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Niosomes As A Drug Delivery System: A Review

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Abstract

The invention of advanced drug delivery systems has received a lot of attention in the last few decades. The sophisticated drug delivery systems are designed to meet two requirements: they deliver drugs at a rate determined by the body's needs over the course of therapy, and they deliver the drug directly to inflamed or damaged tissues and/ or organs. Niosome-based drug delivery is one of these systems that encapsulate the medication in a vesicle. The vesicle formed by a bilayer of non-ionic surface-active agents. Niosomes offer promising drug delivery mechanisms. Being of non-ionic materials makes them less risky; hence, increases the therapeutic index of drugs by restricting their action to target cells. The goal of niosomes construction is to control the drug release in a sustained manner, a further change in the distribution profile of drug and targeting to the specific body site. The use of niosomes to encapsulate drugs may improve the protection of peptide-based medications. Insulin-loaded niosomes; for example, have a high tolerance to proteolytic enzymes. They are also effective in the topical delivery due to their ability to prolong the residence time of the drug and its active components in the stratum corneum and epidermis while minimizing systemic absorption.

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النيوسومات كنظام لتوصيل الدواء: مراجعة

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الملخص

حظي ابتكار أنظمة توصيل الدواء المتقدمة باهتمام واسع خلال العقود القليلة الماضية. وقد صُمِّمت أنظمة توصيل الدواء المتطورة لتلبية متطلبين أساسيين: توصيل الأدوية بمعدل يتوافق مع احتياجات الجسم طوال فترة العلاج، وتوجيه الدواء مباشرة إلى الأنسجة و/أو الأعضاء الملتهبة أو المتضررة. ويُعد توصيل الدواء المعتمد على النيوسومات أحد هذه الأنظمة، حيث يتم تغليف الدواء داخل حويصلات تتكون من طبقة ثنائية من عوامل سطحية غير أيونية.

توفّر النيوسومات آليات واعدة لتوصيل الدواء، إذ إن تكوينها من مواد غير أيونية يجعلها أقل خطورة، مما يؤدي إلى زيادة المؤشر العلاجي للأدوية من خلال حصر تأثيرها في الخلايا المستهدفة. ويهدف تصنيع النيوسومات إلى التحكم في إطلاق الدواء بشكل مستدام، إضافة إلى تعديل نمط توزيعه داخل الجسم وتوجيهه إلى مواقع محددة. كما أن استخدام النيوسومات في تغليف الأدوية قد يُحسّن من حماية الأدوية المعتمدة على الببتيدات؛ فعلى سبيل المثال، تُظهر النيوسومات المحمّلة بالإنسولين قدرة عالية على مقاومة الإنزيمات الحالّة للبروتين. كذلك تُعد فعّالة في التوصيل الموضعي نظرًا لقدرتها على إطالة زمن بقاء الدواء ومكوّناته الفعالة في الطبقة القرنية والبشرة مع تقليل الامتصاص الجهازي.

1. Introduction

The invention of novel drug delivery systems has attracted a lot of attention from the last decade of 20th century. The advanced drug delivery systems are designed to meet two requirements. First, they should be able to deliver the drug of interest at the rate determined by the body's needs over the course of therapy; secondly, they must guide the loaded drug directly to inflamed or damaged tissues and/ or organs(Jain et al., 2014). The main goal of a site-specific method of drug delivery is to make the drug more selective and therapeutic while also lowering its toxicity.(Mujoriya and Bodla, 2011) For targeted delivery of drugs, Vesicular drug delivery systems are especially noteworthy. These systems are defined as ordered assemblies of one or more concentric bilayers that are composed of amphiphilic building blocks and are found in an environment that contains water..(Jain et al., 2014) A variety of vesicular drug delivery systems have been developed, including liposomes, transfersomes, , microspheres, and niosomes (NS). NS has significant advantages over other carriers; this may be due to the improving entrapment efficiency of the drug, target site specificity, drug release. (Kamboj et al., 2013). NS were studied as an alternative to liposomes in 1985 because they have some advantages over liposomes. The low cost of nonionic surfactant in comparison to phospholipids, which are susceptible to ester bond hydrolysis is the main reason behind the cost effectiveness of NS.(Shilakari Asthana et al., 2016) They are novel drug delivery systems that encapsulate the medication in a vesicle formed by a double layer of not-ionic surface active agents. NS provide promising drug delivery mechanisms and being non-ionic makes them less unsafe and increases the therapeutic index of drugs by restricting their action to target cells. (Mahmoud et al.) In the cosmetic industry, NS are frequently used for dermatological purposes. L'Oréal was the first makeup company to create and patent niosomes. In 1987, Lancome was the first company to sell niosomes, a type of cosmetic. later, the anti-ageing cream ‘Niosome Plus' was produced.(Singh et al., 2016) . NS have considered as an excellent and ideal option for the cosmetics industry because of its improved skin penetration, stabilization of entrapped drugs, and greater bioavailability of poorly absorbed components. (Singh and Sharma, 2016) The use of NS to encapsulate drugs may present peptide drugs protection. Insulin-loaded niosomes; for example, have been found to express high tolerance towards proteolytic enzymes.(Kumar and Rajeshwarrao, 2011) They are also effective in topical delivery due to their ability to prolong the residence time of the loaded drug and its active components in the stratum corneum and epidermis while minimizing systemic absorption.(Singh and Sharma, 2016) The aim of this review is to study the niosomal as drug delivery system and its associated .

1.1. Structure of Noisome

The basic structural unit of NS is important because, it defines which materials can be used in its production and the drug delivery mechanism for loaded drugs. NS are known as nonionic surfactant vesicular system that have bilayer structure as shown in Fig.1(Ge et al., 2019),.

