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"A REVIEW: NIOSOMAL NANOTECHNOLOGY A PROMISING APPRAOACH FOR TARGETED DRUG DELIVERY SYSTEM"

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ABSTRACT

Niosomes, non-ionic surfactant-based vesicles, have emerged as a promising drug delivery system for both hydrophilic and lipophilic drugs. This study focuses on the formulation and evaluation of a niosomal gel intended for topical application, offering advantages such as enhanced drug penetration, prolonged release, improved stability, and reduced systemic side effects. Niosomes are structurally similar to liposomes but are more chemically stable and cost-effective due to the use of non-ionic surfactants. Various methods such as ether injection, sonication, thin-film hydration, and reverse phase evaporation are employed for niosome preparation. The prepared niosomes were incorporated into gel bases to enhance patient compliance and ensure localized delivery. Evaluation parameters included entrapment efficiency, vesicle size, in-vitro drug release, and structural integrity. The study concludes that niosomal gels are a potent topical delivery system capable of improving therapeutic efficacy while minimizing unwanted effects. Further research could help in optimizing formulation techniques for better clinical outcomes.

KEYWORDS: niosomes, transdermal drug delivery system, skin permiablity topical formulation.

INTRODUCTION

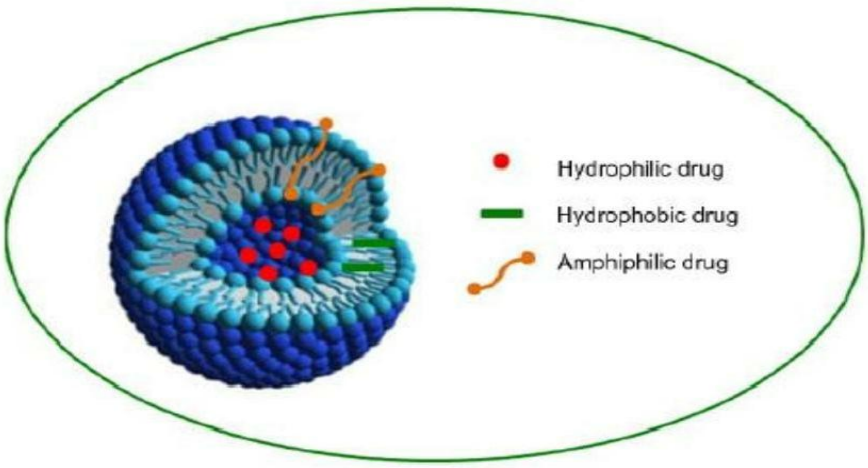

Figure 1: Structure of Niosome

Niosomes are microscopic non-ionic surfactant vesicles attained by the hydration of synthetic non-ionic surfactant with or without inclusion of cholesterol. They are akin to liposomes. Both Niosomes liposomes act as active carriers of both amphiphilic and lipophilic drugs. Difference in the niosomal and liposomal system is that niosomal bilayer is formed by non-ionic surfactant whereas liposomal bilayer made up of phospholipids. Niosomes are formed by the self-assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, bilayered, multilamellar system and polyhedral structures depending on the method used to prepare and the inverse structure in case of non-aqueous solvent. The orientation of the surfactant in niosome in hydrophilic ends exposed outwards while hydrophobic ends: face each other forming bilayer of the surfactant. The size of the niosomes ranges between 10 to 1000nm. Addition of cholesterol and a small quantity of anionic surfactant for instance dicetyl phosphate stabilizes the niosomal vesicles formed by the non-ionic surfactant. Niosomes

are suggested to be better than liposomes because of the higher chemical stability of surfactants than phospholipids which are easily hydrolyzed due to the ester bond and cost effective. Niosomes illustrate a promising drug delivery. Various methods of administration of niosomal formulation include intramuscular, intravenous, peroral, and transdermal.[1] Due to the presence of ester bond, phospholipids are easily hydrolysed. Unreliable reproducibilty arising from the use of lecithins in liposomes leads to additional problems and has led scientist to search for vesicles prepared from other material, such as nonionic surfactants. Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate.[2]

