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REVIEW ARTICLE

RECENT WORK ON NIOSOMAL VESICLES: BILAYER STRUCTURE, BASIC COMPONENTS, PREPARATION AND EVALUATION

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Abstract: Vesicular systems are a revolutionary way of administering drugs in a controlled manner to increase bioavailability and prolong the therapeutic effect. Niosomes are hydrated vesicular structures that include a non-ionic surface active agent, cholesterol, and other lipids. Over the liposomes, niosomes have various advantages, such as delivering drugs to specified sites that are non-toxic, stable for a longer time in different situations, and need low production cost. The first cosmetic industry that produced niosomes was L'Oreal. Later on, in the pharmaceutical sector, its applications were explored. Niosomes are developed by self association of cholesterol and surface active agents in an aqueous phase.Niosomes have the property of biodegradable, biocompatible and nonimmunogenic structure and also show the ability for encapsulation of both types of drugs hydrophilic and lipophilic. Over the last few years, it is studied that niosomes may enhance the drug bioavailability, and provides a novel approach for delivering numerous drugs like- protein therapeutic agents, chemical therapeutic agents and gene substances with less toxicity and desired targeted ability. This review provides complete details on niosomes, structure, types, fabrication processes, factors influencing niosomes competence, benefits and drawbacks, implementations, and cites numerous instance of niosomes studies over the last decade.

Keywords: Niosomes, Non-ionic surfactant, Cholesterol, Non toxic, Liposomes, Vesicles

INTRODUCTION

Liposomes were the first delivery mechanisms for vesicular drugs, but at various pH they have some drawbacks such as toxicity, low cost and stability problems. Research focus has turned towards niosomes due to the drawbacks of liposomes. Unilamellar, oligolamellar or multilamellar can be niosomes [Bhardwaj, P *et al*., 2020]. These are called niosomes because niosomes are made up of non-ionic surfactants, and because of these surfactants, they are non-toxic. They can also include cholesterol, or its derivatives, and charged molecules, in addition to non-ionic surfactants. Cholesterol gives the structure rigidity, and the charged molecule maintains the formulation stable. When nonionic surface-active agents arrange themselves, the development of niosomes happens. Due to their design, both hydrophilic and hydrophobic drugs can be used for the loading and delivered [Akbarzadeh, I. *et al*., 2020, Balin, B. J. *et al*., 1986, Bhardwaj, P *et al*., 2020,Basiri, L *et al*., 2017].The bi-layered arrangement of non-ionic surface active agents is termed niosomes fig. (1). These thermodynamically steady bi-layered structures are produced simply as surfactants and cholesterol is properly combined and the temperature is above the temperature of the phase transition temperature [Bhardwaj, P. *et al*., 2020, Chen, X. Q. et al., 1998., Chen, S. *et al*., 2019]. A void space in the middle comprises this bi-layered structure. Because of their peculiar geometry, hydrophilic and hydrophobic medicines can be encapsulated in their structure by niosomes. Hydrophilic drug molecules may be trapped in niosomes or adsorbed on the bilayer surface in the central aqueous domain, while hydrophobic drugs may be partitioned into the bilayer structure [Bhardwaj, P. *et al*., 2020, Basiri, L. *et al*., 2017].The niosomes' bilayer arrangement is clarified with the aid of Fig. 1, which indicates the two separate drug trapping areas distinctly.

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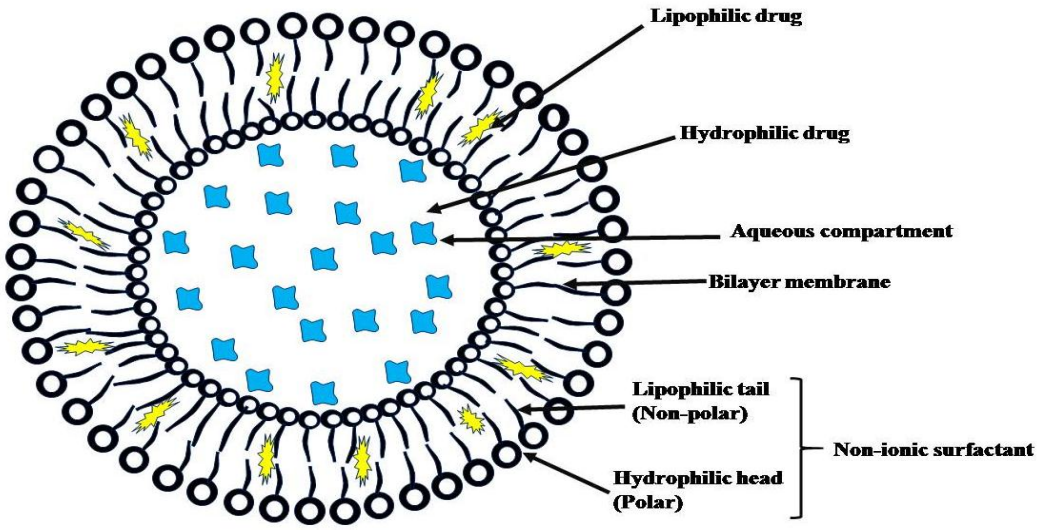