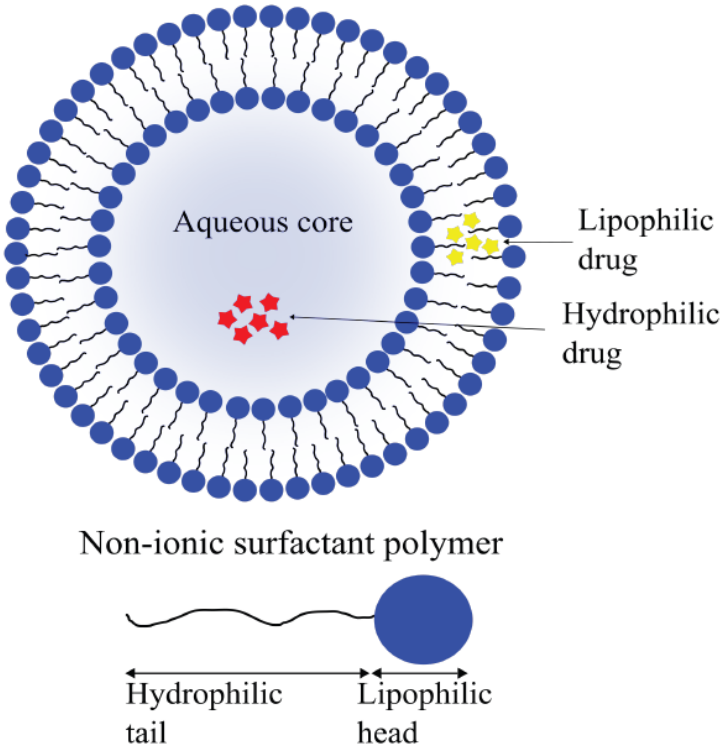

Figure1: Schematic Representation of a Niosome Structure Used as A Drug Delivery System. The figure illustrates a niosomal vesicle composed of a bilayer of non-ionic surfactants enclosing an aqueous core. Hydrophilic drugs are entrapped within the aqueous core, while lipophilic drugs are incorporated within the hydrophobic region of the bilayer. The non-ionic surfactant consists of a hydrophilic head and a lipophilic tail, enabling the formation of a stable vesicular structure suitable for drug encapsulation and controlled release. (Abdelkader et al., 2014).

1.2. Components of Niosome

1.2.1. Non-Ionic Surfactants

Relating to the significant advantage they have in terms of sustainability, harmony and hazardous; the nonionic surfactant agents are widely used in formulating vesicles. They usually are less poisonous, less hemolytic and they are not as disruptive to cell membrane surface, also they preserve pH close to the physiological range, in comparison to anionic, amphoteric or cationic alternatives. Furthermore, nonionic surfactants serve as solubility enhancers, wetting agents, and permeability modifiers (Kumar and Rajeshwarrao, 2011). These surfactants are crucial ingredient in NS formulas. Basically, they own a set of hydrophilic head and lipophilic tail (amphipathic substance) (Nasir et al., 2012). The polar head group of surfactants is used to identified them. Since the head of this surfactant is devoid of charge, it creates structure in solution, where hydrophilic heads face aqueous media, and lipophilic tails face organic media. Due to surfactant's property, NS are generated by self-assembly of nonionic surfactant in aqueous mixture (Moghassemi and Hadjizadeh, 2014). Below, there are the explanation of nonionic surfactant groups as well as their applications in the NS:

1.2.1.1. Alkyl Ethers and Alkyl Glyceryl Ethers

These would be polyoxyethylene alkyl ethers, which are good vesicle producing nonionic surfactant because they consist of hydrophilic and hydrophobic parts that are connected with ether (Sankhyan and Pawar, 2012). Polyoxyethylene alkyl ethers are stable surfactant, they don't cause much irritation to the skin and blend well with

other surfactants. They could be used to surround proteins also peptides because of its high stability, but when coupled with cholesterol their encapsulation ability is decreased. Firstly, polyoxyethelene 4 lauryl ether (Brij® 30) which is the major property of this surfactant is related to HLB value which is about 9.7. In addition, its transition temperature is under 10°C. Briji® 30 is incompatible with benzocaine and oxidizable drugs since oxidation that occurs with these compounds result to product discolorations. Moreover, polyoxyethylene cetyl ethers (Brij® 58) which is polyoxyethylene cetyl derivative having ability to form vesicle and has HLB value of 15.7. It has a capability to form reversed vesicles which are helpful in understanding ion-pumping activity (at the plasma membrane, which is of **unique importance associated with this surfactant. Finally, Polyoxyethylene stearyl ethers (Brij® 72 and 76); they are** polyoxyethylene ether stearyl derivatives which have high vesicle forming potentials. Brij® 72 particularly creates multilamellar vesicles that have great encapsulating ability due to its lower HLB value (4.9) in contrast to Brij® 76 which has HLB value of 12.4.

1.2.1.2. Sorbitan Fatty Acid Esters

Usually known as spans, these are polyoxyethylene esters derivatives with different acyl chain lengths. they have gel transition temperature values proportional to the number of carbon atoms in the side chain. Therefore, span 20 (sorbitan monolaurate) which has nine carbon chain is liquid at standard temperature around 20–22 °C, while the gel transition temperature of span 40 (sorbitan monopalmitate) which have thirteen-carbon chain is 46–47 °C and for span 60 (sorbitan monostearate) that has fifteen-carbon chain is 56–58°C. these high molecular weight spans produce vesicles that are less leaky, more resistance to osmotic gradients and have the highest entrapment efficiency like NS made from span 60 (Kumar and Rajeshwarrao, 2011). Other characteristic of span 60 is the ability to prevent the loaded drug from being degraded by proteolytic enzymes (Bhardwaj et al., 2020).

1.2.1.3. Polysorbate

Polysorbate is a non-ionic surfactant that are widely used in NS preparation where it's a liquid made from ethoxylated sorbitan (a sorbitol derivative) esterified with fatty acids. Because of polyethylene glycol (PEG) chains found within it, NS that contains polysorbate have good potentials for gene delivery in formulation also transfection efficiency (Ge et al., 2019).

