International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 11-05-2024, Accepted: 30-05-2024, Published: 24-06-2024
Volume 9, Issue 2, 2024, Page No. 39-49

Niosomes: A promising carrier system for drug delivery-an in-depth review on formulation strategies characterization techniques and therapeutic

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Abstract
Drug targeting is a type of phenomena where a drug is absorbed into the body and distributed so that it interacts at the cellular or subcellular level with the target tissue, resulting in a desired therapeutic response at one location and no unwanted interactions at other sites. This can be accomplished by using contemporary techniques like niosomes to target the drug delivery system. Niosomes are a novel class of non-ionic surfactant vesicles that are more stable, less expensive, biodegradable, and non-toxic than liposomes. Because of their liposome-like form, they might be thought of as an alternative to liposomes in terms of vesicular systems. Different types of medications tend to be loaded into niosomes. This review article illustrates the detail information of niosome's construction, benefits, drawbacks, various method of preparation of niosomes, characterization of niosomes, applications, current status and various challenges in niosomal drug delivery system along with the future prospects of niosomal drug delivery system.

Keywords: Niosomes, liposomes, drug targeting, niosomal drug delivery system

Introduction of Niosomes [1-4]

The capacity to direct a therapeutic agent at the intended location of action with minimal or no tissue contact is known as drug targeting. The goal of a controlled drug delivery system is to achieve a desired medication release profile over an extended length of time. Niosomes are one of the systems that can be used to create a controlled release mechanism. The tiny lamellar bilayer structure of niosomes, which are non-ionic surfactant vesicles, is created by the self-association of hydrated surfactant monomers. Niosomes can have a multilamellar or unilamellar structure, which is created by combining diethyl ether, cholesterol, and a non-ionic surfactant, then hydrating the mixture in aqueous media. Niosomes are ranges from 10 to 1000 nm. Surfactants that are biodegradable, immunogenic, and biocompatible make up the niosome. Niosomes are superior to liposomes because they have a higher surfactant chemical stability than phospholipids, which are more readily hydrolyzed because of the ester link and are less expensive. The use of vesicular systems, such as lipid vesicles and non-ionic surfactant vesicles, in cosmetics and for therapeutic response may have the following benefits [1, 2, 3]

1. Greater patient compliance as compared to dose forms that are greasy.
2. The medicine may be released from the vesicles in a regulated manner, serving as a depot.
3. Consider pharmacological compounds with various solubilities.

Structure of Niosome [1, 2]

The basic structure of niosomes consists of a bilayer membrane formed by the assembly of surfactant molecules. This bilayer structure surrounds an aqueous core, encapsulating water-soluble drugs or hydrophilic substances and lipophilic drugs encapsulate into the lipid bilayer [1, 2]

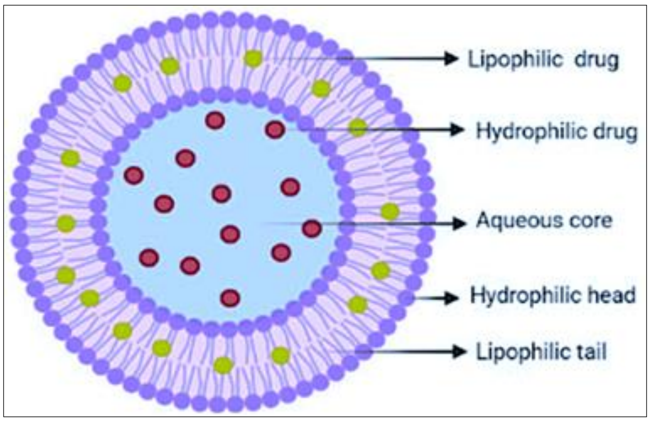


Fig 1: Structure of Niosome

Composition of Niosomes [1]

Niosomes are mainly composed of 2 constituents which are as follows

a. Cholesterol
b. Non-Ionic Surfactant

a. Cholesterol: It is a steroid derivative, which is used to provide rigidity and proper shape, conformation to niosome form. Cholesterol is often incorporated into niosome formulations to enhance the stability of the vesicles. It also helps in reducing membrane permeability and preventing leakage of encapsulated substances [1].

b. Non-ionic Surfactants: Non-ionic surfactants are the primary building blocks of niosomes. These surfactants have both hydrophilic and hydrophobic regions, allowing them to form bilayer structures similar to phospholipids in cell membranes [1].

Examples of non-ionic surfactants generally used includes [1].

Span Series: Span 20, Span 40, Span 60, Span 80.

Tween Series: Tween 20, Tween 40, Tween 60, Tween 80.

Brij Series: Brij 30, Brij 35, Brij 52, Brij 58.

Categories of Niosomes

1. Based on Vesicular Size [5-11]

1.1. Unilamellar vesicles: Unilamellar vesicles, also known as unilamellar liposomes or unilamellar niosomes, are vesicles composed of a single lipid bilayer that encloses an aqueous compartment. These vesicles can be further classified based on their size, leading to the distinctions as follows [5, 7].

1. Small Unilamellar Vesicles (SUVs)
2. Large Unilamellar Vesicles (LUVs)

1. Small Unilamellar Vesicles (SUVs): SUVs are characterized by having a small size, typically ranging from 20 to 100 nanometers in diameter. They consist of a single lipid bilayer, providing a limited encapsulation space. Due to their small size, SUVs are advantageous for drug delivery applications where the rapid release of encapsulated substances is desirable. They can efficiently interact with cell membranes, enhancing drug uptake [6, 7].