Fig. (1) Bilayer structure of niosomes.

Types of niosomes

LUVs: have a single bilayer (0.1 - 10µm in diameter) surrounding the aqueous core. They have a wide aqueous compartment, which may be used to encapsulate.

MLVs: having several bilayer (0.5 – 10µm in diameter) surrounding the aqueous compartment. MLVs may be prepared easily and high stable than both SUVs and LUVs under the specific storage conditions. Due to presence of multiple bilayers, favorable in the loading of lipophilic.

SUVs: (10 - 100µm in diameter) are produced from MLVs, by various techniques like- sonication, extrusion, high pressure homogenization method. SUVs are less thermodynamically stable in comparison to other types of vesicles. SUVs have a higher tendency to form aggregation and less loading capability of hydrophilic molecules.

SUVs: small unilamellar vesicles.

LUVs: large unilamellar vesicles.

MUVs: multi unilamellar vesicles [De, S. *et al*., 2012,Devaraj, G. N. *et al*., 2002].

Advantages

1. Niosomes give numerous improvements in comparison to traditional drug delivery systems.
2. Niosomes assure higher chemical stability and prolonged shelf life- as compared to liposomes.
3. The formation and modification of the surface of the niosomes can achieve smoothly because the hydrophilic head bears a functional group.
4. Niosomes do not bear any charge by which they are less toxic and show more compatibility.
5. They are biologically biodegradable and not able to promote any immunological reactions.
6. They may employ both types of drugs- hydrophilic and lipophilic for the encapsulation.
7. By increasing the physical and biological stability, the bioavailability of the API can magnify.
8. By this formulation, patient compliance is more agreeable while- the formulation gives in the form of an aqueous suspension.
9. They may administer all of the routes- a few of them are parenteral, ocular, transdermal, pulmonary, and oral.
10. Niosomes used in controlled release and sustain release.

Niosomes are also able to enhance the skin permeation of the drug[12,Basiri, L. et al., 2017, De, A. et al., 2018,Escudero, I. *et al*., 2014].

Disadvantages

Although the niosomal delivery system has many benefits, stability may be a cause of concern with the aqueous suspension of niosomes because the compound could be hydrolyzed. There may also be the situation of drug slippage from the site of trapping and aggregate niosome formation [Escudero, I. *et al*., 2014, Frey, W. H. *et al*.,1997].

Basic components and their contributions

Basic components for the formation of niosomes are surface active agents, cholesterol and charge producing substances [Basiri, L. *et al*., 2017, Gharbavi, M. *et al*., 2018 Gutiérrez, G *et al*., 2016]. It is important for the preparation of niosomes with desired properties to understand the physicochemical properties of these key components and their consequences on niosomes [Girigoswami, A. *et al*., 2006, Gaafar, P. M. *et al*., 2014].

