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NIOSOMES IN TRANSDERMAL AND TOPICAL DRUG DELIVERY: A REVIEW

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INTRODUCTION

Topical drug administration is a localized drug delivery method that can be applied topically through the skin, rectal, vaginal, and ocular systems. The skin serves as the primary channel of topical medication delivery and is one of the human body's most accessible organs for topical administration.[1] When applied topically, the stratum corneum, the skin's outermost layer, limits the bioavailability of medications by acting as the skin's most durable barrier against drug penetration. Therefore, it is vital to research and contrast the numerous carriers needed for systemic medicine distribution in order to circumvent the natural skin barrier. A less invasive method of administering medications, transdermal drug delivery offers patient compliance, regulated drug distribution, infrequent dosage, and first pass metabolism prevention.[2] TDDS also has various benefits over oral drug delivery, including avoiding first-pass metabolism, shielding sensitive medications from the harsh gastrointestinal environment, allowing for sustained drug release, and maintaining a more uniform plasma concentration.[3]

Transdermal drug delivery systems (TDDS) are topically applied medications in the form of patches that transfer pharmaceuticals over a patient's skin for systemic effects at a predefined and regulated rate. The potential to avoid the hepatic first pass effect and achieve high systemic bioavailability of drugs that undergo significant or extensive first-pass metabolism and are able to sustain the drug release for a prolonged period of time has made transdermal delivery of drugs for the systemic treatment of diseases one of the many novel drug delivery systems that have garnered increasing interest in recent years. Additionally, it allows for self-administration and quick drug effect cessation as necessary, which improves patient acceptance and compliance.[4]

The first niosome formulations were patented in 1975 by researchers from L'Oréal (France) for cosmetic applications.[5] In 1972, Vanlerberghe et al. confirmed the idea of Bangham et al. (1965) by describing non-ionic particles. The first serious discussions and analyses of niosome-like systems emerged during the 1970s with lamellar phases of non-ionic lipids in cosmetic products by Handjani-Vila et al. back in 1979, and they were known as liposomes.[6] niosomes are self-assembled vesicular The particle size ranges from 10nm100nm. nanocarriers obtained by hydration of synthetic surfactants and appropriate amounts of cholesterol or other amphiphilic molecules. The transdermal route of drug administration ensures systemic delivery of drug by applying a drug formulation onto intact and healthy skin thus ensuring sustained drug release and bypass of first-pass metabolism.[7]

niosomes are one of the promising drug carriers that have a bilayer structure and are formed by self-association of nonionic surfactants and cholesterol in an aqueous phase. niosomes are biodegradable, biocompatible, and non immunogenic. They have long shelf life, show excellent stability, and enable the distribution of medicine to target site in a regulated and/or sustained way.[8] Niosome-medicated vesicles will increase the medication's bioavailability, therapeutic efficacy, drug penetration through the skin, release the drug in a controlled and sustained way, and be utilized to target the intended spot by modifying the composition to lessen adverse effects. [9]

TYPES OF NIOSOMES

Based on size of niosomes it is classify into 3 types

1. Small Unilamellar Vesicles SUV (0.05-0.5µm)
2. Multi Lamellar Vesicles MLV (0.05µm)
3. Large Unilamellar Vesicles LUV (0.10µm).[8]

NIOSOMES COMPOSITION

A typical noisome vesicle would consist of a vesicle forming amphiphilic i.e. a non-ionic surfactant such as Span-60, which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle

The two major components used for the preparation of niosomes are,

1. Cholesterol
2. Nonionic surfactants

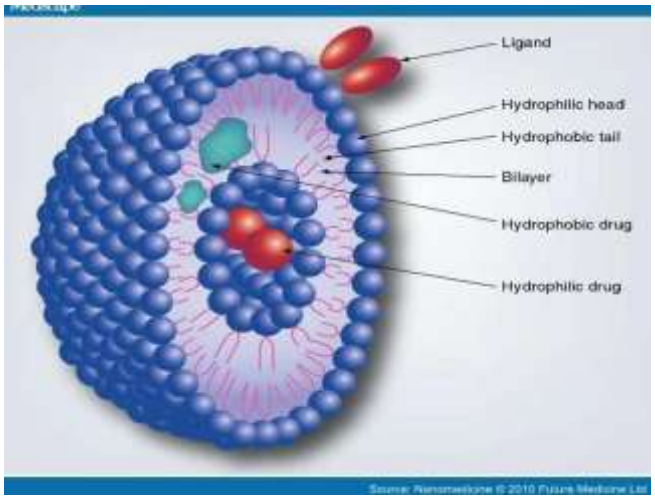

FIGURE 1. STRUCTURE OF NIOSOME

HOW DOES NIOSOMES WOKS

Surfactant works by arranging its hydrophilic heads toward water and hydrophobic tails away from water, causing the surfactant molecules to self-assemble into a stable bilayer vesicle that traps drugs inside or within its membrane. Cholesterol works by inserting itself between the surfactant molecules in the niosomal bilayer, increasing membrane rigidity and stability, reducing leakage of the encapsulated drug, and helping control the drug's release. Charge inducer agents in niosomes These agents prevent the aggregation of the particles by inducing the surface charges of the prepared particles **negative charge**,(like phosphatide acid) which causes **electrostatic repulsion** between vesicles and prevents them from sticking together. Positive charge inducers (like **stearyl amine)** often enhancing cell binding, skin permeability, and uptake.

METHODS OF PREPARATION OF NIOSOMES

1.Thin Film Hydration Method A traditional method for creating niosomes is thin-film hydration, sometimes known as the hand-shaking method. A thin lipid film is created by dissolving surfactants and lipids in an organic solvent, which is subsequently evaporated under low pressure using a rotary evaporator. The lipids swell and separate from the flask wall when this film is hydrated with an aqueous phase at a temperature higher than the surfactant's phase-transition point. Solubility determines how medications are incorporated: hydrophilic pharmaceuticals are added to the hydration medium, whereas hydrophobic drugs are added to the lipid–surfactant mixture. While non-shaking conditions favour large unilamellar vesicles (LUVs), hydration with shaking produces multilamellar vesicles (MLVs).

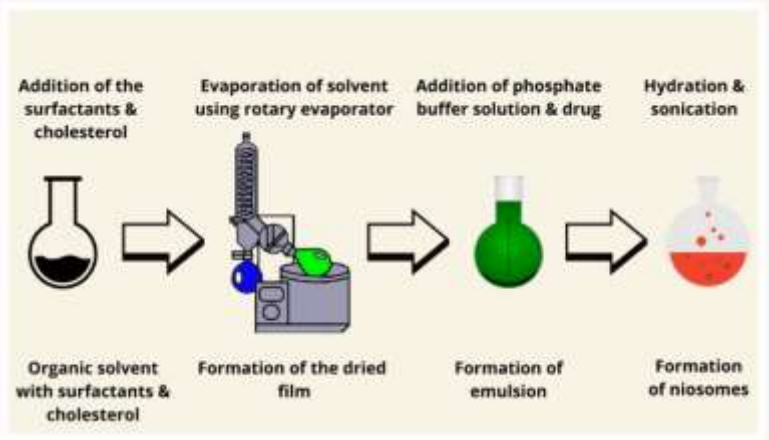

Figure 2. Schematic diagram for the thin film hydration method for the preparation of niosomes.

2. Reverse Phase Evaporation
Reverse-phase evaporation is used to prepare niosomes. Surfactants and cholesterol are combined in different molar ratios in a round-bottomed flask and dissolved in enough organic solvent to create the organic phase. The water-soluble components are dissolved to create the aqueous phase, which is then combined with the organic phase to create the emulsion in a second round-bottomed flask. The niosomes are then created by employing a rotary evaporator to evaporate the organic solvent at 60 °C under low pressure after it has been violently agitated or sonicated.

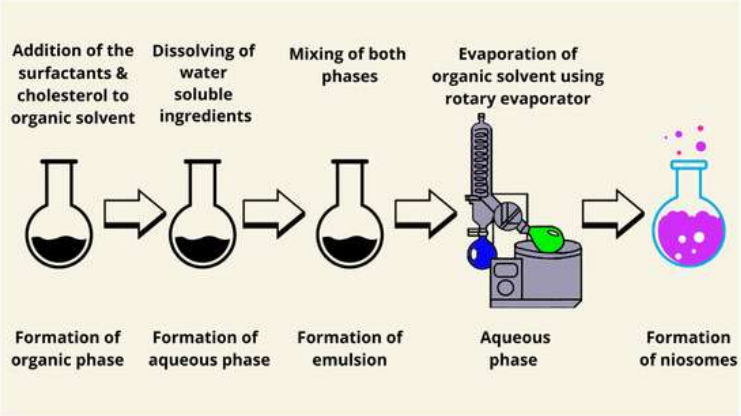

Figure 3. Schematic diagram of reverse phase evaporation for the preparation of niosomes

3. Ethanol Injection Method

Ethanol injection is a fast and straightforward procedure for the creation of tiny unilamellar vesicles. The method involves injecting a lipid ethanolic solution into an aqueous phase, where spontaneous vesicle formation occurs. Ethanol can be used with co-solvents like isopropanol to maximize lipid solubility and improve encapsulation effectiveness. This method's versatility is further enhanced by the ability to control vesicle size and prevent aggregation by varying the temperature and injection speed. The technique is low-cost, doesn't require complex equipment, can be scaled up, and is simple to set up. The size of the niosomes generated by this process is smaller compared to the thin film hydration and microfluidics procedures.

