REVIEW ARTICLE

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Niosomes as a Novel Pharmaceutical Carrier: Structure, Classification and Preparation Methods

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Abstract

Niosomes are non-ionic surfactant vesicles obtained by a hydrating mixture of cholesterol and nonionic surfactants. It can be used as a carrier of an amphiphilic and lipophilic drugs. In the niosomes drug delivery system, the medication is encapsulated in a vesicle. Niosomes are biodegradable, relatively nontoxic, more stable and inexpensive when compared to liposomes. The unilamellar niosomes vesicles are further divided into small unilamellar vesicles (SUV) and large unilamellar vesicles (LUV) whose particle size ranges between 10 – 100 & 100 – 250 nm, respectively. However, multilamellar vesicles (MLV) have vesicles that range in size from 100 to 1000 nm. This article presents an overview of the techniques of preparation of niosome, types of niosomes and characterisation. Also, niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. The drug delivery potential of niosome can enhance by using novel drug delivery concepts like proniosomes, discomes and aspasome. Moreover, niosomes have many advantages over others nanoparticles system, we mention this advantages in this article.

Keywords: Niosomes, non-ionic surfactant, drug delivery, vesicles.

1. Introduction

The idea of targeted drug delivery aims to concentrate the medication in the target tissues while lowering the relative concentration of the drug in the non-target tissues. As a result, the drug is concentrated at the targeted site, so the drug does not affect the surrounding tissues. Additionally, localization of the drug prevents drug loss, resulting in maximum medication efficacy. Numerous carriers, including immunoglobulin, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes and niosomes, have been used to target drugs (Lohumi 2012, Parveen, Misra et al. 2012, Hua, Marks et al. 2015).

Niosomes are one of the best among these

carriers. Niosomes are a special type of bilayer lipid nanostructure that was created by a non-ionic surfactant self-aggregating(Kazi, Mandal et al. 2010, Chen, Hanning et al. 2019). It was initially created by the L'Oreal Company in 1975 for use in cosmetics. They were put to use as a drug delivery method in 1980, five years after their development. While lipid-soluble compounds are included in the hydrophobic layer, they can easily incorporate a variety of medicinal chemicals, proteins, and genes that can be put into the hydrophilic core (Apolinario, Hauschke et al. 2021, Aparajay and Dev 2022).

Based on their amphiphilic nature, non-ionic surfactants produce a closed bilayer vesicle in aqueous media by utilizing some energy, such as heat and physical agitation. While the hydrophilic heads of the bilayer stay in contact with the aqueous solvent, the hydrophobic portions are orientated away from it. The vesicles' characteristics can be changed by altering the vesicles' composition, size, lamellarity, concentration, tapped volume and surface charge (Reddy, Padman et al. 2012, Sharma, Ali et al. 2018).

Numerous forces act inside the vesicle, e.g., repulsive forces resulting from electrostatic interactions between charged groups of surfactant molecules, van der Waals forces between surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc. The vesicular structure of niosomes is maintained by these forces. However, the kind of surfactant, the nature of the medication that is encapsulated, detergents, the storage temperature, the in-situ interfacial polymerization of surfactant monomers, the usage of membrane-spanning lipids and the presence of charged molecules all affect the stability of niosomes. Because they include hydrophilic, amphiphilic, and lipophilic moieties, these can accommodate drugs with a wide range of solubility (Kazi, Mandal et al. 2010, Lin and Klein 2019).

These might serve as a depot, releasing the drug gradually in a controlled manner. Delaying the removal of drug molecules from the bloodstream, shielding them from the biological environment, and preventing them from being hydrated right before usage to produce aqueous niosome dispersions can all improve their therapeutic effectiveness. the aggregation, fusion, and leakage issues associated with niosomes and add to the simplicity of delivery, storage, and dosing (Shakya and Bansal 2014, Ray, Bano et al. 2018).

Niosomal drug delivery is potentially applicable to numerous pharmacological agents for their action against various diseases. It can also be utilized to develop a novel drug delivery system for pharmaceuticals that are not easily absorbed. By overcoming the anatomical barrier of the gastrointestinal system through transcytosis of M cells from Peyer's patches in the intestinal lymphatic tissues, it improves bioavailability. Numerous antineoplastic drugs were encapsulated in this carrier vesicle to reduce drug side effects while maintaining and increasing the anti-tumour efficacy (Jadhav, Morey et al. 2012, Cheng, Li et al. 2021).