Primary component (non-ionic surfactants)

Non-ionic surfactants are the key component that has been used in formulation of niosomes. Non-ionic surfactants that have a polar head and non-polar tail are amphiphilic in nature [Basiri, L. *et al*.,

2017].While these surface active agents do not bear any charge, compared to anionic, cationic and amphoteric surfactants, these are highly stable, compatible, and lesser toxic. These surfactants induce lesser hemolysis and irritation to cell membranes. Non-ionic surfactants like span and poloxamer have a property of high stability, few toxic and more compatible than other surfactants e.g. cationic, anionic, and amphoteric. These surfactants have less ability to create hemolysis and sensitivity on the surface of the cell. Non-ionic surfactants have the property of enhancing solubility by increasing the permeability rate as emulsifiers and wetting agents. An significant characteristic of these surface active agents is that they inhibit P-gp and can thus improve the absorption and targeting [Illum, L. et al., 2000] of anti-cancer drugs (e.g. Doxorubicin, Daunorubicin, Curcumin, Morusin) [Illum, L. *et al*. 2003., Isnan, A. P. *et al*., 2017, Jain, S. et al., 2005, Kumar, G. P. *et al*., 2011] steroids (e.g. Hydrocortisone) [43], HIV protease inhibitor, etc (example-Ritonavir) [Kaur, D. *et al*., 2018]. There is no charge on the polar head of the non-ionic surfactants. They may employ when the specifications are given in the form of rate, duration, and, location for the delivery of drugs. [Basiri, L. *et al*., 2017] The choice of surface active agents is based on their hydrophilic lipophilic balance,critical packing parameter and phase transition temperature [Abdelmonem, R. *et al*., 2021]. Entrapment efficiency of niosomes is affected by the hydrophilic lipophilic balance of the non-ionic surfactants. Higher the HLB value of the surfactant results in increase of size of vesicle and length of alkyl chain. Surfactants with HLB in the range of 14-17 are not acceptable for the production of niosomes. Hydrophilic lipophilic balance 8 demonstrates the highest entrapment efficiency [Escudero, I. *et al*., 2014].

Cholesterol

Stracture of niosomes displayed a new hydrogen bond which is formed due to presence of amphiphilic compound (cholesterol) having hydroxyl group with polar head of surfactant. This new hydrogen bond contributes an improvement of the leakiness of the membrane, increase mechanical rigidity and membrane cohesion. In result the entrapment efficiency of the formed niosomes are improved. The structure and characteristics of the niosomes are also affected by the quantity of cholesterol. Previously it is studied that cholesterol and its quantity both are depend upon the physical and chemical properties of the surfactant and drug used in the formulation of niosomes [Devaraj, G. N. *et al*., 2002].

Hydrophilic-lipophilic balance (HLB)

HLB scale shows the link between the hydrophilic and lipophilic groups present in the surfactants[Bhardwaj, P. *et al*., 2020].The surfactants that have a higher HLB value have a property of more aqueous solubility than the surfactants having a lower HLB value [Kida, S. *et al*., 1993, Kassem, M. A. *et al*., 2017, Kamboj, S. *et al*., 2014, Löwhagen, P. *et al*., 1994].HLB value alters the size of niosomes and entrapment efficiency of the active ingredient [Miller, D. *et al*, 2010]Mathison, S. *et al*, 1998, 51]. The study has confirmed that niosomes can form between the HLB values 4 and 8. In the formation of vesicles, surface active agents which have an HLB value of 6 or greater require more cholesterol. Niosomes are not produced by non-ionic surfactants with an HLB beyond this range [De, S. *et al*., 2012, Marianecci, C. *et al*., 2014, Moghassemi, S. *et al*., 2014, Manosroi, A. *et al*., 2008].

Phase transition temperature

A significant factor responsible for the production of niosomes is the phase transition temperature of the surface active agents. It influences entrapment efficiency, membrane fluidity, permeability of the membrane, and stability of the niosomes. Phase transition temperature and the length of the surface active agents alkyl chain are associated with one another. Smaller alkyl chains often have lower phase transition temperature, which tends to leakyniosomes being formed. Surface active agent that have high phase transition temperature are often highly probable to be sol to gel form, by diminishing bilayer leakage in comparison with surface active agents that have less gel liquid transition temperature[Kamboj, S. *et al*., 2014, Manosroi, A. *et al*., 2008].Phase transition temperature is based upon the degree of the unsaturated alkyl chain. Lack of saturation in the alkyl chain results less phase transition temperature and enhances alkyl chain fluidity and membranes permeability. Analysis revealed that surfactant-formed niosomes with lesser Tc are too elastic than surfactants with supreme Tc. Tc of the surfactant must be lower than the temperature of the hydration medium because temperature influences the fabrication of niosomes and it may also impart in the alteration of bilayer [De, S. *et al*., 2012, Manosroi, A. *et al*., 2011, Mullaicharam, A. R. *et al*., 2006, Manosroi, A. *et al*., 2010].