2. Large Unilamellar Vesicles (LUVs): LUVs are larger than SUVs, with sizes typically ranging from 100 to 1000 nanometers. Like SUVs, they consist of a single lipid bilayer. LUVs provide a larger encapsulation space compared to SUVs, making them suitable for encapsulating a variety of therapeutic agents. They are often used in drug delivery systems where a sustained release of the encapsulated substance is desired [5, 8].

1.2. Multilamellar vesicles (MLVs): MLVs are niosomes with multiple lipid bilayers, resembling onion-like structures. They can range in size from several hundred nanometers to a few micrometres. MLVs are suitable for encapsulating a larger amount of drugs due to their multiple bilayers [10].

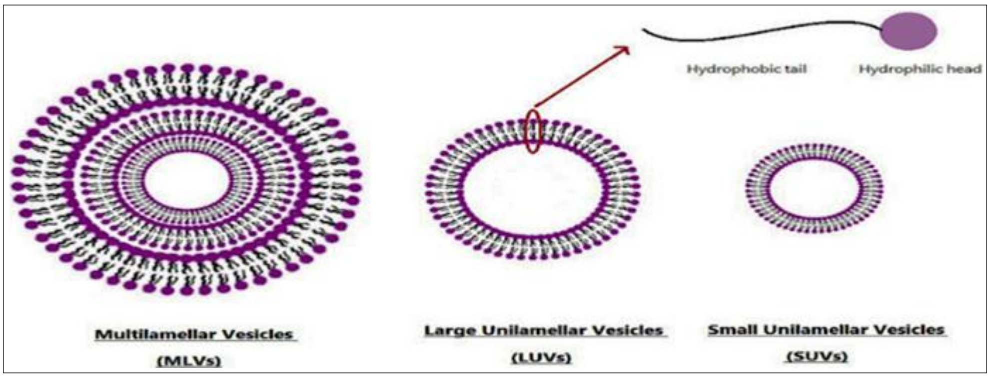


Fig 2: MLVs, LUVs & SUVs

2. Based on structural composition [7-15]

2.1. Polyhedral Niosomes: This type of niosome is created by substituting any non-ionic surfactant and cholesterol in hexadecyl diglycerol ether by using polyoxyethylene 24 cholesteryl ether in its place. These vesicles have peculiar shapes and might include particles that dissolve in water [9, 10]

2.2. Proniosomes: Niosomes aggregate to form proniosomes, which are made up of water-soluble surfactants and transporters. The proniosomes are structures made from dehydrated niosomes that were previously intended to be hydrated for use. For a period, prosniosomes can lessen niosome issues such fusion, aggregation, and drug leakage [7, 8, 9].

2.3. Apsasome: Apsasome is composed of dihexadecyl phosphate (DCP), a highly charged lipid-like substance, and ascorbyl palmitate. The finished product needs to be hydrated and sonicated using a water solvent. Apsasome have the potential to enhance transdermal drug delivery systems and mitigate diseases resulting from reactive oxygen species [7, 8, 9].

2.4. Discomes: Discomes are niosome-based, non-ionic surface active agent-based discoidal vesicles that are utilised for ligand-mediated drug targeting. They are solubilized with non-ionic surfactant solutions (polyoxyethylene cetyl ether class). Discomes have benefits like to those of polyhedral niosomes. On the other hand, discomes with less than 30% mol/mol of cholesterol are made by forming large, multidimensional vesicular systems (11–60 μm) by incubating premade spherical niosomes in cholesteryl poly-24-oxyethylene ether (Solulan C24) at 75◦C for one hour [12]

2.5. Elastic Niosomes: This type of niosome can accommodate tiny holes from side to side since it may be smooth and free of damaging structure. The term "elastic niosomes" probably refers to a variety of niosome that has been altered or specifically formulated to increase its elasticity or deformability. The capacity of the vesicles to bend and squeeze through tiny pores or narrow capillaries without rupturing is referred to as elasticity in this context. Because of its ability to penetrate biological barriers more effectively and increase target cell or tissue absorption, this characteristic may be useful for medication delivery applications. Numerous medications, such as anticancer treatments, anti-inflammatory pharmaceuticals, and vaccinations, have been researched in relation to elastic niosomes possible uses in medical delivery. They are a promising platform for pharmaceutical research because of their adaptability and capacity to be customised for particular medication delivery requirements [14, 15].

Advantages of Niosomes [1-10]

1. Niosome can accommodate a variety of drug moieties such as hydrophilic, lipophilic, as well as amphiphilic drugs.
2. They improve the therapeutic profile of the drug molecules due to delayed clearance from the circulation

3. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.
4. The drug can release in the sustained/controlled manner.
5. No special conditions required for handling and storage of surfactants.
6. Due to the depot formulation, it allows controlled release of the drug.
7. Poorly soluble drugs have increased oral bioavailability.
8. They can enhance the permeation of drugs through the skin.
9. They can protect the active moiety from biological circulation and also from enzymatic degradation.
10. Improve the stability of entrapped drug.
11. Surfactants possess following response biodegradable, biocompatible, non-toxic and non- immunogenic.

Disadvantages [1-10]

1. Susceptible to physical instability
2. Niosomes may aggregate over time.
3. Niosomes may fuse together leading to changes in membrane composition and properties.
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.

Comparative Features of Niosomes and Liposomes [1]

Table 1: Comparative features of Niosomes and Liposomes

Sr.no.	Features	Niosomes	Liposomes
1.	Composition	Vesicles composed of surfactants with or without cholesterol incorporation	Vesicles composed of concentric phospholipid bilayer
2.	Toxicity	Less toxic	Comparatively more toxic
3.	Stability	Non-ionic surfactants are stable	Used phospholipids are unstable
4.	Storage conditions	No special storage conditions are needed	Special storage conditions are required
5.	Fabrication techniques	There is no need for special methods for such formulations	A special method for phospholipid handling and purification is needed
6.	Size	The size varies between 10 to 100 nm	The size varies between 10 to 3,00 nm

Methods of Preparation of Niosomes [1-20]

There are several methods for the preparation of niosomes. These are categorized into 3 main types and novel techniques are as follows.