DESCRIPTION AND STRUCTURE OF NIOSOME

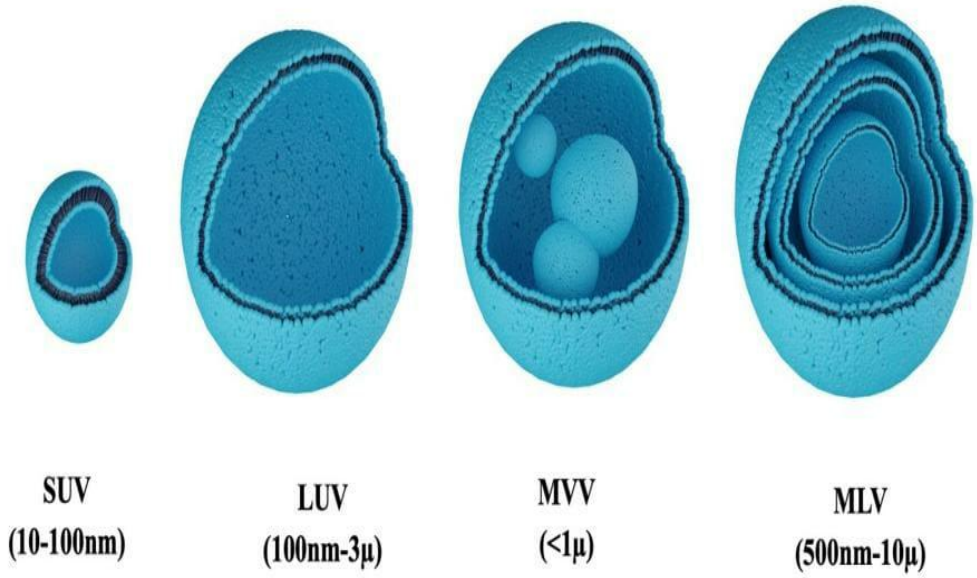

Figure No.2: niosomes structure based on size.[3]

Niosomes are self-assembling vesicles that are made of non-ionic surfactants. They can capture hydrophilic cargos in an aqueous core, and lipophilic compounds could be entrapped into the bilayer domains. The non-ionic surfactants, which are the main component of niosomes, are cheap, non-toxic, and well-tolerated in both external and internal administration. Niosome bilayers are more stable than liposomes, especially against oxidation. They need no excessive manufacturing procedures to protect them from oxidation and have higher shelf life than liposomes. Furthermore, niosomes showed great stability in the GI tract when administered orally. Nowadays, niosomes have attracted many researchers to employ it in the design of novel drug delivery systems for the oral delivery of chemical and natural compounds. Particularly they showed that they could be a good choice for delivery of peptides and proteins, which tend to de compose by extreme variations in pH and the effects of digestive enzymes in the GI tract. Based on the structure, niosomes are spherical vesicles consisting of one or more bilayers and based on their size, they could be categorized into four categories as follows.

- Small unilamellar vesicles (SUVs) with a size between 10 to 100 nm.
- Large unilamellar vesicles (LUVs) with a size between 100 nm to 3 µm.
- Multi-lamellar vesicles (MLVs) which have more than one bilayer in size between 500nm to 10 µm.
- Multi-vesicular vesicles (MVVs) defined as niosomes with an outer vesicle, which contain smaller vesicles inside, and generally, their size is more than 1 µm (Figure 2).[3]

ADVANTAGES

- Reduced side effects and shows maximum duration of action.
- Patient compliance is more compared to other delivery system.
- Quantity of drug used is very less for achieving its desired effect.
- Active ingredient or constituent present in the preparation is protected by bilayer from various factors present inside and outside the body.
- Act as depot formulation, thus the drug is released in a controlled manner.

- Drug is protected from first pass metabolism and gastro-intestinal degradation.
- Possess stable structure even in emulsion form.
- Niosomes are available in oral, topical as well as parenteral routes.[4][5][6][7]

DISADVANTAGES

- Time consuming process.
- Specialized equipment's are required for processing.
- Limited shelf life due to- 1) Fusion

2) Aggregation
3) Leakage of entrapped drugs
4) Hydrolysis of encapsulated drugs.

