Revolutionizing Topical Drug Delivery: Niosomal Gels

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Abstract*— Niosome size range from 10 nm to 100 nm. Niosomes offer numerous advantages over traditional Niosomes provide numerous advantages over traditional medication delivery methods. There are several ways for manufacturing Niosomes, some of which are described below, including the ether injection approach, thin film hydration method, reverse phase evaporation method, and sonication method. Also highlighted here are several applications of Niosomes produced formulations above conventional ones.

Indexed Terms- Niosomes, Surfactant, Cholesterol.

I. INTRODUCTION

Drugs are contained in a vesicle and delivered specifically by niosomes. A bilayer of non-ionic surface-active substances makes up niosomes, which are vesicles. Niosomes are minuscule under a microscope. They are nanometric in size. The sizes of particles range from 10 to 100 nm [1]. Niosomes are amphiphilic non-ionic surfactant-based self-assembling vesicles. To improve system stability and stiffen the bilayers, cholesterol and occasionally charged species are used. Although they resemble liposomes, niosomes were created to get over the problems with liposome stability, sterilization, and large-scale production. Niosomes can contain hydrophilic and hydrophobic medications in their hydrophilic and bilayer compartments, respectively, just like liposomes can. Drugs have long been used topically to affect the skin's surface, epidermis, dermis, and hypodermis, among other layers. The stratum corneum, the outermost layer of the skin, and low percutaneous penetration and absorption into the systemic circulation are two major drawbacks of conventional topical medications. These days, studies outline a number of methods for administering drugs topically, such as injecting absorption boosters. [2] Because of its exceptional qualities, which include enhanced drug penetration, a prolonged pattern of drug release, and the ability to transport both hydrophilic and lipophilic medications, niosomes have recently become more and more prominent in the field of topical drug delivery. The potential of niosomes in topical administration systems is discussed in this review, with an emphasis on their therapeutic application [3].

Niosomes

Niosomes composition

Niosomes contain nonionic surfactants, cholesterol, and sometimes ionic amphiphiles. Both hydrophilic and hydrophobic drugs can be encapsulated in niosomes, either in the hydrophilic core or the hydrophobic bilayer area. Non-ionic surfactants are the principal constituent of niosomes, which are amphiphilic molecules with a polar head group and a non-polar tail. c.[5]

Niosomes structure

Salient features of niosomes . [6]

1. Niosomes and liposomes both have the ability to capture solutes.
2.Osmoticallyactive and stable are niosomes.
3. Because niosomes' infrastructural hydrophobic and hydrophilic components are primarily combined, they can also
4. The structural properties (size, content, and fluidity) of niosomes are flexible and can be tailored to the intended scenario.
5. Drug compounds' performance can be improved by niosomes.
6. By shielding the medication from the biological environment, it becomes more available at the specific location.
7. Surfactants from niosomes are non-immunogenic, biodegradable, and biocompatible.

Types of niosomes

Different types of niosomes have been described in literature. These are classified into several classes based on their size or number of lamellar layers. There are two types of unilamellar vesicles: tiny (SUV) and large. There are two types of vesicles based on the number of bilayers: multilamellar (MLV) and small unilamellar (SUV).[7] The size of niosomes is also an important element in determining the delivery route. Submicron vesicles are appropriate for intravenous or transdermal treatments, whereas those up to 10 μm are generally used for intraperitoneal, intramuscular, nasal and oral administration. [8] SUVs are produced from MLVs through techniques such as sonication, high pressure extrusion and high shear homogenisation. The size of SUVs varies between 10 to 100 nanometer. They are thermodynamically less stable than other types of niosomes, have a low drug loading capacity for hydrophilic drugs, and are more prone to aggregation. LUVs are approximately 0.1-1 μm in diameter and contain a single bilayer surrounding an aqueous core. LUV niosomes have a large aqueous compartment and are therefore useful for the encapsulation of hydrophilic medicinal compounds. The structure of multilamellar vesicles (MLVs) comprises several bilayers encapsulating the individual aqueous lipid compartments. These have a diameter of 0.5-10 μm. MLVs are more straightforward to prepare and less likely to undergo degradation as compared with the other two types of niosomes under standard storage settings. Besides, they have a more favorable condition regarding the loading of lipophilic drugs due to multiple bilayer membrane.[9]