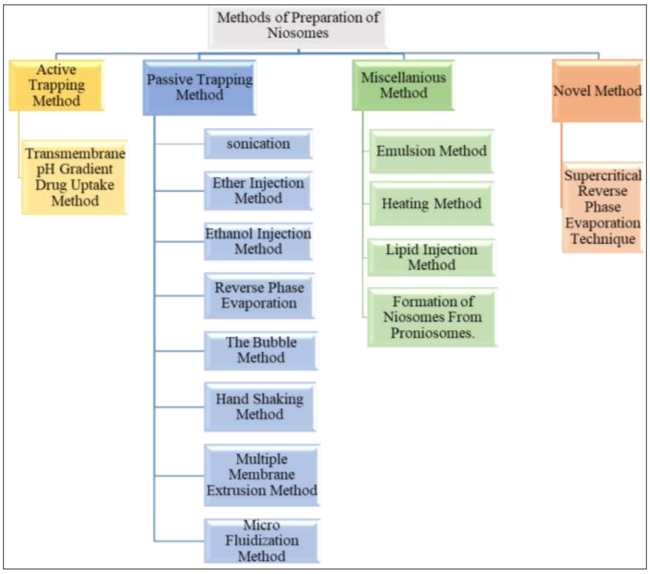


Fig 3: Methods of Preparation

1. Active Trapping Method [15,16]

This involves the medication being loaded subsequent to niosome synthesis. To help the medicine enter niosomes, a pH gradient or an ion gradient must be maintained while the niosomes are being formed. The noisome form has several benefits, including complete entrapment, elevated drug-lipid ratios, no leakage, economical viability, and appropriateness for medications that are labile [15, 16].

1.1. Trans Membrane pH Gradient Drug Uptake Process [15, 16]

In this method transmembrane pH gradient is maintained along the lipid vesicles formation. In this method of preparation vortex sample (an aqueous solution containing 10 mg/ml of the drug and maintained at the pH of 7.0-7.2 using 1 M disodium phosphate) is used. following is the step by step procedure of this method [15, 16].

- Surfactants and cholesterol are dissolved in an organic solvent (chloroform) during the remote loading process.
- Reduced pressure causes the organic solvent to evaporate, leaving a thin layer on the round bottom flask's wall.
- The thin film is then hydrated with the mixture of vortex sample and 300mM citric acid (pH- 3-4).
- After that three freezing and thawing cycles are followed by sonication.
- Thereafter the mixture is heated for ten minutes at 60°C to produce niosomes.

2. Passive Trapping Method [1-20]

The majority of niosome preparation techniques fall under this category since they involve the incorporation of drugs into the niosomes during their development rather than during their preparation.

2.1. Sonication Method [1, 13, 14]

It is the common and simple method for the production of niosomes. The resulting vesicles from this method are generally small and unilamellar. In this method titanium probe Sonicator is used. The process of niosome formulation by sonication method as follows.

- The drug dissolved in distilled water or phosphate buffer (pH -7.4) to form an aqueous phase.
- The surfactant and cholesterol dissolved in chloroform or diethyl ether to form organic phase.
- Then Aqueous phase is added to the organic phase and this two-phase system is probe sonicated at 60°C for 3 minutes which results to the formation of niosomes.

2.2. Ether Injection Method [17]

This method is also known as solvent injection method.

- Firstly, surfactant and cholesterol dissolved in the diethyl ether to form organic phase.
- Drug is dissolved in distilled water to form aqueous mixture which is maintained at 60°C.
- Then the organic phase is slowly injected into aqueous mixture through 14 gauze needle at the rate of 0.25ml/min
- There is the rapid evaporation of organic solvent due to temperature difference between two phases; results in the formation of single layered vesicles size diameter ranges from 50-1000nm depending upon condition used.

2.3. Ethanol Injection Method [1-6]

This method utilizes the ethanol as an organic solvent. overall this method is similar to the ether injection method.

- Firstly, surfactant and cholesterol are dissolved in the ethanol to form organic mixture; and drug is dissolved in aqueous solvent to form aqueous phase.
- After that the organic mixture is injected rapidly into the aqueous phase through fine needle.
- There is a rapid evaporation of the ethanol and this leads to the formation of the niosomes.

2.4. Reverse Phase Evaporation Method [14-16]

This method produces the large unilamellar vesicles.

- The surfactant and cholesterol dissolved in the mixture of organic solvent (ether and chloroform) in a 1:1 ratio and the aqueous drug solution is prepared by dissolving drug into distilled water.
- When the aqueous drug solution is added into organic mixture, a water-in-oil emulsion forms with two phases that are sonicated at 4-5 ° C.
- In a rotary evaporator set at 40°C and at reduced pressure the organic phase is eliminated and a transparent semisolid gel of large vesicles forms.
- The transparent gel is mixed with a little amount of phosphate buffered saline (PBS), and then sonicated.
- Niosomes are formed by further diluting the viscous niosomal solution with phosphate buffered saline and heating it on a water bath for 10 minutes at 60° C.

2.5. The "Bubble" Method [19-20]

It is one step procedure by which liposomes and niosomes are manufactured without the use of organic solvents.