1.3. Cholesterol

In the NS structures, cholesterol is an amphiphilic compound that can cooperate with surfactant to construct hydrogen bonding among hydroxyl groups of cholesterol with hydrophilic head of the surfactant as explain in the interaction between span 60 surfactant and cholesterol, where hydrogen bond can formed between hydroxyl groups of cholesterol and hydrophilic head of surfactant(Gharbavi et al., 2018). The amount of cholesterol in NS affect their structures as well as physical characteristic like entrapment efficiency, long term stability, payload release and bio stability. Furthermore, cholesterol increases vesicle rigidity, allows NS to be more stable against destabilizing risks caused by plasma and serum components. Cholesterol reduces vesicles permeability for entrapped molecules thus prevent leakage (Ag Seleci, 2017). The entrapment efficiency of drug has an important part in the process of NS formulation and it can be adjusted by changing amount of cholesterol in NS. Upon increasing cholesterol, Agarwal et al. showed that cholesterol enhances the stability of NS loaded with enoxacin resulting in greater entrapment efficiency(Noothi, 2018). On the other hand, cholesterol has been referred as "mortar" of bilayer due to its molecular shape and solubility

characteristics where it occupies the empty spaces between amphiphiles, thus stabilizing them into firm bilayer structure. It's also said to improve membrane stability, reduces the membrane fluidity and change membrane permeability (Abdelkader et al., 2014).

1.4. Charge Inducer Molecule

Charged molecules, enhance the stability of vesicles by adding charged groups to the bilayers structures and usually prevent vesicles aggregation by increasing the density of surface charges. The negatively charged dicetyl phosphate and phosphatidic acid are commonly used in NS preparation while positively charged molecule like stearyl amine and stearyl pyridinium chloride are also used in NS formulation. For a regular NS preparation, the charged molecules is added in a percent of (2.5-5 mol %) ;however, increasing the amount of them can prevent the NS construction (Ag Seleci, 2017). When the cationic lipid [di (tetradecyloxy) propan-1-amine] mixed with non-ionic surfactant to produce cationic NS, the positively charged cationic NS react electrostatically with the DNA's negatively charged (phosphate group) to improve the transfection efficiency as well increase encapsulation efficiency of the drug. the cationic NS can also increase skin penetration particularly in niosomal complex formation.(Ge et al., 2019) (Abdelkader et al., 2014).

1.5. Hydration Medium

Phosphate buffer at different pH is widely used as a hydration medium for NS preparation. The solubility of the substance that is being encapsulated determine the pH of the hydration medium that is why at pH 5.5 phosphate buffer was used for production of ketoconazole NS, while meloxicam NS was prepared by phosphate buffer at pH 7.4 (Kumar and Rajeshwarrao, 2011).

1.6. Niosomes' Sizes

1. **SUV (Small Unilamiellar Vesicles)**

Sonication, .extrusion under higher pressure, and higher shear homogenizaition are some of the methods used to make them from multilamellar vesicles. The size of an SUV is between 0.025 and 0.05 μm. These vesicles have some disadvantages such as reduced thermodynamic stability in comparison with other forms of NS which have a lower drug loading potentials for water soluble (hydrophilic) drugs and greater tendency to accumulate (Chen et al., 2019).

2. **MLV (Multi lamellar Vesicles)**

Many bilayers come together to form these vesicles. that covers the water-filled compartment.separately. MLV are commonly used NS due to its characteristics such as easy to fabricate and remain mechanically stable when stored for long period of time. The diameter of these vesicles is between 0.5 and 10 μm. Also, it is the best drug carrier for lipophilic molecules (Shirsand and Keshavshetti, 2019).

1.7. Types of Specialized Noisomes

1.7.1. Proniosomes

They are niosomal formulations that contain a surfactant and a carrier; they must be hydrated before use. Aqueous NS dispersion is formed as a result of the hydration. Aggregation, leakage, and fusion problems associated with NS formulation are reduced by using proniosomes (Jadon et al., 2009). The use of proniosomes has been confirmed to improve the oral bioavailability of orlistat (poorly water-soluble drug). In addition, it was found that they have greater percutaneous absorption than other semisolid preparations. Spray coating, coacervation phase separation, and the

slurry methods can all be used to make proniosomes (Bhardwaj et al., 2020). Dry granular proniosomes and liquid crystalline proniosomes are the two types available, depending on how they are produced (Chen et al., 2019).

1.7.2. Bola- Noisomes

Bola NS formed by bola surfactants (alpha omega-hexadecylbis-(1-aza-18-crown-6). This type of surfactant was found in the membranes of archaebacteria in the early 1980s. It has two hydrophilic heads and one or two lipophilic linkers that connect them. According to studies, bola surfactants have a superior assembling capacity, as evidenced by their significantly higher surface tension and lower critical micelle concentration (CMC), over traditional surfactants (Chen et al., 2019). Bola-niosomes, which are made of Bola surfactant-Span 80-cholesterol [2:3:1 molar ratio], showed acceptable tolerability for both in vitro and in vivo (Khoee and Yaghoobian, 2017).

1.7.3. Aspasomes

Ascorbyl palmitate, cholesterol, and the highly charged lipid diacetyl phosphate are all used to make aspasomes (AP). These ingredients help to organize vesicles and keep the preparation stable. (Pande et al.). The final product is hydrated with water solvent and sonicated (Gharbavi et al., 2018). Researchers have looked into using them to deliver drugs through the skin, and they found that AP can help drugs get through the skin barrier. Gopinath and his team made aspasomes that were loaded with azidothymidine (AZT) for use on the skin. AZT loaded in AP had a much higher transdermal penetration than AZT solution or ascorbyl palmitate aqueous dispersion. Although no research has been conducted to elucidate the mechanism of permeation enhancement through AP, it is hypothesized that due to its lipophilicity, aspasome integrates into skin lipids and modifies the intercellular matrix owing to its distinctive amphiphilic properties. Aspasome has a bright future as a transdermal drug delivery system because it has antioxidant properties and can help drugs get through the skin. (Chen et al., 2019).