Procedures for preparation of niosomes

Various procedures are used in the preparation of niosomes, few of which are discussed in this literature.

Thin film hydration method

It is a common method used in the manufacturing of the niosomes fig. (2), also known as hand shaking method [Akbarzadeh, I., 2020]. In this technique organic- solvent is taken in a round bottom flask (RBF). Cholesterol and surfactants are added in a proper proportion into the RBF, and then the organic solvent from the RBF is evaporated with the help of vacuum rotary evaporator. Afterwards, on evaporation process, a thin film is formed in the inner surface of the flask. The formed layer is hydrated (with water or phosphate buffer) at temperature higher than the surfactants' phase transition temperature. Then formed thin layer is swells and multilamellar vesicles of the niosomes

having the drug takes place [Akbarzadeh, I. et al., 2020, Basiri, L. et al., 2017, Mayer, L. et al., 1985.,Martin, F. *et al*., 1990]. Thin-film hydration methods are used to prepare the niosomes [Escudero, I., 2014] of Zidovudine [Ma, H. *et al*., 2018], Benzylpenicillin [Martin, F. *et al*., 1990], Ten of ovirdisoproxil fumarate [Manconi, M. *et al*., 2003], Paclitaxel [Mahale, N. B. *et al*., 2012], Gallidermin [Mehrabi, M. R. *et al*., 2020], Lornoxicam [Mirzaie, A. et al., 2020], Prednisolone [Naderinezhad, S. et al., 2017], and Green tea extract [Onochie, I *et al*., 2013].

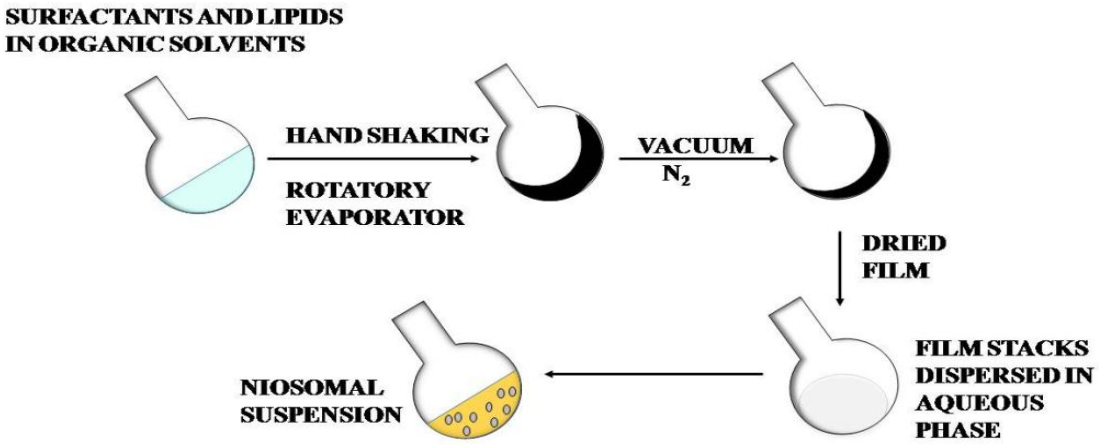

Fig. (2) Schematic diagram for the preparation of niosomes using thin film hydration method.

Ether injection method

In this procedure, the surface active agent and active pharmaceutical agent are mixed in diethyl ether and gently infused into aqueous phase fig. (3), the diethyl ether is heated over its boiling point [Basiri, L. *et al*., 2017, De, S. *et al*., 2012, Pajouhesh, H. *et al*., 2005]. This technique generates LUVs and can be further handled to decrease the size. Niosomes prepared by this method has a range of 50 to 1000 µm in diameter. Through this approach, Shree *et al*., produced niosomes of Stavudine[Escudero, I. *et al*., 2014, Perloff, M. D. *et al*.,2001].