Niosomes' sustained release activity can be used to deliver medicines with low water solubility and low therapeutic index. Due to their small size and poor penetration into connective tissue and epithelium, niosome drug delivery is one method for achieving localized drug activity. This method keeps the medication localized at the site of administration. Localized drug action increases the efficacy of the potency of the drug and, at the same time, reduces its systemic toxic effects. Niosomal drug delivery technology is still in its infancy, but cancer chemotherapy and anti-leishmanial therapy have shown promise for this sort of drug delivery system (Kazi, Mandal et al. 2010, Shakya and Bansal 2014).

2. Structure of niosomes

The bi-layered structure of non-ionic surfactant is called a niosome. Only when surfactants and cholesterol are combined in the right ratio and the temperature is above the gel liquid transition point can these thermodynamically stable bi-layered structures development. In the center of this two-layered structure lies a hollow area. Niosomes can encapsulate both a hydrophilic and a hydrophobic drug because of their special geometry. Hydrophilic drugs can bind to the surface of the bilayer or the center aqueous domain of niosomes for entrapment, whereas hydrophobic drugs partition into the bilayer structure. The bilayer structure of the niosome is explained with the help of (Fig. 1), which clearly shows the two different areas for drug entrapment (Bhardwaj, Tripathi et al. 2020).

3. Classification of niosomes

Niosomes are widely categorized regarding the number and size of vesicular lipid layers. Based on this classification, vesicles are classified into unilamellar and multilamellar vesicles. The unilamellar vesicles are further divided into small

unilamellar vesicles (SUV) and large unilamellar vesicles (LUV) whose particle size ranges between 10 – 100 & 100 – 250 nm, respectively. However, multilamellar vesicles (MLV) have vesicles that range in size from 100 to 1000 nm (Khoee and Yaghoobian 2017). Additionally, niosomes are categorised according to the non-ionic surfactant and other excipients utilized in manufacturing as well as the various therapeutic applications.

3.1. ***Proniosome:*** These formulations are water-soluble dry powders that have surfactant coatings. When used, these are rehydrated, which helps to get beyond the limitations of niosomes such as the leaking of medicinal moieties, aggregation, and fusing of vesicles (Bachhav 2016).

3.2. Aspasome: These are multi-layered vesicles created utilizing cholesterol, ascorbyl palmitate (ASP), and more negatively charged lipids like diacetyl phosphate. This preparation reduces the negative effects brought on by reactive oxygen species (ROS) and improves transdermal medication delivery (Aparajay and Dev 2022).

3.3. Bola niosomes: These niosomal formulations were created by mixing span 80, cholesterol, and Bola surfactants α, ω-hexadecyl-bis-(1-aza-18-crown-6) (Bola C16). These formulations are typically employed in transdermal drug delivery applications to increase permeability (Singh, Ansari et al. 2016, Aparajay and Dev 2022).

3.4. Discome: These MLVs are formulated using cholesteryl poly-24- oxyethylene ether (Solulan C24) and a small amount of cholesterol. These formulations, whose sizes range from 11 to 60 μm, are used to create a sustained-release formulation for ocular delivery (Umbarkar 2021).

3.5. Polyhedral niosomes: These niosomes are commonly formulated without cholesterol by substituted non-ionic surfactants either with polyoxyethylene cholesteryl ether or hexadecyl diglycerol ether (C16G2). These vesicles can entrap water-soluble particles while not having a defined shape (Yadav, Kulkarni et al. 2011, Keshav 2015).

3.6. Vesicles in w/o emulsion system: Niosomal vesicles are made using this method as a water-in-oil emulsion. Typically, a mixture of chemicals including span 60, cholesterol and solulan C24 (poly-24-oxyethylene cholesteryl ether) is used to create these vesicular systems. Enzymes and peptides that are sensitive to the environment are typically delivered using these formulations (Gharbavi, Amani et al. 2018, Sharma, Kumar et al. 2019).

3.7. Niosomes in carbopol gel: Cholesterol and a suitable non-ionic surfactant are used to create niosomes. After that, fabricated niosomes are added to the carbopol gel. These formulas could improve mucoadhesion ability (Aparajay and Dev 2022).