- The RBF with a three necks and circular bottom is used as a bubbling unit, and the temperature is adjusted by placing it in a water bath at 70°C.
- The first neck contain thermometer, second neck contain the cooled reflux, while the third neck houses the nitrogen supply.
- Cholesterol and surfactant is mixed in the buffer (pH-7.4) for 15 seconds by using high pressure homogenizer; and pass it into the round bottom flask (RBF)
- This mixture is bubbled by passing nitrogen gas into RBF at 70°C; which results into the formation of niosomes
- Further size reduction should be done by using Sonicator.

2.6. Thin Lipid Film Hydration method [1, 5, 19]

This method requires specialized equipment that is Rota Evaporator. This method produces multilamellar vesicles ranges from 100-1000nm. Following is the step by step procedure of this method.

- In a round-bottom flask, the mixture of surfactant and other vesicles-forming components, such as cholesterol, is dissolved in a volatile organic solvent such as diethyl ether, chloroform, or methanol.
- Dissolve the drug in distilled water to form aqueous phase.
- On Rota Evaporator the organic solvent is removed which leaves a thin film of solid mixture(lipid Film) on the wall of the flask.
- After that film is rehydrated with aqueous phase at 60°C with gentle stirring for 1-1.5 hrs; this results into the formation of multilamellar vesicles.
- Further size reduction can be done by using Sonicator.

2.7. Multiple Membrane Extrusion Method [13-16]

This is the most effective way to control niosome size.

- An aqueous drug solution is prepared by dissolving drug into distilled water.
- A surfactant, cholesterol, and diacetyl phosphate are dissolved in chloroform, and the organic solvent is evaporated to form a thin film by using Rota Evaporator.
- The film is then hydrated with an aqueous drug solution, and the resulting suspension is extruded through polycarbonate membranes that are arranged in line for up to eight passages, which will produce the niosomes of the desired sizes.

2.8. Micro fluidization method [17]

It's a relatively new method that uses the submerged jet concept.

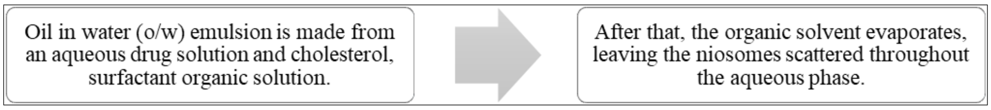
- Dissolve a drug and surfactant in an organic phase, then pressurizing it through a reservoir and into an interaction chamber.
- The drug & surfactant fluidized flow mix in precisely specified micro-channels into the inter-action cell at ultrahigh velocities in this approach.
- The solution will pass through the cooling pipe in order to avoid the heat produced during the procedure will be diminished.

- Due to high-speed impact and the energy involved in this procedure results in more homogeneous, smaller, and reproducible niosomes.

3. Miscellaneous Methods [20-22]

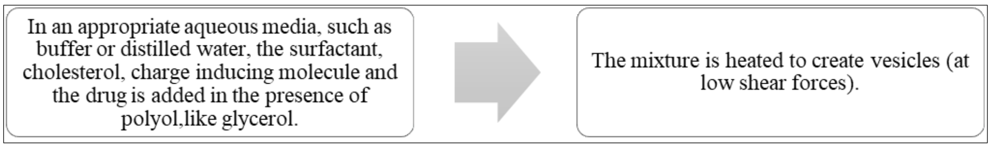
1. Emulsion Method [21]

In this method oil in water emulsion is formed by mixing mixture of cholesterol and surfactant in organic solvent and aqueous mixture of the drug so it is called as an emulsion method.



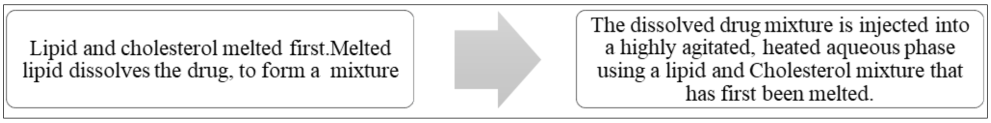
2. Heating Method [20, 21]

This method is in one-step, scalable and non-toxic and also based on the patent procedure. This approach is non-toxic, scalable, and one-step; it is also predicated on the patent procedure.



3. Lipid Injection Method [22]

The costly organic phase is not needed for this procedure.

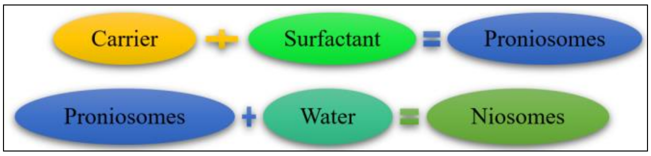


4. Formation of Niosomes from Proniosomes [21, 22]

Proniosome is a dry formulation where a thin layer of dry surfactant covers each water-soluble particle. When there is brief agitation at T > Tm, the niosomes are recognized by the addition of an aqueous phase.

Tm is the mean phase transition temperature, while T is the temperature.