Advantages of Niosomes [10]

1. Vesicular systems (lipid and non-ionic surfactant vesicles) used in cosmetics and medicine may offer a number of benefits.
2. By delaying the drug's removal from the bloodstream, shielding it from the biological environment, and limiting its actions to certain cells, they improve the therapeutic efficacy of drug molecules.
3. To control the delivery, niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase.
4. The drug's rate and the typical vesicle's administration in the external non-aqueous phase.
5. They improve the stability of the entrapped medication and are osmotically stable and active.
6. No specific conditions are needed for the handling or storage of surfactants.
7. They increase the epidermal penetration of medications and the oral bioavailability of poorly absorbed medications.
8. Oral, parenteral, and topical methods can be used to formulate them to attain site of action.
9. They can also host medicinal molecules with a broad spectrum of solubility because of their architecture, which contains of hydrophilic, amphiphilic, and lipophilic moieties together.
10. The parameters of the vesicle formulation can be adjusted. A variable The characteristics of vesicles can be controlled by altering their composition, size, lamellarity, tapping volume, surface charge, and concentration.
11. Drugs can be delivered in controlled ways using vesicles as a depot.

DISADVANTAGES:

1. Preparation of multilamellar vesicles using the extrusion and sonication method involves time-consuming procedures and requires specialized equipment.
2. Niosomes aqueous suspension shelf life short due to entrapment fusion, aggregation, leakage of drug. [11].

MECHANISMS OF NIOSOME PENETRATION THROUGH SKIN DELIVERY

Niosomes are the most difficult technology for dermatological diseases. Besides that, peptide drugs and cosmetics were delivered via niosomes. Niosomes applied topically may inhibit systemic medication absorption and extend the time the drug resides in SC and epidermis. They probably enhance the properties of the stratum corneum by making the layer smoother and restituting lost skin lipid with an effect of reducing TEWL. Therefore, niosomes function as penetration enhancers.

1. Strong thermodynamic activity gradient created at the interface by the fusion and adsorption of niosomes onto the skin's surface accelerates the absorption of lipophilic drugs.
2. The penetration-enhancing effects of vesicles are to reduce the barrier properties of the stratum corneum. Surfactants, which are the building blocks of niosomes, enhance skin wetting, promote medication

distribution, and reduce surface tension to enhance transdermal penetration and percutaneous absorption.
3. Niosome lipid bilayers act as a rate-limiting barrier for drugs.[12,13]

PREPARATION OF NIOSOMES:
Since the preparation procedures influence the number of bilayers, size, size distribution, and entrapment efficiency of the aqueous phase as well as the membrane permeability of the vesicles, the choice of preparation procedures should go along with the application of niosomes. These comprises Ether injection method,Reverse phase evaporation method, Thin film hydration method, sonication,Microfluidization.[14,15]

Ether injection method
This process entails dissolving a mix of surfactant and cholesterol in diethyl ether. The mixture is subsequently added gradually into a warm aqueous solution containing the drug. The temperature of the solution is kept above the boiling point of the organic solvent. When the organic solvent is evaporated, very large unilamellar vesicles are usually obtained.

Reverse-phase evaporation method
In this method, a mixture of surfactant and cholesterol is dissolved in an organic solvent like ether and chloroform. An aqueous solution of the drug is added to it. The two immiscible phases are homogenized and sonicated to form an emulsion, which is then removed under decreased pressure to yield large unilamellar niosomes scattered in the aqueous phase.

Thin-film hydration method
Thin-film hydration is a simple technique for preparing niosomes. Surfactant and cholesterol (membrane-forming ingredients) are dissolved in organic solvent in a round-bottomed flask of a rotary evaporator, which is evaporated to produce a dried thin film on the bottom flask. The aqueous medium, either water or buffer, is added to the film at a temperature greater than the surfactant's transition temperature for a set period of time with constant gentle agitation in order to form multilamellar vesicles that can then be sonicated to yield unilamellar vesicles. Drugs for encapsulation are dissolved in either the aqueous or organic phase, depending on their solubility. This technique is then followed by sonication for niosomes to form with homogeneous size distribution.