4. Components of niosomes

Niosomes are usually formulated using three main active components: non-ionic surfactants, appropriate additions like cholesterol, and charge-inducing agents. Non-ionic surfactants must typically be hydrated with or without additive agents (which, in the absence of cholesterol, leads to the formation of gels) for niosome formation. Charge-inducing substances can occasionally give the lipid bilayer vesicular structure additional stability (Chen, Hanning et al. 2019, Aparajay and Dev 2022). Non-ionic Surfactants are a specific type of surfactant whose polar head lacks a charge. They are often non-ionic because they depend on the functional group, which deprotonates them to a shallow degree. This non-ionic surfactant feature allows the nonpolar group to be put together in an aqueous dispersion to produce vesicular niosomes (Demissie, Lu et al. 2021, Aparajay and Dev 2022).

Non-ionic surfactants are divided into the following categories: alkyl ethers, polyoxyethylene fatty acid esters, sorbitan fatty acid esters, alkyl glyceryl ethers, and block copolymers. These preparations usually require additional energy from outside sources, such as heat, mechanical stirring, or sonication (Gharbavi, Amani et al. 2018, Shah, Prajapati et al. 2021). To create a stable, nontoxic, biodegradable, nonimmunogenic, ligand targeted, cost-effective, dual drug-loaded niosomal formulation for numerous diseases such as cancer, viral infections, etc., all non-ionic surfactants are used in a variety of clinical applications, either alone or in combination with other surfactants and additive agents. A white waxy substance known as cholesterol is crucial in the formation of niosomal structures. It is an amphiphilic molecule that joins with the hydrophilic head of the non-ionic surfactant to generate hydrogen bonds.

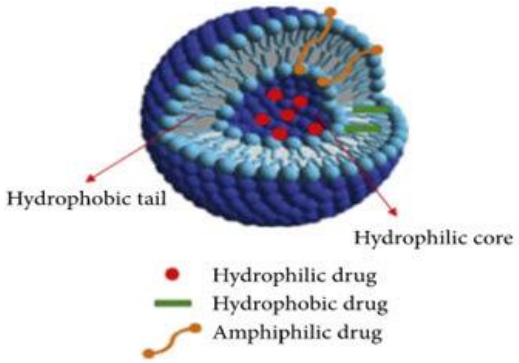

Figure 1: Structure of Niosome (Sharma, Ali et al. 2018).

It significantly contributes to the strength of the niosomal structure by giving vesicles mechanical rigidity, improving encapsulation effectiveness, and reducing vesicular niosome leakiness (Shinu, Nair et al. , Mousa, Hammady et al. 2022). Additionally, it is essential for creating formulations with controlled and sustained releases in which the amount of cholesterol in niosomal preparations regulates or determines the rate at which the therapeutic moiety is released. Additionally, the size of the vesicle is also influenced by the cholesterol concentration (Bnyan, Khan et al. 2018). To give charge over the surface of the niosomal formulation, charge-inducing agents are added. These charges give vesicles additional stability because the electro-repulsive force they produce prevents niosomes from aggregating, allowing them to stay suspended in the vehicle for a longer time. Depending on the choice of charge-inducing molecules, these charges might be positive or negative. For example, phosphatidic acid and diacetyl phosphate (DCP) produce negative charges, whereas stearyl pyridinium chloride and stearylamine (STR) are employed to induce positive charges (Aparajay and Dev 2022). They also aid in the creation of hybrid niosomal complexes and improve the effectiveness of encapsulation and skin permeation. These charge-inducing agents have been added in concentrations ranging from 2.5 to 5 molar, and too much addition could prevent the development of niosomes (Kassem, El-Sawy et al. 2017, Verma, Tiwari et al. 2021).

5. Advantages of niosomes

Niosomes offer several advantages over the conventional delivery system.

(i) Niosomes have greater chemical stability, longer shelf life, and osmotic activity when compared to liposomes.

(ii) The surface of niosomes can be easily formed and modified because of the presence of a functional group on the hydrophilic head.

(iii) Niosomes don't contain any charge, making them less poisonous and more compatible.

(iv) The biological systems can break down niosomes, and they don't cause immunogenic reactions.

(v) Both hydrophilic and hydrophobic medicines can be enclosed in niosomes

(vi) By improving both the physical and biological stability of the active pharmaceutical substance, niosomes can improve its bioavailability.

(vii) Given an aqueous suspension, patient compliance is increased.

(viii) Niosomes can be administered practically everywhere, including orally, parenterally, transdermally, ocularly, and pulmonary.

(ix) By adjusting the different parameters, such as additives, their ratio, or their use in combination, their shape, size, and entrapment can be altered.

(x) Niosomes can be used to deliver drugs in a targeted, controlled, and sustained manner (Khoee and Yaghoobian 2017, Kaur and Kumar 2018, Bhardwaj, Tripathi et al. 2020).