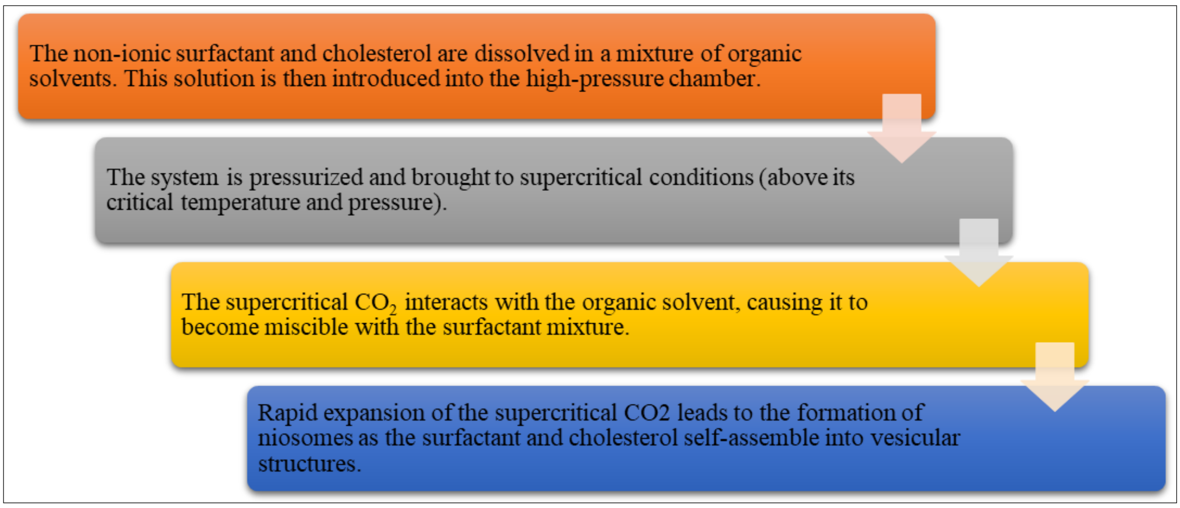
Proniosomes are made up of a carrier and a surfactant, whereas niosomes are made up of proniosomes plus water.



4. Novel Techniques [23-25]

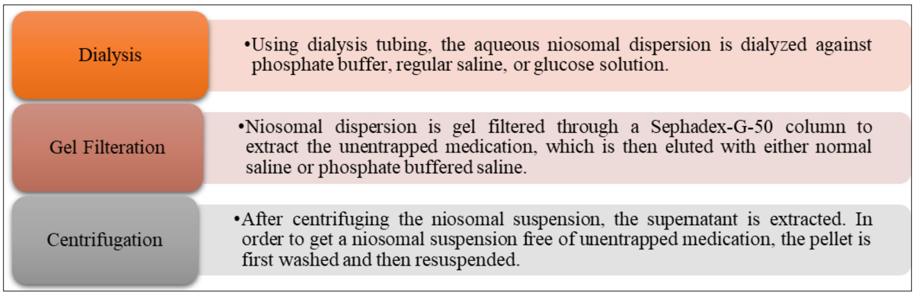
1. Supercritical Reverse Phase Evaporation Technique

The supercritical fluid technique for niosome formation involves the use of supercritical carbon dioxide (SC-CO_2) as a solvent or co-solvent during the preparation of niosomes. This method has gained attention due to its ability to produce niosomes with desirable characteristics, such as small particle size, high encapsulation efficiency, and improved drug delivery properties. The supercritical fluid technique offers advantages over traditional methods, as it allows for precise control over particle size, reduced use of organic solvents, and scalability. The process usually involves the use of a high-pressure system where supercritical CO_2 is generated. The process is usually performed at a temperature above the critical temperature of CO_2 but below the phase transition temperature of the surfactant. Here's a brief overview of the process [25].



Separation of Unentrapped Drug: [20-23]

There are several methods for removing the unentrapped solute from the vesicles, including



Factors Affecting Niosomal Formulation [25-30]

1. Nature of Surfactant [25, 27]

As surfactant hydrophobicity increases and surface free energy decreases, surfactant HLB values rise, which causes an increase in niosome mean size. Niosome bilayers can exist in two different states: a liquid and a gel. It is dependent on cholesterol, surfactant type, and temperature. In the gel form, alkyl chains are well-organized, but in the liquid state, they are disorganized. The gel, liquid phase transition temperature (TC) of the surfactant influences entrapment efficiency. For example, span 60 with a higher TC shows superior entrapment. Surfactants with an HLB value between 14 and 17 are not suitable for use in niosomal preparations. The entrapment efficiency is reduced when the HLB value of surfactants drops from 8.6 to 1.7; the maximum entrapment efficiency is achieved when the HLB value is 8.6.

2. Nature of Encapsulated Drug [26, 29]

physical and chemical characteristics of the encapsulated drug have a significant impact on the charge and rigidity of the niosomal bilayer. When raises charge, causes the surfactant bilayer to repel one another, and enlarges the vesicle. The level of entrapment is influenced by the drug's HLB.

3. Hydration Temperature [30]

It has an impact on the niosome's size and shape. The ideal hydration temperature is higher than the liquid phase transition temperature of gel. The assembly of surfactants into vesicles and the modulation of vesicle shape are impacted by temperature changes. The alteration is also explained by the hydration period and medium volume. When the hydration temperature, duration, and medium volume are not chosen properly, fragile niosomes and drug leakage issues may occur.

4. Cholesterol Content [30]

The entrapment efficiency and hydro-dynamic diameter of niosomes are increased when cholesterol is added. There are two ways in which cholesterol functions: Firstly, it makes liquid state bilayers chain order higher. Reduces gel state bilayers chain order. Raising the cholesterol content results in stiffer bilayers and slower encapsulated material release.

5. Charge [30]

When there is charge present in a multilayer vesicle structure, the interlayer distance between subsequent bilayers increases and the total entrapped volume increases.

6. Resistance to Osmotic Stress [26-29]

Vesicle diameter decreases upon the addition of hypertonic solution. Because the vesicle structure mechanically loosens under osmotic stress, inhibition of the eluting fluid from the vesicles causes a sluggish release at first, followed by a rapid release in a hypotonic solution.