1.8. Discomes

Discomes are large disk-shaped structures (Gharbavi et al., 2018). Made when vesicles of nonionic surfactants were made from a hexaadecyl diglycerol ether, cholesterol, and dicetyll phosphate [69:29:2 molar ratio] by handshaking and then using sound waves, then incubated at 74°C with different amounts of solulan 24 to help it dissolve, Four distinct phases emerged: a lamellar phase, a micellar phase, an uncharacterized coexistence phase, and a novel phase designated as the discome phase.(Azeem et al., 2009) Discomes ranging in size from 11 to 60 μm.(Bhardwaj et al., 2020) they are characterized by large size and high drug loading capacity; additionally, discomes may be used as an ocular drug delivery carrier because they released the administered drug in a regulated manner at the site of action (Wadhwa et al., 2009).

1.8.1. Elastic Noisomes

Elastic NS are able to bend and being flexible without losing their original form, and they can get through holes that are smaller than their dimensions (Khoee and Yaghoobian, 2017). Nonionic surfactants, water., and ethanol. are present in these vesicles (Fig.2). The flexible structure of this type of NS increase its penetration to the intact skin layers (Gharbavi et al., 2018). Manosroi and his colleagues developed diclofenac diethylammonium as an elastic NS for transdermal delivery which had a deformability index 14 times that of traditional NS, (Chen et al., 2019).

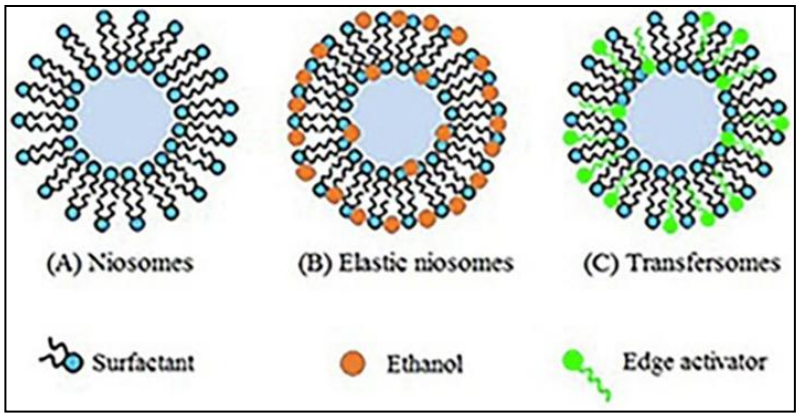

Figure2: Schematic Representation of Different Vesicular Drug Delivery Systems
(A) Conventional niosomes composed of non-ionic surfactants forming a bilayer vesicle; (B) Elastic niosomes containing ethanol, which enhances membrane fluidity and deformability; (C) Transfersomes incorporating edge activators that increase vesicle elasticity and facilitate penetration through biological barriers. Symbols indicate non-ionic surfactants, ethanol molecules, and edge activators. (Chen et al., 2019).

1.8.2. Transfersomes

A lipid bilayer softening component is added to make the lipid bilayer more flexible and permeable. This is called an edge activator, and it usually has a nonionic single-chain surfactant in it that makes the lipid bilayer less stable, which makes it more fluid and elastic shown in (Fig.2). As a result, they have both hydrophobic and hydrophilic parts, transfersomes can hold drug molecules that are soluble in a wide range of substances. (Chen et al., 2019)15).

1.9. Polyhedral Niosomes

The shape of non-ionic surfactant vesicles that formed by hexadecyl diglycerol ether and a sequence of polyoxyethylene alkyl ethers varies depending on the membrane constituent and composition. These surfactants when mixed with an equimolar amount of cholesterol lead to produce a mixture of mostly spherical and tubular NS. Polyhedral NS develop facets polyhedral complexes in the absence of cholesterol. Despite this, polyhedral NS that are loaded with luteinizing hormone releasing hormone show a slow the release pattern in comparison to the solution, but to a minor degree (Arunothayanun et al., 1999, Goyal et al., 2015).

1.10. Advantages of Niosomes

NS can be used for encapsulation of both hydrophilic drugs [loading in the inner space] and hydrophobic drugs [in the lipid area], also amphiphilic drugs, which is why they're used in drug targeting, controlled release, and drug permeation enhancement (Sharma et al., 2019). The surfactants are biodegradable, biocompatible, and non-immunogenic, they can be safely used in niosome preparation. NS can improve drug-taking behavior in one of these ways either by delaying the clearance of the drug, protection of the drug from biological environment or restriction of the drug to the target site(Kaur and Kumar, 2018). NS are osmotically active and stable, as well as improving the stability of the entrapped drug. Penultimately, they possess flexibility in structural properties which including composition, size, lamellarity, fluidity, trapped volume surface charge; hence, they can be developed according to the desired need (Azeem et al., 2009). Finally, the vesicles will function as a depot, lead to slowly releasing the loaded drug and allowing for a controlled release (Arunachalam et al., 2012).

1.10.1. Disadvantages

As a result of the effect of dispersion media, the entrapped drug can sediment, accumulate, fuse or leak throughout storage. Additionally, there is a risk of inadequate hydration of surfactants mostly during hydration process (Pande et al.). Multilamellar vesicle preparation methods like an extrusion or sonication are time-consuming and can necessitate the use of specialized equipment (Muzzalupo and Tavano, 2015) as well as they are physical instability (Arunachalam et al., 2012).