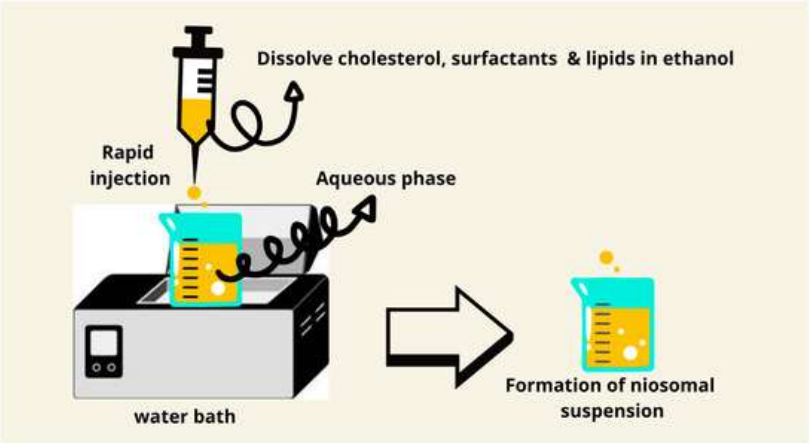

Figure 6. Schematic diagram of the ethanol injection method for the preparation of niosomes.

4. Ether Injection Method

Nonionic surfactants and other chemicals are dissolved in diethyl ether, and the combination is then injected into an aqueous solution at a constant temperature of 60 to 65 °C. The solvent will evaporate due to the temperature differential between the organic and aqueous phases. This approach produces huge unilamellar niosome types. By injecting an ether solution of lipids into a heated aqueous phase, the ether injection technique creates niosomes; the slow evaporation of ether permits the creation of a bilayer. Due to the greater solubility of lipophilic medicines in ether, this approach is extremely useful for.

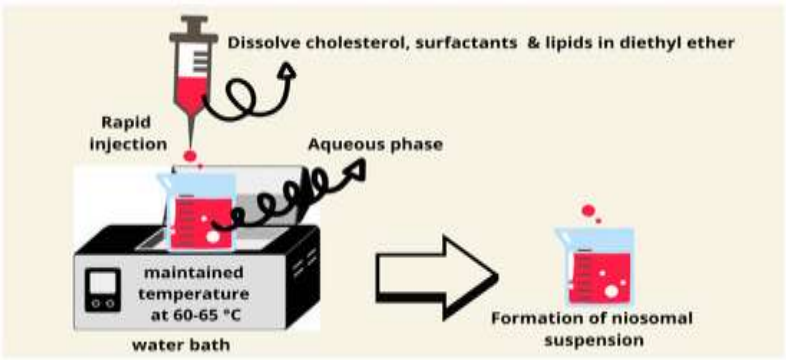

Figure 7. Schematic diagram of the ether injection method for the preparation of niosomes.

5. Sonication Method

One environmentally friendly way to prepare niosomes is by sonication. It is a simple, low-cost process, and does not involve the use of organic solvents. Briefly, the aqueous phase and the drug are mixed with surfactant and cholesterol. The mixture is sonicated for a few minutes at 60 °C using a titanium probe sonicator. Typically, the niosomes are gathered by freeze-drying or filtering using filter sheets. The key advantage of this process is that the niosomes produced are very small in size without requiring any form of organic solvent. According to the aforementioned assertion, this approach is not a good fit for medications that are insoluble in water. This approach could yield tiny multilamellar vesicles.[6]