Benefits and Drawback of Methods of Preparation of Niosomes [31-35]

Table 2: Benefits and Drawbacks of Method of Preparation of Niosomes

Sr.no.	Method of Preparation	Benefits	Drawbacks
1.	Trans Membrane pH Gradient Drug Uptake Process	High drug entrapment efficiency	Use of organic solvents
2.	Sonication Method	Scalability, time efficient	Not ideal for heat sensitive drugs
3.	Ether Injection Method	A simple laboratory technique	Not ideal for heat-labile drugs
4.	Ethanol Injection Method	Versatility in drug encapsulation	Ethanol residue
5.	Reverse Phase Evaporation Method	High drug entrapment efficiency	Use of organic solvents
6.	The “Bubble” Method	No use of organic solvents	Not ideal for heat-labile drugs
7.	Hand Shaking Method	A simple laboratory technique	Use of organic solvents
8.	Multiple Membrane Extrusion Method	Increase encapsulation efficiency	Equipment requirement Sensitivity to lipid composition
9.	Micro fluidization method	No use of organic solvents	Not ideal for heat-labile drugs
10.	Emulsion Method	A simple laboratory technique	Use of organic solvents.
11.	Heating Method	Uniform size distribution	Thermal sensitivity of bioactive compounds
12.	Lipid Injection Method	No use of organic solvents	Not ideal for heat-labile drugs
13.	Formation of Niosomes from Proniosomes	No use of organic solvents, better physical stability	Total drug retention during hydration is not possible
14.	Preparation using micelle solution and enzymes	No use of organic solvents	Enzymatic degradation of the active ingredient
15.	Supercritical Reverse Phase Evaporation Technique	No use of organic solvents	Need of special equipment

Characterization of Niosomes [10-30]

1. Morphology: Morphological characterization of Nano systems like niosomes can be done by evaluating following parameters [10, 15].

a. Number of Lamellae: The number of lamellae refers to the layers or concentric membranes within the vesicle structure. Here are some techniques commonly used to characterize the number of lamellae in niosomes, these are Small-Angle X-Ray Scattering (SAXS), Transmission Electron Microscopy(TEM), Dynamic Light Scattering(DLS) and Nuclear Magnetic Resonance(NMR). [10]

b. Bilayer rigidity and homogeneity: Characterizing the layer rigidity and homogeneity of a material, such as a lipid bilayer in niosomes, involves assessing the structural integrity, flexibility, and uniformity of the layers. Rigidity of the bilayer affects niosome biodistribution and biodegradation. Using techniques such as Fourier transform-infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and nuclear magnetic resonance (NMR), homogeneity can be detected both inside niosome structures and between niosomes in dispersion [25].

c. Bilayer Disruption Studies: Techniques that induce or measure bilayer disruption, such as osmotic swelling or detergent-induced disruption can be used to assess the rigidity of lipid layers. Monitoring changes in vesicle size or morphology can provide insights into layer stability. It is carried out by using Differential Scanning Calorimetry (DSC), Small Angle X0Ray Scattering (SAXS), X-Ray Diffraction (XRD) and Nuclear Magnetic Resonance (NMR) techniques.

2. Size and Shape: A variety of techniques are employed to determine the mean diameter, including electron microscopy, molecular sieve chromatography, photon correlation microscopy, optical microscopy, and laser light scattering. Size and shape of the niosomes can be evaluated with the help of Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Small-Angle X-Ray Scattering (SAXS) techniques. [20]

3. *In Vitro* Drug Release: *In vitro* drug release studies are essential for understanding the release kinetics and behaviour of a drug from a delivery system, such as niosomes. These studies help researchers and pharmaceutical scientists evaluate the performance of the drug delivery system and predict its behaviour *in vivo*. Some common methods used for *in-vitro* drug release studies are Dialysis Bag/Tube Diffusion Technique, Dissolution Apparatus (USP Apparatus I, II, or IV), Franz Diffusion Cell. [10]

4. Vesicle Charge: The vesicle charge often referred to as the zeta potential, It is a crucial parameter in understanding the stability and behaviour of niosomes. The zeta potential represents the electric potential at the slipping plane of a particle or vesicle and is influenced by the surface charge of the vesicle. Here's a brief overview of the importance of vesicle charge and how it affects in various aspects. [10]

⇒ Zeta Potential Measurement [26]

Zeta potential is typically measured using techniques such as electrophoretic light scattering or laser Doppler electrophoresis. These methods involve subjecting vesicles to an electric field and measuring the velocity of their movement, from which the zeta potential is calculated. The zeta potential can be positive, negative, or close to zero, depending on the composition of the vesicle and the surrounding medium.

⇒ Interpretation of Zeta Potential Values [26]

a. Highly Positive or Negative (>±30 mV): Indicates good stability due to strong electrostatic repulsion.
b. Low Zeta Potential (near zero): May lead to increased vesicle aggregation and reduced stability.
c. Positive Zeta Potential: May enhance cellular uptake due to interaction with negatively charged cell membranes.
d. Negative Zeta Potential: Reduces the risk of interactions with blood components, potentially minimizing adverse effects.

5. Stability Study: Stability experiments are conducted on niosomal formulations by storing them in a thermostatic oven for three months at 4° C, 25° C and 37° C. One month later, the drug content is measured using the entrapment efficiency metric for each formulation. Stability studies are crucial to assess the long-term stability, shelf-life, and quality of niosomes or any other drug delivery system. These studies help to identify potential changes in physicochemical properties, efficacy, and safety over time. Here are some key aspects and methods involved in stability studies for niosomes [10]:

1. Physical Stability: It refers to the ability of niosomes structures to maintain their structural integrity, size, and morphology over time. Changes in physical stability can impact the performance and efficacy of niosomes, especially in drug delivery applications. Following parameters are evaluated in the physical stability includes Changes in appearance, colour, and aggregation of niosomes, Measurement of size distribution and shape over time, Monitoring for phase separation or sedimentation.