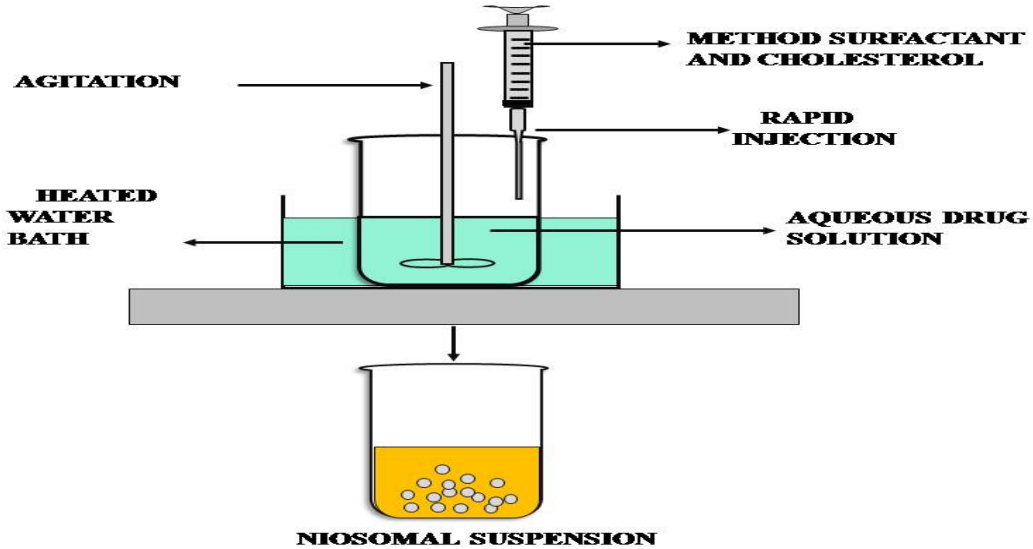

Fig. (3) Schematic diagram of the preparation of niosomes via Ether injection method.

Reverse Phase Evaporation method

In an organic solution (like- chloroform and ether) the non-ionic surfactants are dissolved fig. (4). In other hand the drug is dissolved in an aqueous solution, and added to the organic solution. Homogenize these two immiscible phases. By using the reduced pressure, the organic solvents are removed to get the niosomes suspension[Patel, J. *et al*., 2015]. It is an ideal method to develop the hydroxylchloroquine niosomes because of better entrapment efficiency and, big size of the particles having a small variation [De, S. *et al*., 2012,Rajera, R., Nagpal, K. *et al*., 2011].

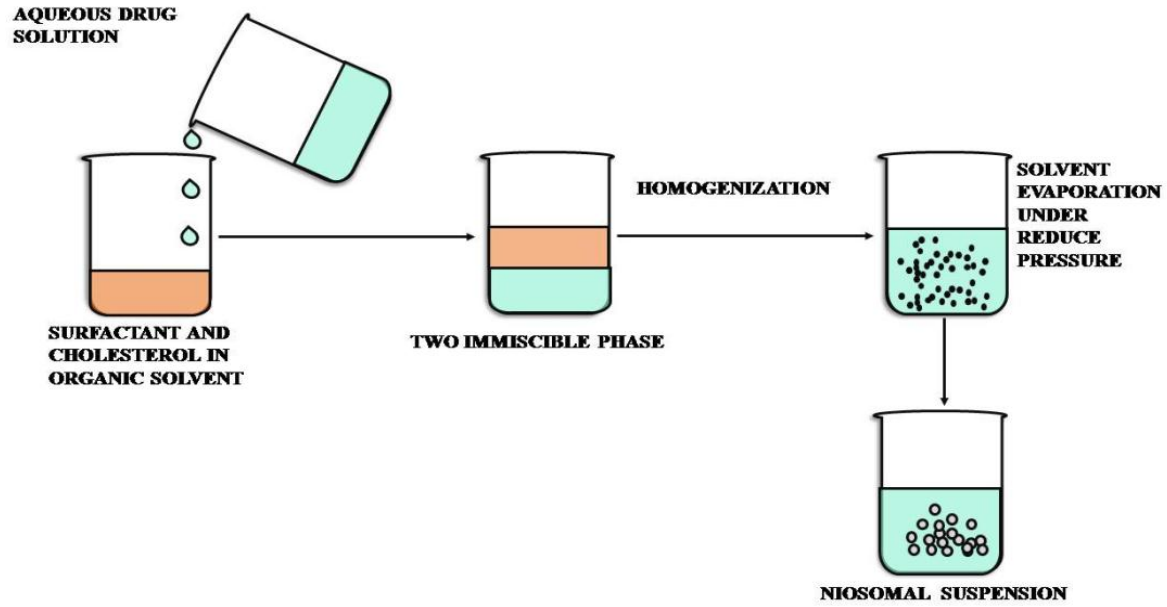

Fig. (4) Schematic diagram of the preparation of niosomes via Reverse phase evaporation method.