1.11. Methods of Preparation

1.11.1. Ether Injection Method (EIM)

Surfactants in this process are dissolved with additives in an organic solution like a diethyl ether and slowly injected via a needle into an aqueous solution [containing drug] held at a constant temperature (about 60°C). A rotary evaporator was used to evaporate the organic solvent. Surfactants are led to the development of single-layered vesicles upon ether vaporization. The final vesicle's diameter varies from 50 to 1000 nm, based on the conditions. EIM has been used for explain the preparation of NS as presented in Fig.3 (Moghassemi and Hadjizadeh, 2014). Hydration time and temperature determine the consistency of the shape. When the hydration time is longer, the structure and dimensions of the NS become more stable and uniform. The optimal hydration time is 45 minutes. (Khoee and Yaghoobian, 2017, Mahale et al., 2012). The drawback of this method is that a small amount of ether is often left in the vesicle suspension, making removal difficult. Furthermore, Proteins and other easily denatured substances may be damaged if the niosomal formulations active ingredient is exposed to ether or an organic solvent (Azeem et al., 2009).

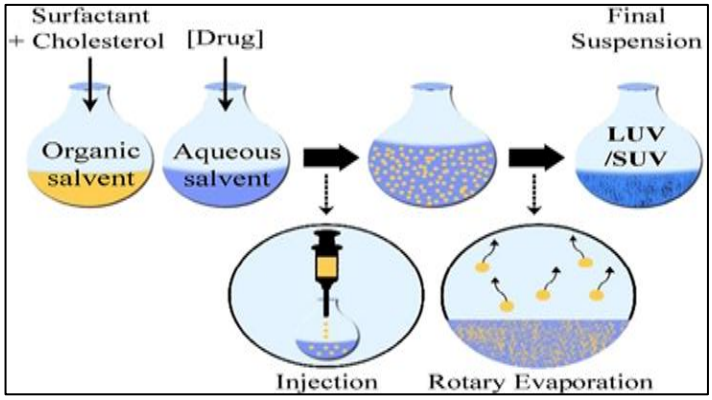

Figure3: EIM method of preparation of NS (Moghassemi and Hadjizadeh, 2014)

1.12. Hand Shaking Method (Method for Hydrating Thin Films)

Use an organic solvent, like chloroform or diethyl ether, to dissolve the surfactant and cholesterol mixtures in a flask with a circular bottom. the organic solvent is then eliminated at room temperature using a rotary vacuum evaporator (Gökçe et al., 2016). On the inner surface of the round bottom flask, a thin film forms as the liquid evaporates (Bhardwaj et al., 2020). By gentle shaking or sonication at 50-60 C, the dry film is hydrated with water or PBS (Phosphate-buffered saline) containing the drug of interest (Gökçe et al., 2016). The surfactant swells and peels away from the support, forming a film. Swollen amphiphiles fold into vesicles, which contribute to the formation of NS

(Fig.4). This method produces MLV niosomes which are between 300 and 500 nm in size (Khoee and Yaghoobian, 2017). This method is commonly used to make NS that comprise drugs like insulin, doxorubicin and other extracts (Ge et al., 2019).

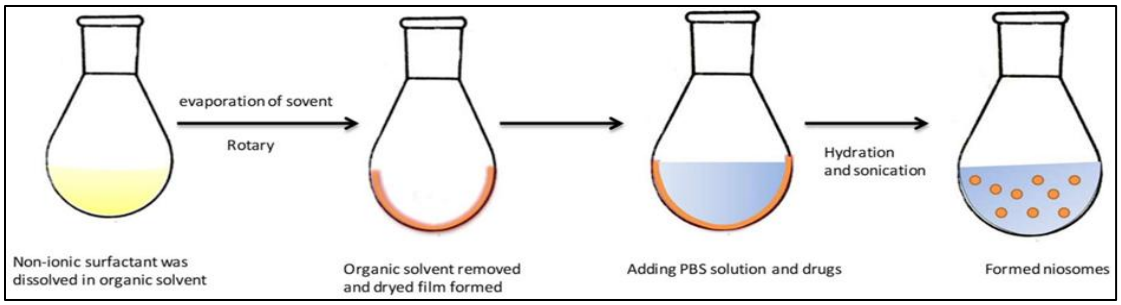

Figure4: Hand Shaking Method (Method For Hydrating Thin Films).(Ge et al., 2019)

1.13. Reverse-Phase Evaporation Method (REV)

The ability to control the size of NS is a benefit of this process, although the drug's solubility in ether and the difficulty of completely removing ether from the final formulation are disadvantages. With this process, the solvent is removed from the emulsion, which is the most crucial step. (Khoee and Yaghoobian, 2017). A 1:1 mix of ether and chloroform is used to dissolve cholesterol and surfactant in order to make an emulsion. The mixture is then added to an aqueous phase that contains the drug. The final mixture is sonicated at 4-5°C and comprises two phases. A small amount of phosphate buffered saline (PBS) is applied here to form the transparent gel, which is then sonicated further. After ultrasound, the organic phase is removed at 40 °C and low pressure. The thick, smelly suspension is mixed with PBS and heated for 10 minutes in a water bath at 60 °C to make NS. (Fig.5) (Sharma et al., 2019). REV has been used to prepare NS as carriers for diclofenac sodium delivery (Homaei, 2016).

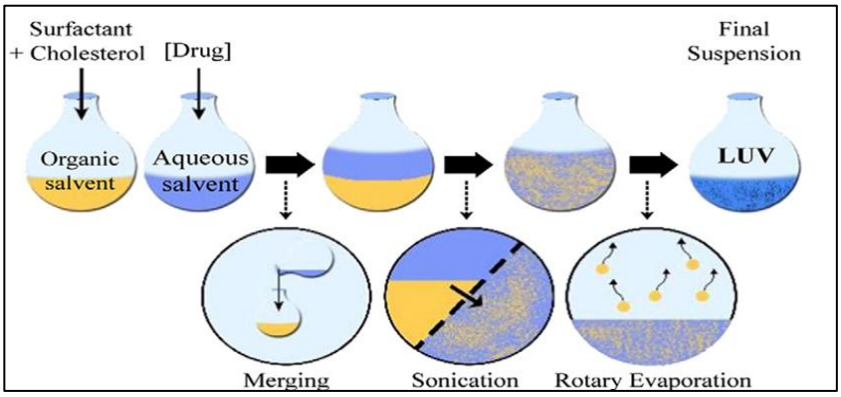

Figure5: Reverse-Phase Evaporation Method (REV) (Moghassemi and Hadjizadeh, 2014)