2. Chemical Stability: Chemical stability of niosomes is critical to ensuring the preservation of the composition and integrity of the lipid-based vesicular structures, especially in drug delivery applications. Chemical instability can lead to degradation of lipids, surfactants, and encapsulated drugs, affecting the efficacy and safety of the formulation. Some key considerations and methods for assessing the chemical stability of niosomes are assessment of drug degradation within the niosomes, Monitoring changes in chemical composition, degradation of lipids or surfactants which are done by analytical techniques like HPLC, mass spectrometry, or spectroscopy.

3. Biological Stability: Biological stability of niosomes refers to their ability to interact with biological components, such as proteins, cells, and tissues, without causing adverse effects or compromising their structural integrity. This aspect is crucial, especially in the context of drug delivery systems, where niosomes need to remain biocompatible and maintain their properties in biological environments. This is carried by assessment of interactions with biological components (e.g., proteins, cells) that may affect stability and evaluation of potential immunogenicity or cytotoxic effects.

6. Niosomal Drug Loading and Encapsulation Efficiency: It is critical parameters in the development of niosomal drug delivery systems. They determine the amount of drug effectively encapsulated within the niosomal vesicles, influencing the system's efficacy, stability, and therapeutic performance. Here's an overview of these two concepts [10].

1. Drug Loading: Drug loading refers to the amount of drug present in the niosomal formulation, expressed as a percentage of the total weight of the formulation. The drug loading can be calculated using the following formula [15]

$$\text{Drug Loading}(\%) = \frac{\text{Amount of drug encapsulated}}{\text{Total weight of niosomes}} \times 100$$

2. Encapsulation Efficiency: It represents the percentage of the drug that is successfully entrapped within the niosomal vesicles concerning the total amount of drug used during the formulation. High encapsulation efficiency is desirable for maximizing the therapeutic efficacy and minimizing potential drug wastage. The encapsulation efficiency can be calculated using the following formula [15].

$$\text{Encapsulation Efficiency }(\%) = \frac{\text{Amount of drug encapsulated}}{\text{Total amount of Drug added}} \times 100$$

Applications of Niosomes [1-30]

1. Localized Drug Action & Sustained Release

Niosomes have a wide range of application in targeted drug delivery system. Niosomes deliver the drug at the targeted site and release the drug in sustained order [1].

2. Niosomes as Hemoglobin Carriers

Hemoglobin can be transported by niosomes. The visible spectrum of niosomal suspension is super-imposable to that of free hemoglobin. The hemoglobin dissociation curve of vesicles may be altered in a manner akin to that of non-encapsulated hemoglobin, and they are permeable to oxygen [1].

3. Niosomes as a Drug Carrier

Niosomes are the most promising for various drugs especially for the drugs (peptide drugs) which are difficult to deliver at the specific site in the body. Niosomes have also been employed as delivery systems for the diagnostic drug iobitridol, which is used in X-ray imaging. Topical niosomes can work as a solubilization matrix, a local site for the prolonged release of chemicals that are dermally active, penetration enhancers, or a membrane barrier that limits the rate at which medications are absorbed systemically [30].

4. Targeting of Bioactive Agents

1. To reticulo-endothelial system (RES)

The vesicles are selectively absorbed by the RES cells. Niosomes are also taken up by the cells due to opsonins which are circulating serum factors that identify and label niosomes for clearance. However, the treatment of animal tumours known to spread to the liver and spleen as well as hepatic parasite infection has made use of this type of localised medication accumulation [15].

2. To organs other than RES

Antibodies can be used to target the carrier system to particular bodily locations. Immunoglobulins appear to attach to the lipid surface rather easily, providing a practical way to target the drug carrier. It is possible to use the innate ability of many cells to identify and bind specific carbohydrate determinants to guide transport systems to specific cells [1].

Delivery of Peptide drugs

For a long time, oral peptide medication administration has struggled to avoid enzymes that would break down the peptide. Research is being done on the effective use of niosomes to shield peptides from gastrointestinal peptide degradation. The stability of the peptide was shown to be greatly enhanced by the trapping of a vasopressin derivative in niosomes, as demonstrated by an oral administration method used in an *in vitro* investigation [23].

Cosmetics and dermatology

Niosomes are employed in cosmetic and dermatological formulations for the delivery of vitamins, antioxidants, and skin-care agents. They can improve the stability and penetration of these compounds into the skin. Niosomes have several advantages in cosmetic and skin care applications, such as improving skin penetration, bioavailability of poorly absorbed substances, and stability of entrapped medications [21].

Cancer therapy

The most often used medications in niosomal drug delivery cancer therapy include vincristine, doxorubicin HCL, methotextrate, bleomycin, and daunorubicin HCL. When doxorubicin is given as a free medication, cardiac toxicity occurs; however, cardiac toxicity is lessened when the drug is given as a niosomal formulation. Doxorubicin has been found at higher levels in tumour cells, serum, and lungs by niosomal formulation. Additionally, it lengthens the life span of tumor-bearing mice and lowers the pace at which tumour cells proliferate. When methotrexate is ensnared by niosomes, its plasma level rises and its half-life lengthens, resulting in a longer duration of action and a delayed rate of drug clearance [1].

Leishmaniasis

A parasite belonging to the genus Leishmania infects the liver and spleen cells, causing leishmaniasis. The use of niosomes in experiments enables for bigger medication dosages to be administered without causing adverse effects, which improves therapy efficacy [10]

Gene delivery

Niosomes, which are non-ionic surfactant vesicles, have shown promise as potential carriers for gene delivery. Here are some key aspects of using niosomes in gene delivery [27].