Sonication method:
The ultrasonic method is one of the popular methods for vesicle preparation. In a 10 ml glass vial containing cholesterol and surfactant, there is an aqueous phase containing the active ingredient in the buffer. The mixture is sonicated for three minutes at 60°C using a titanium sonic probe, which results in small niosomes of uniform size. Niosomes loaded with rifampicin were prepared using the probe sonication method as a drug model for low-soluble drugs. This injection of lipids avoids the use of chemical solvents, which are expensive and toxic when used in vivo. Niosome formation occurs when molten surfactant and cholesterol are injected into a heated aqueous phase containing dissolved drug molecules.

Microfluidization:
A new technique for manufacturing unilamellar vesicles with a predetermined size distribution is applied here. The submerged jet principle underpins this technology, in which two fluidized streams collide at extremely high speeds in the interaction chamber's precisely built micro channels. Because niosomes form where a thin liquid sheet impinges on a common front, the energy supplied to the system is contained inside that region. As a result, more compact, consistent, and repeatable niosomes are produced.

Bubble Method:
This is a newly developed technology, wherein the organic solvents for the preparation of niosomes are not required. In order to maintain the constant temperature, the three-necked, round-bottom flask used in the bubbling machine is placed in the water bath. The first and second necks offer water-cooled reflux and thermometer; the third neck supplies nitrogen. At 158°F, cholesterol and surfactant mixture is prepared in a pH 7.4 buffer. This dispersion is mixed for 15 seconds with a high-shear homogenizer before niosomes are formed by bubbling nitrogen gas at 158°F.

SEPARATION OF UNENTRAPPED DRUG: [16,17]
The free solute can be extracted from the vesicles using a variety of techniques, such as:
1. Dialysis: The fluid of niosomal scattering is

dialyzed against phosphate buffer, standard saline, or glucose solution using dialysis tubing.
2. Gel Filtration: The unentrapped medication is removed by gel filtration of niosomal scattering through a Sephadex-G-50 column and elution with phosphate-buffered saline or regular saline.
3. Centrifugation: After centrifugation, the supernatant is extracted from the niosomal solution. The pellet is flowed across and then resuspended to provide a niosomal suspension free of unentrapped particles.
Gelling agents used in Niosomal gel

Gelling agents play an important role in niosomal gel formulations, as these agents provide the necessary viscosity and stability to the gel.
Types of Gelling Agents
1. Carbopol : A synthetic polymer, it is rich in viscosity and stability; hence, it is highly used in topical formulations.
2. Hydroxypropyl Methylcellulose: It is a semi-synthetic polymer, which imparts good film-forming characteristics and controlled drug release.
3. Sodium Alginate: It is a natural polysaccharide that gels in the presence of calcium ions, providing good bioadhesion and controlled release.
4. Xanthan Gum: It is a natural polysaccharide that provides excellent viscosity and stability to the gel.
5. Carrageenan: It is a natural polysaccharide derived from red seaweed, used for its gelling and stabilizing properties.
Preparation of Gel Base: Suspend a gelling agent such as Carbopol 934 in water or a combination of water and glycerol. Neutralize and thicken the suspension with triethanolamine.
Mixing of Niosomes: Add the niosomes to the gel base to create the finished niosomal gel.
Evaluation of Niosomes
Niosome characterizations are needed for evaluating the quality of the prepared vesicles and their applications. Size, size distribution, zeta potential, entrapment efficiency, shape, and in vitro release commonly were evaluated since these parameters influence how stable and active niosomes are in vivo
1. Zeta potential, particle size, and particle size distribution:
The mean particle size, particle size distribution (polydispersity index, PDI), and zeta potential all affect the physical properties, homogeneity, and stability of manufactured niosomes. There are many ways to determine niosome size. Among these, dynamic light scattering, undoubtedly, is one of the most common methods for rapidly and non-destructively assessing the size and size distribution of nanomaterials. It is based on the particles' random Brownian motion. Before measurement, one mL of freshly prepared sample is usually diluted with the suitable solvent, such as distilled water or phosphate-buffered saline (PBS), and sonicated in a water bath. For accuracy, measurements for each formulation should be carried out in triplicate. PDI indicates niosomal size distribution: Lower PDI values (0.3) indicate a more homogeneous, uniform dispersion.[18]