Microfluidization method

This newly developed technique produced smaller unilamellar vesicle with a distribution of small sizes. A surfactant and drug solution is pumped under pressure at a rate of 100 ml/min into an interaction chamber fig. (5). to remove the heat generated during microfluidization to form niosomes, the solution was further processed into a temperature control device [Bhardwaj, P. *et al*., 2020, De, S. *et al*., 2012].

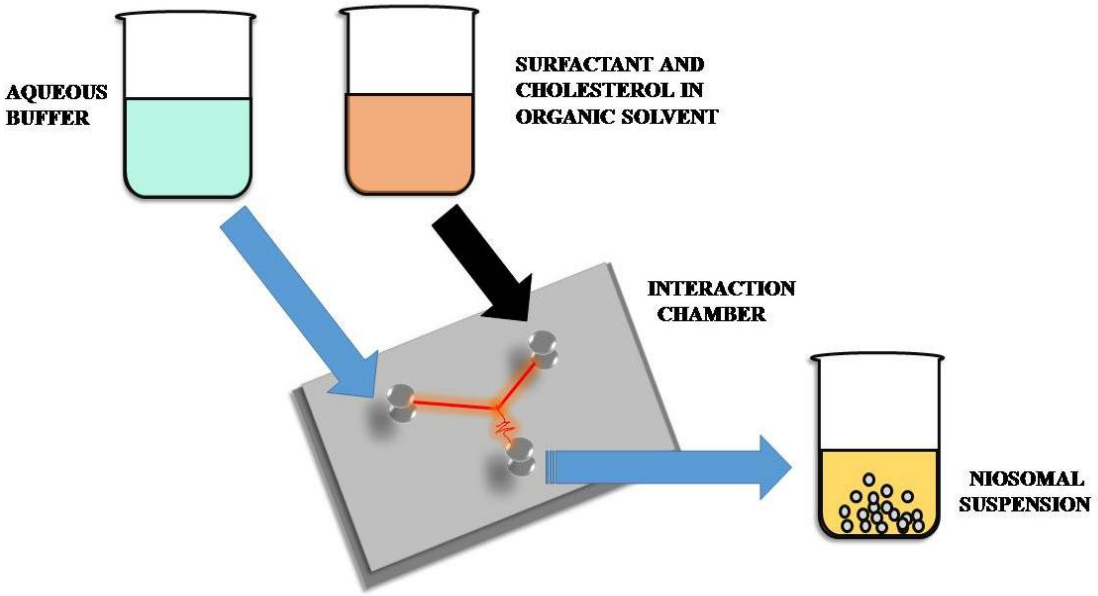

Fig. (5) Schematic diagram of the preparation of niosomes via Microfluidization method.

Transmembrane pH gradient

In this process, the same proportions of non-ionic surfactants and cholesterol are dissolved in chloroform (organic solvent) fig (6). This organic solvent separated under reduced pressure, in result a thin lipid film is formed in the inner surface of RBF. Citric acid or other acidic solution is used for the hydration of formed thin lipid film by vortex mixing. This resultant solution undergoes the freeze-thaw cycle, and by vertex mixing the aqueous solution of drug is added. Using disodium hydrogen phosphate solution, the final pH may be adjusted. The remote loading of the drug can be formed by this method [Abdelmonem, R. *et al*., 2021,Akbarzadeh, I. *et al*., 2020,] Escudero, I. *et al*., 2014,Ritwiset, A. *et al*., 2016,Ruckmani, K. *et al*., 2010].