- Encapsulation of Nucleic Acids
- Protection of Nucleic Acids
- Enhanced Cellular Uptake
- Endosomal Escape
- Tailorable Formulations
- Biocompatibility and Reduced Immunogenicity
- Targeted Gene Delivery
- Stability and Storage

Biomedical Research

Niosomes are used as research tools in studies related to cell biology, drug targeting, and cellular uptake mechanisms due to their ability to encapsulate and deliver a variety of bioactive molecules.

Overall, the versatility and biocompatibility of niosomes make them promising carriers for various therapeutic and diagnostic applications in the field of medicine and biotechnology [27].

Current Challenges in Niosomal Drug Delivery System [7]

Several challenges exist in the field of niosome research and application.

1. Scalability and Reproducibility

One significant challenge is achieving consistent production of niosomes on a large scale. Ensuring batch-to-batch reproducibility is crucial for industrial applications, and optimizing manufacturing processes to scale up production remains a challenge.

2. Storage Stability

Maintaining the stability of niosome formulations during storage is a concern. Factors such as aggregation, leakage of encapsulated substances, and changes in vesicle size over time can affect the shelf life of niosome-based products.

3. Drug Loading and Release Kinetics

Achieving high drug-loading capacity and controlling the release kinetics of drugs from niosomes are ongoing challenges. Researchers are working to fine-tune these parameters to ensure sustained and controlled release profiles based on the specific therapeutic needs.

4. *In Vivo* Stability and Biodistribution

Niosomes face challenges related to stability and biodistribution *in vivo*. Strategies to enhance stability under physiological conditions and improve targeted delivery to specific tissues or cells are areas of active research.

5. Immunogenicity and Clearance

Understanding and mitigating potential immunogenic responses and clearance mechanisms are important considerations. The reticuloendothelial system (RES) and other clearance pathways can impact the pharmacokinetics and therapeutic efficacy of niosomal drug delivery systems.

6. Combination Therapies

Developing niosomal formulations for combination therapies, where multiple drugs are delivered simultaneously, presents additional challenges. Co-encapsulation of different drugs with varying physicochemical properties requires careful consideration of compatibility and release profiles.

Researchers and pharmaceutical scientists are actively addressing these challenges through ongoing research and technological innovations. Advancements in nanotechnology, materials science, and formulation design are expected to contribute to overcoming these hurdles and improving the effectiveness of niosomal drug delivery systems.

Future Aspects

A promising molecule for medication delivery is niosomes. Niosomes offer a great deal of potential as drug carriers because they can be used to encapsulate toxic anti-cancer, anti-infective, anti-AIDS, anti-inflammatory, antiviral, and other medications. This will improve the drugs bioavailability and targeting capabilities while also lowering their toxicity and side effects. While niosomal carriers are safer, ionic drug carriers are comparatively harmful and inappropriate. The future of niosomal drug delivery systems holds promising prospects as researchers continue to address challenges and explore innovative applications. Here are some potential future aspects and trends in the field:

1. Personalized Medicine

Niosomal drug delivery systems can be tailored to individual patient needs, enabling personalized medicine approaches. This could involve the customization of drug formulations based on patient-specific factors such as genetics, disease characteristics, and response to treatment.

2. Combination Therapies

Niosomal formulations offer the potential for co-delivery of multiple drugs, allowing for combination therapies. This can be particularly valuable in the treatment of complex diseases where a synergistic effect of different drugs is desired.

3. Theranostics

Integrating diagnostic and therapeutic capabilities within a single niosomal system is an emerging concept in Theranostics. Niosomes can be designed to carry both therapeutic agents and imaging agents, enabling simultaneous treatment and monitoring of disease progression.

4. Responsive Drug Delivery Systems

Smart or responsive niosomal systems that can release drugs in response to specific stimuli, such as pH, temperature, or enzymatic activity at the target site, are being explored. These systems aim to provide on-demand drug release for improved therapeutic outcomes.

5. Remote Monitoring and Feedback Systems

Integration of technologies for remote monitoring and feedback systems could enhance the effectiveness of niosomal drug delivery. Real-time monitoring of drug release and patient responses may enable adjustments to treatment plans for optimal outcomes.

6. Global Healthcare Access

Niosomal drug delivery systems have the potential to improve global healthcare access by providing more effective and affordable treatments. Cost-effective production methods and versatile formulations could contribute to the widespread availability of these therapeutic approaches.

Overall, the future of niosomal drug delivery systems is likely to involve a convergence of multidisciplinary efforts, including nanotechnology, pharmacology, and materials science. Continued research, collaboration, and technological advancements will play a crucial role in unlocking the full potential of niosomes for improving drug delivery and patient outcomes.

Conclusion

There has been an increasing demand for the development of nanocarriers targeting multiple diseases with a broad range of properties. Due to their tiny size, giant surface area and feasible targetability niosomes getting popular as nanocarrier based drug delivery system. Niosomes have optimized efficacy, decreased side effects and improved stability over conventional drug dosage forms. Pharmaceutical research seeking to enhance drug bioavailability, increase stability and improve organ targeting has been progressively advanced. Niosomes have been investigated as a liposome substitute. Several benefits over liposomes, including better purity, comparatively higher chemical stability, and comparatively lower cost. Non-ionic surfactant vesicles change the drug's cellular interaction, metabolism, tissue distribution, and plasma clearance kinetics. They are the most promising nanocarrier due to their ability to encapsulate both hydrophilic and hydrophobic drugs with potential improvements for drug stability and bioavailability. Niosomes can shield drug molecules from the biological environment, which can improve the therapeutic performance of various drug molecules.

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