier's in vivo stability. Due to the excellent chemical and physical stability of the ingredients that formed niosomes, they were substantially more stable as described. Because of this, their stability before targeting during in vivo circulation may be improved. The zeta potential of their surfaces, for example, has an impact on their stability. Positively charged nanoparticles have been shown to cause non-specific adsorption and accumulate in several organs, including the liver. Surface charge measurements, zeta potential, gel electrophoresis, and ELISA were used in certain experiments to simulate in vivo scenarios to assess how well the niosomes functioned in biological contexts(5)

CONCLUSION AND FUTURE PROSPECTIVE –

This review paper presents a thorough explanation of the chemical makeup, structure, advantages, mechanism, recent studies and recent advancements in the use of niosomes as transdermal and topical drug delivery systems. By employing new preparation niosomes' potential can be increased. For the creation of niosomal formulations that can be sold commercially, more investigation and study of these areas are required. We can conclude from this review article that the niosomes are very important drug delivery tool which is used for incorporation or targeting of drug for various therapeutic activities and provides various advantages over other drug delivery tools. The niosomes will be proved as a great reward for the future perspective.

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