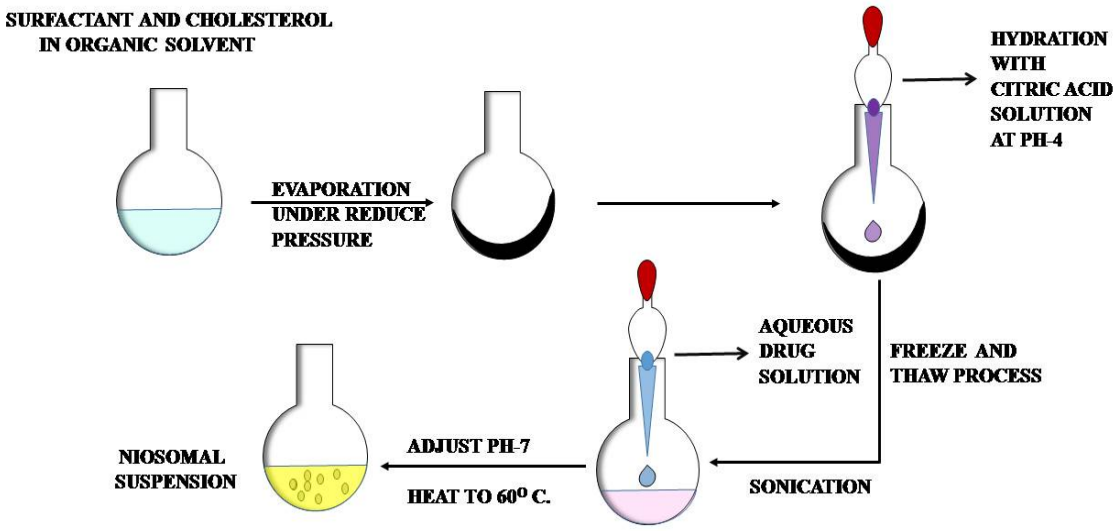

Fig. (6) Schematic diagram of the preparation of niosomes via the trans-membrane pH gradient drug uptake process.

The enzymatic method

In this technique, niosomes are formed from a mixed micellar solution via an enzymatic route. Ester bond is sliced by esterases causing breakdown of formulating ingredients like cholesterol and polyoxyethylene, which are in combination with dicetyl phosphate and other lipids that yield multilamellar vesicles. The surface active agents taken in this procedure are polyoxyethylenestearyl derivatives [Sherry Chow, H. *et al.*,1999] and polyoxyethylene cholesteryls ebacetatediacetate [Devaraj, G. N. *et al.*, 2002, Shinichiro, H. *et al.*, 1981].

Sonication method

Bansal et al. developed the niosomes of cefdinir with the help of the sonication method. Non-ionic surface active agents and cholesterol are added to the solution of the drug in the phosphate buffer. A probe sonicator is used to sonicate the resultant mixture sonicated at a temperature 60°C. Multilamellar vesicles are formed, to get the unilamellar vesicles it should be further ultra-sonicated[Escudero, I. *et al.*, 2014, Sahin, N. *et al.*,2007].

Supercritical reverse-phase evaporation

Manosroi and colleagues reported that the supercritical fluid involves in the development of niosomes [Mathison, S. *et al.*, 1998]. In this method, there is no need for an organic solvent. The organic solvent may be toxic and hard to remove. For the production of niosomes on a large number, this method is easy to scale up. By this method, the size range of the niosomes vesicles is 100 to 500 nm. The vesicles of these ranges lie in large unilamellar vesicles. Further, these vesicles undergo sonication or extrusion method to get small unilamellar vesicles [Bhardwaj, P. *et al.*, 2020, De, S. *et al.*, 2012, Mehrabi, M. R. *et al.*, 2020]

Supercritical carbon dioxide fluid

Manorisroi *et al.* described this method for the production of niosomes [Mathison, S.*et al.*1998].The solvent used in this method should have the following characteristics like non-inflammable, non-toxic, and volatile. The size of the prepared niosomes ranges from 100 to 400 nm by this method [Escudero, I. *et al.*,2014, Mathison, S. *et al.*, 1998].

Evaluation, depiction of niosomes

The following factors are used in the evaluation of niosomes.

Techniques involve in physical characterization

Numerous studies are performed for the detection of the surface morphology, distribution characteristics of the niosomes and size of niosomes, such as coulter counter, zeta seizer, freeze-fracture replicator, Meta seizer, photon correlation spectroscopy, light microscopy, Transmission Electron Microscope and Scanning Electron Microscope[De, S. *et al.*,2012.,Shehata, T. *et al.*,2016, Sharma, V. *et al.*,2015].