- Physically unstable.[8][9][10]

Method of preparation

1. **Ether injection method**
2. **Hand shaking method (thin film hydration)**
3. **Sonication method**
4. **Micro fluidization method**
5. **Multiple membrane extrusion method**
6. **Reverse phase evaporation technique**
7. **Bubble method**
8. **Trans membrane pH gradient drug uptake process.**

Reverse Phase Evaporation Technique (REV)

In the REV method, a 1:1 ratio of cholesterol and surfactant mixture is dissolved in organic solvents like chloroform and ether. The drug is dissolved in the aqueous phase and added to the above mixture to form two phases, which are then sonicated at 4-5°C. A clear gel is formed and further sonicated after the addition of phosphate buffered saline. The organic phase is removed at 40°C under low pressure. The resulting niosomes solution is viscous and is diluted with phosphate buffer, followed by heating in a water bath at 60°C to obtain niosomes with high yield.

Sonication Method

Various methods are employed for the preparation of niosomes. One such method involves adding the drug solution into a buffer system, followed by the addition of this mixture into a surfactant or cholesterol mixture in a 20ml glass vial. The combination is then sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to produce niosomes.

Hand shaking method (Thin film hydration techniques)

In this technique, surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether, chloroform, or methanol in a round bottom flask. The organic solvent is evaporated at 20°C using a rotary evaporator, leaving a thin layer of solid mixture on the flask surface. The dried film of surfactant can be rehydrated with an aqueous phase at 0-60°C with gentle agitation to form multilamellarniosomes.

Micro fluidization method

A modern approach to preparing unilamellar vesicles with a well-defined size distribution involves the use of micro fluidization. This method relies on two fluidized streams at ultra-high velocities interacting with each other. By directing the narrow liquid film onto a typical surface, the level of energy supplied to the system is preserved at a suitable level for the creation of niosomes. The outcome is niosomes with enhanced uniformity, smaller size, and improved reproducibility.[11][12]

Trans membranes PH gradient (inside acidic) Drug Uptake Process

Surfactant + cholesterol in chloroform Evaporation of solvent under reduce pressure Thin film is deposited on the walls of RBF. Hydrated with citric acid by vortex mixing 3 cycles of freezing and thawing then sonication, Add solution of aqueous drug and vertexing. Raised PH to 7.0-7.2 by 1M disodium phosphate RBF as bubbling unit with three necks in water bath Reflux, thermometer and nitrogen supply by three necks Cholesterol + surfactant dispersed in buffer pH 7.4 at 70°C Above dispersion is homogenized for 15 sec and then bubbled with nitrogen gas at 70°C To form Niosome.[13][14][15]

Multiple membrane extrusion method

This is the best method for controlling size of niosome. In this method mixture of surfactant, cholesterol and diacetyl phosphate in chloroform and these all add in rotary flash evaporator for evaporation of organic solvent and forms thin layer. 90 The aqueous phasecontaining drug polycarbonate membrane solution add in it. The resultant suspension extruded through which are placed in series for up to 8 passage.[16][17]

Ether injection method

Both drug and surfactant are dissolved in diethyl ether and slowly injected in aqueous phase with continuous heating above the boiling point of diethyl ether. The prepared niosomes after evaporation are further treated for size reduction.[19].[20]

Bubble method

Bubble method does not require the use of organic solvent. Cholesterol and surfactant are dissolved into the buffer solution and heated up to 70°C. At 70°C temperature, the solution is homogenized using a high shear homogenizer for 15 s, and nitrogen gas is passed through the solution which leads to the formation of niosomes.[21]

Evaluation of niosomes

a) Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation, or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay

method for the drug. Where, Entrapment efficiency (EF) = (Amount entrapped total amount) x 100

b) Diameter Vesicle

Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing(keeping vesicles suspension at –20°C for 24 hrs and then heating to ambient temperature) of niosomes increases the vesicle diameter, which might be attributed to fusion of vesicles during the cycle.

c) *In-vitro* release

A method of in-vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method.[22]