Morphology of niosomes:
Niosomal vesicle morphology can be examined using microscopic techniques such as transmission electron microscopy, scanning electron microscopy, and atomic force microscopy. TEM is the most sought technique in the investigation of niosome morphology. In this process, a drop of the samples is placed on copper grids coated in carbon that are colored with, say, 2% phosphotungstic acid, and left to dry before imaging. Niosomes consist of cholesterol, Span 60, and Tween 40 in a 2:1:1 M ratio.[19]

Entrapment efficiency:
The entrapment efficiency is the amount of drug present in niosomes. The amount of free medication in the supernatant after centrifuging the loaded niosomal solution is determined (an indirect measure of entrapment efficacy), and this can be calculated using equation.[20,21]
Entrapment efficiency (%) = Total amount of initially added drug minus unentrapped drug / Total Amount of initially added drug × 100
In vitro release of drug:
The in-vitro drug release rate can be studied by using dialysis tubing. A dialysis sac is washed and soaked in distilled water. The niosomal dispersion is pipetted into this bag and sealed. The containing bag of vesicles is placed in a 250 ml beaker containing 200 ml of phosphate-buffered saline of pH 7.4 by placing the appropriate assay drug contents. Constant shaking at 37±1°C. At different time intervals, the buffer is analyzed for drug content by using appropriate assay method.[22,23]

EVALUATION PARAMETER OF NIOSOMAL GEL [24]

1.Opacity: It is determined by visual examination under a black and white background, and it is rated as follows: translucent, opaque, and transparent.

2. Spreadability: A spreadability test should conducted by squeezing 0.5 g of gel between two glass slides with the help of a 20 g weight and taking it off for around 5 minutes till no more spreading is observed. The breadth of the formed circle should measured and used as the value for spreadability.

3. Extrudability: A 5 g mass of gel should be filled in a clean 10 ml syringe suspended using an answer stand; 0.5 kg of weight should be placed on the free end of the plunger, and the amount of gel extruded within 5 minutes was recorded.

4. PH: A 1 g quantity of gel should be dispersed evenly in 100 ml of purified water by an attractive stirrer. The pH of the 1% w/v dispersion of the niosomal gel should be determined by employing a computerised pH meter.

5. Viscosity: The viscosity of 1% w/v dispersion should be determined by the employment of a rotational viscometer using a spindle.

6. Homogeneity: It is determined by a visual assessment for the appearance of protuberance and the nearness of any aggregate

APPLICATIONS OF NIOSOMAL GEL:

a) Ocular drug delivery: The basic drawback of ophthalmic preparations, including eye drops, suspensions, and ointments, is that they do not easily achieve high bioavailability because of tear formation, short residence times, and impermeability of the corneal epithelium. Niosomal drug delivery can enhance the bioavailability of the drug. [25]

b) Drug administration via transdermal application: Niosomes' structural features enhance penetration and allow for direct vesicle fusion with the stratum corneum, the skin's outermost layer, enhancing the penetration of loaded pharmaceuticals.[26]

c) Nose administration: The incorporation of the drug into niosomes enhanced brain bioavailability, drug targeting efficacy, direct transport percentage, and brain absorption via the direct nose-to-brain channel, indicating improved central nervous system targeting via the nasal Pathway.[27]

CONCLUSION

Niosomes are a relatively new drug delivery system that comprises two layers of nonionic surfactants. A variety of drugs can be incorporated into niosomes by varying the experiment parameters and the surfactant/cholesterol ratio used. As niosomes are amphipathic, they can also incorporate hydrophobic and hydrophilic drugs. Due to their amphipathic nature, hydrophobic and hydrophilic fluids can also accumulate inside niosomes. Niosomes reduce pharmaceutical toxicity, retard the release of sedatives, and enhance the stability of drugs. Unlike other sedate transportation strategies, niosomes do not need to be organized or kept under specific conditions. In summary, it seems that further research will lead to a profitable future market for niosomes in pharmaceutical biotechnology. Niosomes can be used for parenteral, topical, ophthalmic, targeted, and other applications. More thought is needed in the comprehensive study of the possible consequences of this new medicine distribution method. Niosomal drug carriers are safer than ionic, which are harmful and inappropriate. No special conditions are required to handle and store niosomes.

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