1.14. Heating Method (Hm)

It is based on the patented procedure of and is non-toxic, modular and one-step(Durak et al., 2020). When there is a polyol, like glycerol,, mixtures of non-ionic surfactant, cholesterol and/or charge producing molecules are applied to an aqueous medium (e.g. buffer, distilled H2O, etc.) (Reddy et al., 2012). After hydration, the cholesterol solution is left to boil for an hour at 120 degree Celsius to dissolve it. The temperature of the solution is then lowered, and surfactant and other additives are then added to the buffer solution while stirring constantly as illustrated in Fig.6 (Bhardwaj et al., 2020). NS are formed at this stage, then left to cool at room temperature until being stored at 4-5°C in a nitrogen atmosphere until needed (Ag Seleci et al., 2016). The benefits of this technique include low toxicity issues due to the lack of detergent, organic solvent or any other harmful components as well as a scalable technique for producing stable and safe niosomes (Kamble et al.). A modified heating method was used to develop α-Tocopherol-loaded noisome (Basiri et al., 2017).

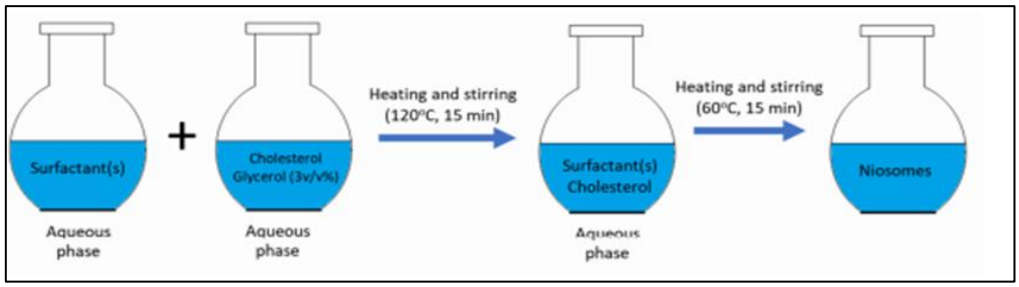

Figure6: Schematic illustration of the preparation of niosomes by the aqueous heating method. The figure shows the preparation process in which non-ionic surfactants and cholesterol are dissolved in an aqueous phase containing glycerol, followed by heating and stirring at 120 °C for 15 min. The mixture is then further heated and stirred at 60 °C for 15 min, resulting in the formation of niosomal vesicles. (Durak et al., 2020).

1.15. Sonication Method

The size of NS prepared by reverse phase evaporation and hand-shaking is typically in the micron range. The size of NS produced by hand shaking can be lowered to 100-140 nm using the sonication technique (Durak et al., 2020). By using sonication to deliver high energy, the average size of vesicles can be decreased. This is capable by ultrasonic irradiation of multilamellar vesicles. Therefore, it is thought that the most common method for generating small vesicles is sonication. There are two types of sonication: probe and bath ultrasonic sonicator. The probe used for dispersions that need a lot of energy in a small volume, while the bath is appropriate for large volumes (Nasir et al., 2012).

1.16. The “Bubble” method

Surfactants, additives and the buffer are placed in a glass flask with three necks in this process. The components of NS are distributed at 70°C and combined with a homogenizer (Figure 7). After that, the flask is immediately put in a water bath and nitrogen gas is bubbled at 70°C. Large unilamellar vesicles are formed when nitrogen gas is passed through a sample of homogenized surfactants (Ag Seleci et al., 2016).

1.17. Transmembrane pH value gradient drug uptake process

An organic solvent is used to dissolve surfactants and cholesterol in this process., as observed in figure 8. Then, this solution is evaporated at a low pressure to make a thin film on the wall of the round bottom flask. To hydrate this film, a citric acid solution with a pH of 4 and vortex mixing is used. The resulting vesicles are then frozen and thawed three times before being sonicated. Then, an aqueous drug solution is applied and vortexed. To produce multilamellar vesicles, This solution is heated to sixty degrees Celsius with a pH of seven. (Arunachalam et al., 2012).

1.18. Dehydration-rehydration method

vesicles were made using a thin-film hydration method, then frozen in liquid nitrogen and freeze-dried overnight. Phosphate buffer saline (pH 7.4) was used to hydrate powder NS at 60°C. (Bhardwaj et al., 2020) Vesicles dehydrate during the drying process and small vesicles fuse to form a multilamellar film with encapsulating material sandwiched between successive layers of film. When the film is rehydrated using a pH 7.4 phosphate buffer at sixty degrees Celsius. large vesicles form; encapsulating a significant proportion of the encapsulating content. The lipid-to-encapsulating-material ratio should be between 1:2 and 1:3 (Kamble et al.).

1.19. Freeze and thaw method

In this process, NS are frozen and thawed using a thin-film hydration technique. They used of niosomal suspension and put it through five cycles of freezing in liquid nitrogen for 1 min and then thawing in a water bath at 60 °C for another 1 min. (Bhardwaj et al., 2020) To prepare multilamellar NS, a freeze and thaw technique was used. (Kamble et al.) The NS prepared with unsaturated surfactants shrank after being frozen and thawed. The entrapment efficiency of NS was also decreased by the freeze-thaw cycle (Bhardwaj et al., 2020).