6. Disadvantages of niosomes

Although the niosomal delivery system has several advantages, stability may be a problem when niosomes are suspended in water because the drug may be hydrolyzed. There may also be issues with drug leakage from the location of entrapment and niosome aggregation development (Khoee and Yaghoobian 2017, Bhardwaj, Tripathi et al. 2020).

7. Methods of niosomes preparation

There are many ways to prepare formulations depending on the particle size, lamellarity, and potential uses for different therapeutic purposes. In the sections that follow, some crucial niosome fabrication techniques are addressed. Their diagrammatic representation is also shown in Fig. 2.

7.1. Thin-film hydration technique:

The creation of niosomes is accomplished using this method, which is widely employed. First, in this method, non-ionic surfactants and cholesterol are typically dispersed in an appropriate organic solvent (chloroform, ethanol, etc.). The rotatory evaporator is then used to create a thin film from the resultant solution. The attained film is hydrated using water or buffer as a hydrating media at a temperature above the gel-liquid transition to produce a milky suspension of niosome (Gokila 2011, Aparajay and Dev 2022).

7.2. *Handshaking method:*

In this method, surfactants and additives are often distributed in the organic solvent. The organic solvent is next removed from the above combination using a rotary evaporator, and the film is finally hydrated with water or PBS (phosphate buffer saline, pH 7.4) using mechanical shaking for an hour to create a cloudy white suspension. Multilamellar vesicles are generally generated using this technique (Moghassemi and Hadjizadeh 2014, Bhardwaj, Tripathi et al. 2020).

7.3. *Bubble method:*

Without the use of any organic solvent, this technique creates niosomes in a single step. A three-neck round bottom flask is filled with a mixture of non-ionic surfactant, cholesterol and buffer. In two necks, water-cooled reflux is used to control the temperature, while nitrogen is delivered through the third neck. In a homogenizer with high shear, the aforementioned dispersion is mixed for 15 seconds before 70°C nitrogen gas is gradually added. This technique is mainly used to create large unilamellar vesicles. Although, a continuous nitrogen supply can be used to regulate vesicle size (Yeo, Lim et al. 2017, Bhattacharya 2020).

7.4. Ether injection method:

In this technique, surfactant with another additive (Cholesterol) is dispersed in diethyl ether and then injected in an aqueous solvent with a 14-gauge needle at a temperature above 60 °C. A rotatory evaporator must be used to completely evaporate the organic solvent; while ether evaporates slowly, surfactant aggregates to form vesicles with single-layered (Nishu, Karmoker et al. 2018, Kulkarni, Rawtani et al. 2021, Shewaiter, Selim et al. 2022).

7.5. *Sonication method:*

This method involves dispersing cholesterol and a non-ionic surfactant in a buffer that also contains a therapeutic moiety. Niosomes are produced by subjecting this mixture to a probe sonicator for a further three minutes at 60 °C. Sonication has been used to create niosomes that are loaded with diallyl disulfide (DADS) (Khan, Bashir et al. 2019, Khan, Bashir et al. 2020).

7.6. Reverse phase evaporation technique:

This method is typically used to create LUVs when cholesterol and a non-ionic surfactant are mixed in an appropriate organic solvent. To create an emulsion, the resulting mixture is further sonicated. At 40–60 °C, gradual evaporation of an organic solvent creates the vesicular niosomes (Yamaguchi, Kimura et al. 2016, Sharma, Dua et al. 2019)

7.7. Microfludization method:

To release a large amount of energy that had been trapped in the section, two fluidized streams connect precisely through microchannels inside an interaction chamber at very high speeds, which eventually results in the development of niosomes. This technique utilizes the submerged jet concept to produce compact, homogenous unilamellar niosomes that are more repeatable (Chen, Hanning et al. 2019, Bhardwaj, Tripathi et al. 2020).

7.8. Heating method:

This procedure involves heating cholesterol (solution A) and non-ionic surfactant (solution B) separately in PBS (pH 7.4) for 60 to 90 minutes under a nitrogen atmosphere. For 15-20 minutes, both solutions are heated at a temperature of 120 °C. Finally, solution A and solution B are combined and agitated for 15 minutes at a reduced

temperature of 60 °C to produce niosomes. The obtained niosomes are stored at 4 °C after swelling them at room temperature (Kaur and Kumar 2018, Bhardwaj, Tripathi et al. 2020).