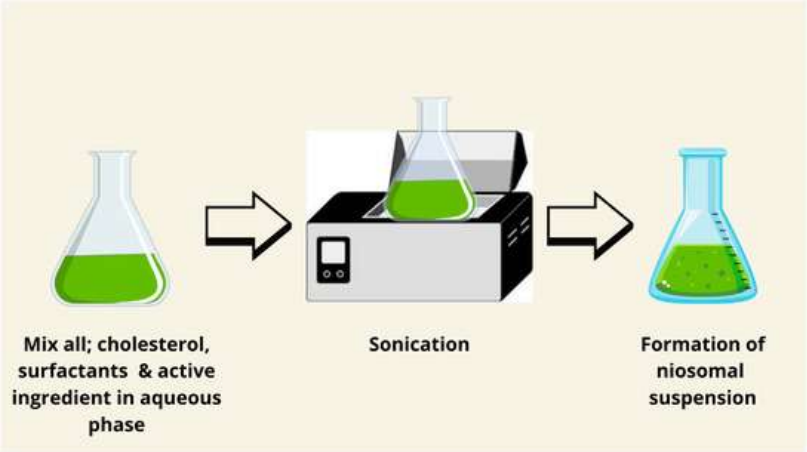

Figure 9. Schematic diagram of the sonication method for the preparation of niosomes using water bath sonication.

ADVANTAGES

L'Oreal was the first company to use niosomes in cosmetics because they provided the following benefits.

1. Compared to oil-based solutions, the water-based vesicle suspension delivers better patient compliance.

2. Niosomes can be employed for a range of medications since their structure provides space for hydrophilic, lipophilic, and amphiphilic chemical moieties.

3. The features like as size, lamellarity etc. of the vesicle can be changed depending on the necessity.

4. The vesicles can operate as a depot to release the medicine slowly and enable a controlled release.

DISADVANTAGES

1. Physical instability

2. Aggregation of niosomes

3. Fusion niosomes

4. Leaking of entrapped drug

5. Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion

APPLICATIONS

Here are some applications of niosomes that have been demonstrated or are being investigated.

1. It is utilized as Drug Targeting. It is used to treat cancer, or antineoplastic disease.

2. It is used to treat leishmaniasis, which includes mucocutaneous and dermal infections like sodium stibogluconate.

3. It is used act as Delivery of Peptide Drugs.

4. It is employed in Studying Immune Response. Niosomes as Haemoglobin Carriers and Transdermal Medication Administration Systems Making Use of Niosomes It is utilized in ophthalmic drug delivery Other Applications: Niosomes can also be exploited for sustained drug release and localized drug activity to dramatically boost the safety and efficacy of many medications. Niosomal encapsulation may be a safe way to administer toxic medications that require greater dosages.[11]

CHARACTERIZATION OF NIOSOMES

Size and Morphology Niosome size and morphology are widely assessed using DLS, SEM, TEM, FF-TEM, and cryo-TEM. Particle-size data and dispersion uniformity are provided by DLS; a homogeneous system is indicated by a single sharp peak and a polydispersity index less than 0.3. Microscopy techniques enable direct observation of vesicle form and structural characteristics. Together, these procedures ensure reliable assessment of noisome size and shape.

2. Zeta Potential

Surface zeta potential of niosomes can be measured using zetasizer and DLS instruments. Niosome behavior is significantly influenced by the surface charge of the noisome. Compared to uncharged vesicles, charged niosomes are often more resilient against aggregation.

3. Bilayer Characterization

Bilayer features of niosomes have an effect on drug entrapment efficiency. AFM, NMR, and small angle X-ray scattering (SAXS) can be used to determine the number of lamellae in multilamellar vesicles. The mobility of a fluorescent probe as a function of temperature can be used to determine the membrane stiffness of niosomal formulations.

4. Entrapment Efficiency

Entrapment efficiency (EE%) is defined as the portion of the applied drug which is captured by the niosomes. Unencapsulated free medication can be extracted from the niosomal solution by centrifugation , dialysis, or gel chromatograph. After this process the loaded medicine can be released from niosomes by destruction of vesicles. Niosomes can be killed by the addition of 0.1% Triton X-100 or methanol to niosomal suspension. The loaded and free drug concentration can be measured by a spectrophotometer or high-performance liquid chromatography (HPLC).

5. Stability

The mean vesicle size, size distribution, and entrapment efficiency during several months of storage at various temperatures can be used to assess the stability of niosomes. The percentage of medicine that is kept in the niosomes is determined using UV spectroscopy or HPLC techniques when the niosomes are sampled at regular intervals throughout storage.

6. *In Vitro* Release

The use of dialysis tubing is one often used technique to investigate in vitro release. A dialysis bag is cleansed and immersed in distilled water. The drug-loaded niosomal suspension is moved into this bag after 30 minutes. The vesicle-containing bag is submerged in buffer solution at either 25°C or 37°C while being continuously shaken. Samples were taken out of the outer buffer (release medium) and replaced with the same amount of new buffer at predetermined intervals. An appropriate assay method is used to analyze the samples for drug content.[12]

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