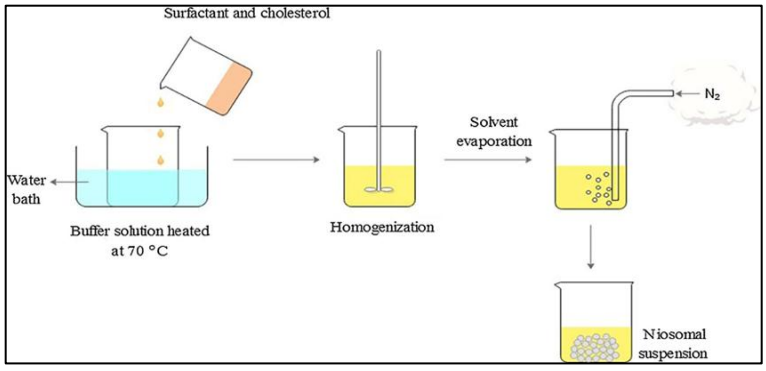

Figure (7): Bubble method (Chen et al., 2019)

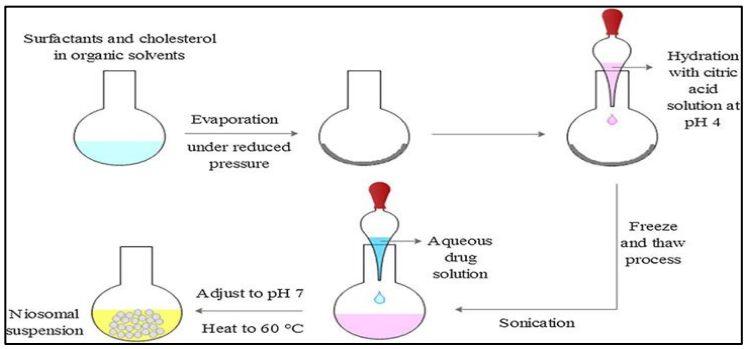

Figure (8): Trans-membrane pH gradient drug uptake method (Chen et al., 2019)

Some other methods are also used for the preparation of NS, such as supercritical carbon dioxide fluid method (solvents employed are nonflammable, nontoxic, and volatile.). The size of NS made this way is between 100 and 440 nm. (Bhardwaj et al., 2020). Additionally, the Handjani: Vila method (Mahale et al., 2012),The single pass technique (Kumar and Rajeshwarrao, 2011), The enzymatic method (Khoee and Yaghoobian, 2017), Multiple membrane extrusion method (Sharma et al., 2019) and Microfluidic hydrodynamic focusing (Bhardwaj et al., 2020).

2. Route of administration

2.1. Topical and transdermal delivery

In the case of skin diseases, the dermal route is often used to deliver drugs locally. It is only used for local actions. Drug-loaded niosomal formulations enable a large amount of drug to accumulate in the skin, improving local drug delivery for a longer period of time (Bhardwaj et al., 2020). The active ingredients in transdermal drug delivery are delivered via the skin for systemic circulation, which has many advantages over other routes of administration. It has a high bioavailability because first-pass hepatic metabolism is prevented. It is non-invasive because no needed for needle and it escapes degradation by acid and enzymes in the gastrointestinal tract (Chen et al., 2019). The main disadvantage of transdermal delivery is the limited penetration of drugs into the skin due to the stratum corneum (SC). The transdermal delivery of drug incorporated in NS resulted in a higher penetration rate (Arunachalam et al., 2012). There is no specific or definitive explanation for how NS increase drug transmission through the skin but there are several theories or mechanisms that have been suggested like intracellular diffusion through the stratum corneum layer (Jothy and Shanmuganathan, 2015); or modifying the structure of the SC by disruption of the closely packed lipids that occupy the extracellular spaces of the SC and increasing the hydration of SC leading to loosening of its tightly packed cellular structure and improving permeability of drugs (Rahimpour and Hamishehkar, 2012). Brief explanation for the mechanism of action of noisome as a dermal and transdermal application through the skin was shown in figure (9).

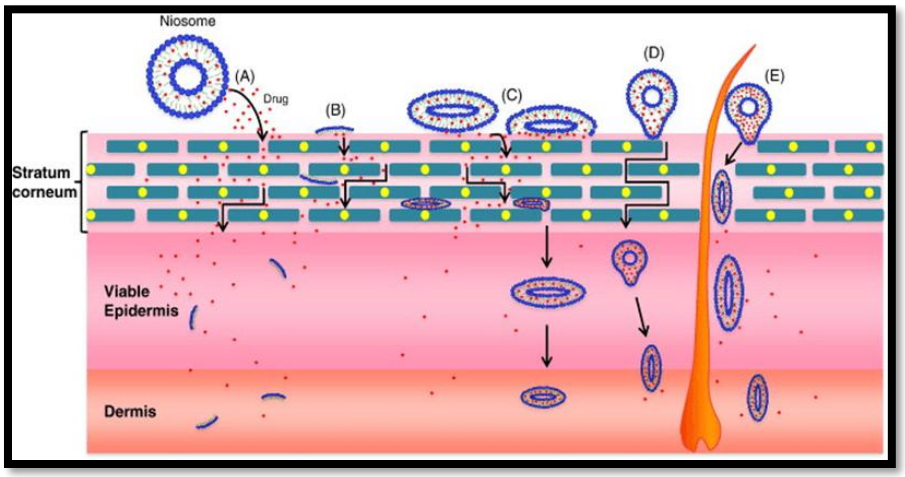

Figure (9): Mechanisms of action of noisome in dermal and transdermal application: (A) releasing of drug molecules by Niosomes, (B) acting of niosomal constituents as a penetration enhancers, (C) adsorption or fusion of through or with stratum cornium, (D) penetration of whole noisome across the intact skin, (E) penetration of noisome through pilosebaceous units or hair follicles (Chen et al., 2019)

Furthermore, topical application of NS is often restricted by the liquid nature of the preparation; when applied, they may leak from the site of application; this may be solved by adding gelling agents to the NS dispersion, resulting in the formation of a niosomal gel. It may provide a drug reservoir in the SC for sustained release, resulting in high accumulation of drug in the dermis and epidermis. Due to the occlusion effects of gel formation, which can improve skin hydration and thereby increase drug absorption and penetration across the skin, the gel can also facilitate drug penetration throughout the SC. When applied to the surface of the skin, this function allows them to squeeze through the intercellular regions of the SC under the control of a transdermal water gradient (Chen et al., 2019). For topical use, Manosroi and co-workers developed novel elastic NS entrapped with the non-steroidal anti-inflammatory medication diclofenac diethylammonium. tween 61 or span 60 was combined with various molar ratios of cholesterol and ethanol at 0%–25% (v/v) to create a variety of formulations. Because of their higher stability, elastic tween 61 niosomes were chosen.