7.9. ***Freeze and thaw method:***

This method typically prepares a thin film of nonionic surfactant. By liquid nitrogen, the thin film is then frozen for one minute and thawed for 60 seconds at 60 °C in an aqueous solution. Multilamellar vesicles are primarily generated and thawed using this technique (FAT-MLVs) (Bartelds, Nematollahi et al. 2018, Bhardwaj, Tripathi et al. 2020).

7.10. Proniosome technology:

With the use of high homogeneity shear or high-pressure extrusion, SUVs are created using this process from MLVs. Large-curvature MLVs are broken by strong energy to create SUVs (Mittal, Chaudhary et al. 2020).

7.11. ***Enzymatic method:***

The niosome has been prepared by an enzymatic process using a mixed micellar solution. Esterase is used to break down the ester bonds between cholesterol and polyoxyethylene, and it is then mixed with dicetyl phosphate and another ingredient to produce multilamellar niosomes. Surfactants made of polyoxyethylene stearyl and polyoxyethylene cholesteryl derivatives are employed most frequently (Gharbavi, Amani et al. 2018, Chen, Hanning et al. 2019).

7.12. Single-pass method:

This technique is one of the patented ones, in which the lipid suspension is extruded typically through a specified porous device before being allowed to pass through a nozzle. For a narrow range of niosomes, the whole system is linked to high-pressure extrusion and homogenization (50 – 500 nm) (Bhardwaj, Tripathi et al. 2020).

7.13. ***Hand jani-vila method:***

In this procedure, an aqueous solution of the active ingredient is combined with an equal amount of lipid (or a mixture of lipids) and agitated using ultracentrifugation or agitation. The final step is to homogenize the resulting mixture at a controlled temperature to create a homogeneous lamellar phase (Aparajay and Dev 2022).

8. Factors affecting vesicles size, entrapment efficiency, and release characteristics

8.1. Drug

The interaction of the solute with surfactant head groups, which raises the charge and mutual repulsion of the surfactant bilayers, increases the vesicle size when the drug is trapped in niosomes. Drugs are imprisoned in the lengthy PEG chains of polyoxyethylene glycol (PEG)-coated vesicles, which decreases the tendency for them to expand in size. The degree of entrapment is influenced by the drug's hydrophilic-lipophilic equilibrium (Sharma, Ali et al. 2018, Gad, Mousa et al. 2022).

8.2. Amount and type of surfactant

Since the surface free energy lowers as the hydrophobicity of surfactants increases, the mean size of niosomes rises correspondingly as the HLB of surfactants such as Span 85 (HLB 1.8) to Span 20 (HLB 8.6) increases. Depending on the temperature, the kind of lipid or surfactant, and the presence of additional elements like cholesterol, the bilayers of the vesicles can either be in the so-called liquid state or the gel state (Nasr, Moftah et al. 2022). Alkyl chains are present in a well-ordered form in the gel state, whereas the structure of the bilayers is more disordered in the liquid state. The temperature at which the gel-liquid phase transition (TC) occurs describes the surfactants and lipids. The efficacy of entrapment is also influenced by the phase transition temperature (TC) of surfactants; for example, Span 60 with a higher TC offers better entrapment (Taymouri and Varshosaz 2016, García-Manrique, Machado et al. 2020).

8.3. Cholesterol content and charge

Cholesterol improves the hydrodynamic diameter and trapping effectiveness of niosomes. In general, cholesterol has two fold effects. Cholesterol both raises the chain order of bilayers in the liquid state and decreases the chain order of bilayers in the gel state. A liquid-ordered phase develops from the gel state at high cholesterol concentrations. The bilayers' rigidity increased with increasing cholesterol content so it reduced the rate at which material was released from its encapsulation. In multilamellar vesicle structure, the presence of charge tends to increase the interlamellar distance between succeeding bilayers and results in a larger overall entrapped volume (Ahmed, Ghourab et al. 2013, Shaker, Shaker et al. 2015).