Entrapment efficiency (% EE)

Niosomes were assimilated with "50% n-propanol or 0.1%ton X-100" (organic solvents) and evaluated with an efficacious analytical procedure[De, S. *et al.*,2012].

EE percentage is assessedby the given equation as below-

$$\text{Percentage EE} = \frac{\text{Amount of therapeutic agents entrapment}}{\text{Total amount of therapeutic agents}} \times 100$$

Number of lamellae

For quantifying the numbers of lamellae, numerous different methods such as atomic force microscopy, small-angle X-ray spectroscopy, nuclear magnetic resonance and electron microscopy may be utilized. To interpret the thickness of bilayer of niosomes, the small-angle X-ray spectroscopy may be combined with energy dispersive X-ray diffraction [De, S. *et al.*,2012].

Zeta potential

For ascertaining the physical stability of vesicles, zeta potential, also recognized by surface charge,

contributes important information. Zeta potential may be evaluated by LDA. Magnitude of surface potential gives an interpretation of the degree of the electrostatic repulsion among two surrounding particles. For the acceptable stability, the range of surface potential should be higher than '+30 MV and lower than – 30 MV' for the niosomes[De, S. *et al*.,2012, Shtil, A. *et al*., 2000, Shaker, D. *et al*.,2015].

***In-vitro* release**

Membrane dialysis method for in-vitro drug release-

Niosomes are filled in dialysis bag and put in a container with phosphate buffer (dissolution medium)

↓

the container is kept on a magnetic stirrer, temperature at 37°C

↓

at a specific time interval the sample is withdrawn, concentration of drug is determined by any method given in literature[Abdelmonem, R. *et al*.,2021, Akbarzadeh, I. *et al*.,2020., Mirzaie, A. *et al*.,2020., Thorne, R. *et al*.,2001].By using the membrane dialysis method Temozolomideniosomes Paclitaxel and Curcumin cationic PE Gylatedniosomes [Thorne, R. *et al*., 2001] and Diltiazemniosomes [Tavano, L. *et al*.,2011] in-vitro release is studied.

Niosome stability

One of the most challenging tasks in the vesicular system is its stability. It is a biggest issue in the niosomes physical, chemical and biological stability. Stability of the niosomes is determined by checking the surface potential and size of vesicles over time, if there is a difference in both parameters shows possible in-stability. Niosomes stability is generally determined within three month having the different conditions such as 4°C, 25°C, 40°C at 75 % relative humidity. These different conditions are performed to assess the result of temperature on stability [De, S. *et al*., 2012, Manosroi, A. *et al*.,2011,Teaima, M. *et al*., 2020, Ueda, K. *et al*., 1992].

Recent work on niosomes in drug delivery

Table 1.

Types of drugs	Name of drug	composition	Method of preparation	Year	References
Glaucoma treatment Elevate intraocular pressure	Acetazolamide Carvidilol	Span 20, Tween 20, Span 60, Tween 60, and Cholesterol	Reverse-phase evaporation technique	2021	[Verma, S.*et al*., 2019]
Breast cancer	Simvastatin	Chloroform, Methanol, Spans (20,40, 60, 80)	Thin film hydration method	2020	[Vora, B. *et al*., 1998]
Ocular drug delivery	Pilocarpine hydrochloride	Spans and Tweens (20, 40, 60 & 80), cholesterol	Ether injection and Thin film hydration methods	2020	[Vora, B. *et al*., 1998]
Anti-emetic	Ondansetron HCl	Tween 20, Tween 80, cholesterol Span 60, Span 80,	Thin film hydration techniques	2020	[Waddad, A.*et al*., 2013]
Anticancer	Vincristine Sulfate,	Cholesterol, span 60, PEG-3000	Thin-film hydration technique	2020	[Yuksel, N.*et al*., 2016]
Antibacterial and Anti-cancer effects	Doxycycline	Span 60, Tween 60, and Cholesterol	Thin-layer hydration method	2020	[Zhang, S, *et al*., 2005]
Antibacterial and Anti-biofilm efficacies against ciprofloxacin-resistant methicillin-resistant S. aureus strains	Ciprofloxacin	Tween 60, Cholesterol, Span 60,	Modifying a remote-loading technique	2020	[Zubairu, *et al*., 2015]

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