2.2. Oral delivery

Oral administration is commonly considered as the most accessible and suitable method of drug administration particularly, when there is needed for repeated administration. When preparing oral drugs, many factors must be considered, including the acidic condition of the stomach, enzymatic degradation in the gastrointestinal tract, first-pass metabolism, slow absorption and variable drug bioavailability. NS have been studied to see whether they can help with these issues by increasing absorption and bioavailability (Chen et al., 2019). The bioavailability of methotrexate was greatly improved by this noisome formulation (Khoee and Yaghoobian, 2017). Metformin is an oral hypoglycemic drug that is often used as a first-line therapy for the treatment of type 2 diabetes, when administered at high dose of 2–3 times per day; it has a variety of side effects, including

lactic acidosis, gastric irritation, difficulty breathing and allergies. NS formulations of metformin are made by mixing span 60, span 40 and cholesterol in an equimolar proportion were suggested to decrease side effects and dose frequency. This formulation achieves excellent entrapment efficiency and sustained drug release over a prolonged period of time, consequently improving the drug's performance (Marianecci et al., 2014).

2.3. Pulmonary delivery

Researchers are studying drug delivery through respiratory system since; it allows the drug to directly target the lung, for both local and systemic effect. It's fascinating how the pulmonary delivery has characteristics such as great permeability and wide surface area of alveolar region. Along with these advantages; there are some drawbacks like low respiratory system efficiency, little drug mass per breath and less drug formulation stability. As a solution NS may be used to reduce these issues and allow efficient delivery of the drug to the respiratory tract (Khoee and Yaghoobian, 2017). Administration of NS drugs via pulmonary route has great benefits such as enhanced mucus penetration, continuous drug delivery and targeting, along with improved therapeutic effect (Bhardwaj et al., 2020). Patients with asthma the treatment is based on inhalation but it's limited by lack of drug infusion through hydrophilic mucus. Terzano et al. described the use of beclomethasone dipropionate as polysorbate 20 based noisome in the treatment of chronic obstructive pulmonary disease. (Gharbavi et al., 2018)

2.4. Ocular delivery

High bioavailability is hard to maintain in the traditional ocular dosages (ophthalmic solution, suspension, and ointment) due to many restrictions like impervious corneal epithelium and precorneal tear film that restrain proper drug absorption(therefore, the bioavailability of drugs administrated through ocular route is usually less than 5% (Khoee and Yaghoobian, 2017)). Vesicles have been selected as the preferred delivery system of ocular drugs not only because these vesicles provide sustained and regulated action at corneal surface but, also aid in controlled release of ocular drugs by inhibiting the breakdown of the drug by enzymes found in tear/corneal epithelial surface. In addition to that, vesicles provide a way to meet the requirements of proper ophthalmic drop delivery system, where it maintain and localize therapeutic effect at its site of action (Biswas and Majee, 2017). Ocular delivery of NS drug is favored due to its the size which is large enough to prevent drainage through tearing reflex and eye blinking; likewise the structure of NS which stays on eye surface (Khoee and Yaghoobian, 2017). A controlled release of NS and discomes for naltrexone delivery through ocular route was prepared by Abdelkader et al., where they noticed that the permeation of naltrexone across the cornea is enhanced with the use of anionic niosome compared to neutral noisome.

2.5. Nasal route

Because of the lack of pancreatic and gastric enzymatic activity, the neutral pH of nasal mucus and less dilution by gastrointestinal contents, nasal mucosa has been regarded as a possible administration route to achieve faster and higher levels of drug absorption. Quick onset of action, avoidance of first pass metabolism while enhancing bioavailability over oral and rectal doses, delivery to the systemic circulation via nasal drug delivery for drugs that cannot be absorbed orally and exhibit of low oral absorption for polar compounds may be especially suited for this route of delivery are all advantages of nasal drug delivery (Khoee and Yaghoobian, 2017). Nasal administration has several disadvantages such as a limited residence period in the nasal cavity due to mucociliary clearance, airflow obstruction and nasal mucosa sensitivity; both of which affect drug permeation and systemic bioavailability. Niosomal diltiazem delivered by nasal has greater bioavailability and less elimination than normal diltiazem (14).

2.6. Parenteral Route

Parenteral administration is a general method for administering pharmaceutical ingredients with low bioavailability and a limited therapeutic index. In emergency clinical cases, the parenteral route has many benefits including ease of access, rapid onset of action and suitability for conditions where the oral route is inconvenient such as trouble swallowing, delayed gastric emptying and intestinal motility, vomiting, and unconsciousness (44)(46). The advantage of injecting the drug is that it enters the systemic circulation immediately; conversely, the NS improves the drug's stability and prolongs its time in the blood. With certain changes, the medication may also be administered to a specific location. Many drug's NS are delivered by the intravenous route. NS of morin hydrate are prepared for intravascular administration. Paeonol NS were PEGylated to increase its stability and bioavailability. (14)(47)

3. Conclusions

NS is a promising drug delivery carrier due to various characteristics like cost, stability, release profile, targeting, encapsulating both hydrophilic and lipophilic drugs simultaneously. They can be used to encapsulate drugs of natural origin, enzymes, peptides, genes, anti-cancer and almost all varieties of drugs. Furthermore, they offer flexibility in the route of administration. No special conditions are required for handling and storage of them, compared with other drug-delivery systems such as liposomes. However, the technology utilized in NS preparation is still in its infancy. Hence, researches are going on to develop a suitable technique for large scale production because it is a promising targeted drug delivery system.

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