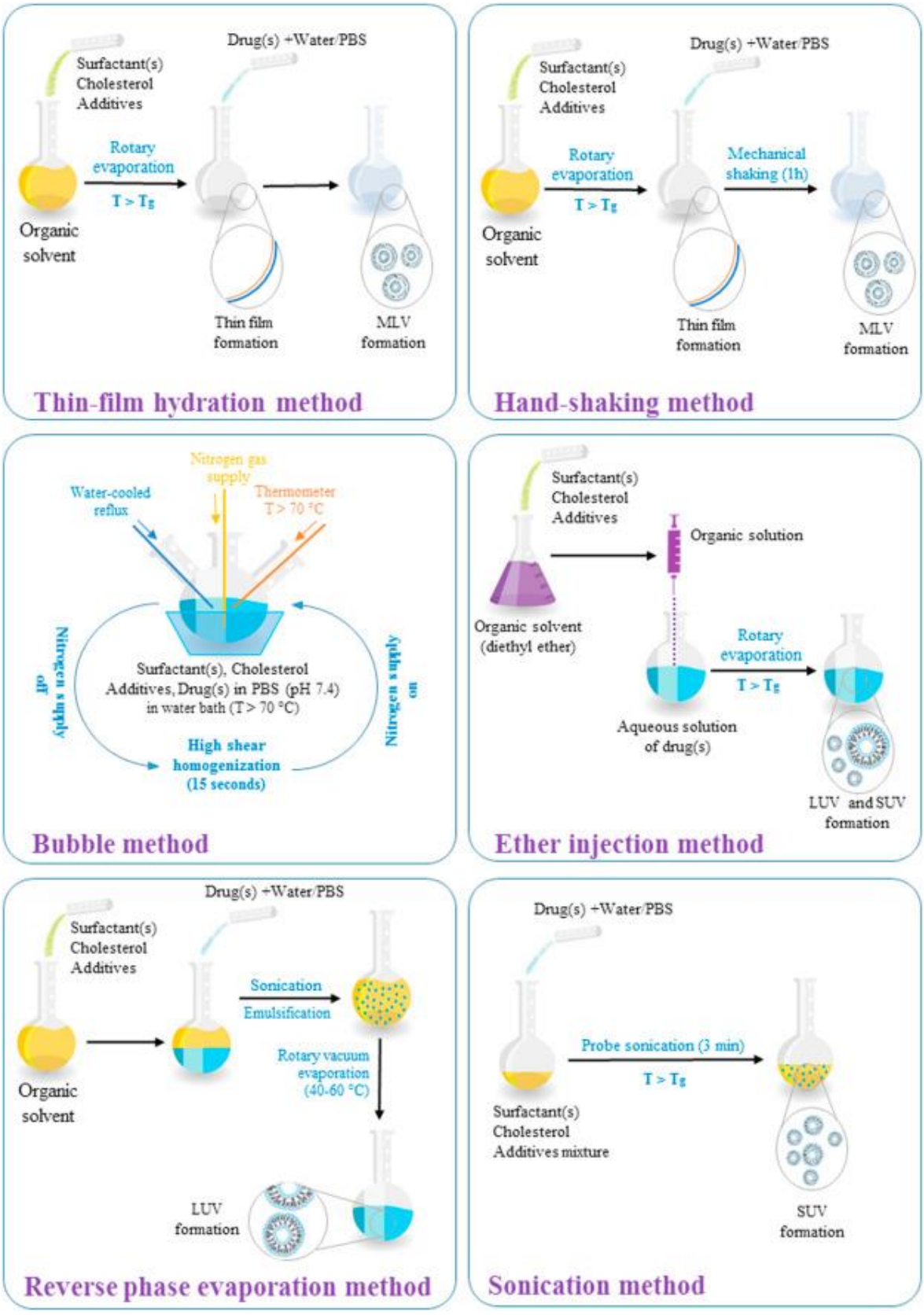

Figure 2: Methods of niosomes preparation (Masjedi and Montahaei 2021).

8.4. Methods of Preparation

The ether injection method forms vesicles with a lower diameter (50-1,000 nm) compared to the hand shaking method. The Reverse Phase Evaporation (REV) method can be used to create small niosomes. The microfluidization method produces smaller and more uniform vesicles (Ahmed, Ghourab et al. 2013, Correia, Briuglia et al. 2017).

8.5. Resistance to osmotic stress

Niosomes are reduced in diameter when a hypertonic salt solution is added to a suspension of niosomes. In a hypotonic salt solution, there is a sluggish initial release with slight vesicle swelling that is likely caused by vesicle fluid elution being inhibited, followed by a quicker release that may be caused by mechanical loosening of the vesicle structure under osmotic stress (Shakya and Bansal 2014, Badri, Sailaja et al. 2022).

Conclusion:

One of the many examples of the enormous development in drug delivery technology is the niosomal drug delivery system. Many scientists and academics subscribe to the idea that drugs can target specific sites on niosomes by integrating with them. They serve as alternatives to liposome-based vesicular systems and have several benefits over liposomes, including cost, stability, and other factors. Niosomes characterize a promising drug delivery technology.

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