FACTORS INFLUENCING NIOSOMAL FORMULATION

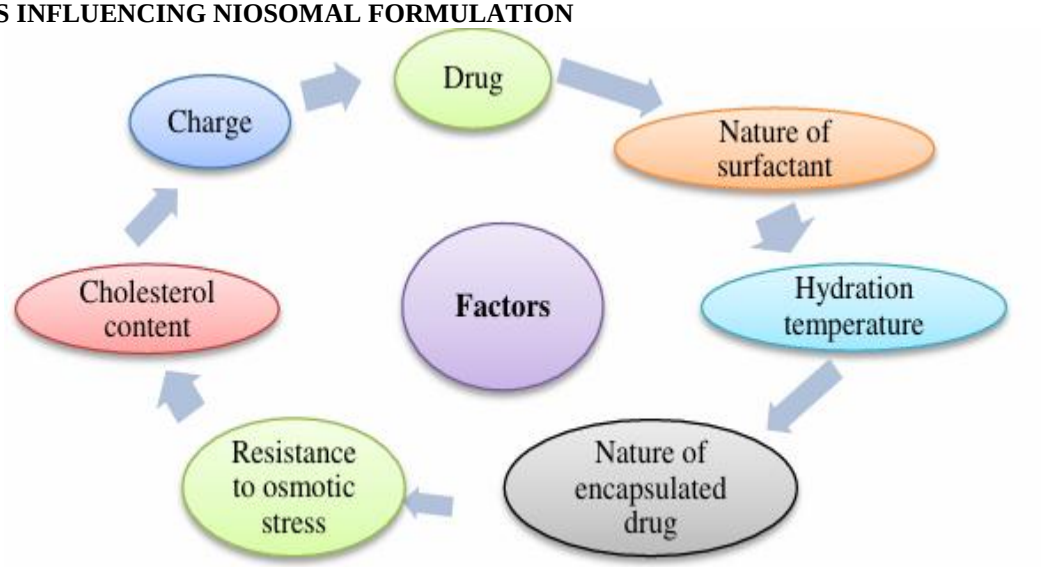

Fig. 3: factor influencing niosomal formulation.

1. Nature of Surfactant

As surfactant hydrophobicity increases and surface free energy decreases, a rise in surfactant HLB value causes an increase in the mean size of niosomes. Niosome bilayers can exist in two different states: liquid and gel. Temperature, cholesterol, and surfactant type all play a role. While alkyl chains are chaotic in the liquid state, they are well organized in the gel state. The gel, liquid phase transition temperature (TC) of the surfactant has an impact on entrapment efficiency. For instance, superior entrapment is shown by span 60 with a higher TC. Surfactants with an HLB value of 14–17 are not appropriate for use in niosomal preparations. Entrapment efficiency is reduced as the HLB value of surfactants drops from 8.6 to 1.7, with an HLB value of 8.6 exhibiting the highest entrapment efficiency.

2. Nature of Encapsulated Drug

The physical and chemical characteristics of the encapsulated drug have a significant impact on the charge and rigidity of the niosomal bilayer. Drug entrapment happens when it interacts with the surfactant head groups, increasing the charge and causing the surfactant bilayer to repel one another, which in turn increases the size of the vesicle. The level of entrapment is influenced by the drug's HLB.

3. Hydration Temperature

The temperature of hydration has an impact on the niosome's size and shape. The temperature at which hydration occurs should be higher than the gel's liquid phase transition temperature. The assembling of surfactants into vesicles and the alteration of vesicle shape are both impacted by temperature changes. The change is also explained by the hydration medium's volume and duration. Fragile niosomes and drug leakage issues can result from improperly choosing the hydration temperature, duration, and medium volume.

4. Cholesterol Content

Adding cholesterol improves the niosomes' hydrodynamic diameter and trapping efficiency. In liquid state bilayers, cholesterol increases the chain order; in gel state bilayers, it decreases the chain order. The

bilayers become more stiff and the pace at which the encapsulated material releases decreases as the cholesterol concentration rises.

5. Charge

In a multilamellar vesicle structure, the presence of charge results in a larger overall entrapped volume and an increase in the interlamellar distance between succeeding bilayers.

6. Resistance to Osmotic Stress

Vesicle diameter decreases when a hypertonic solution is added. Because of the mechanical loosening of vesicle structure under osmotic stress, inhibition of eluting fluid from vesicles in hypotonic solution causes a gradual release at first, followed by a quicker release.[23]

CONCLUSION

The development of niosomal gel formulations presents a promising advancement in topical drug delivery systems. Niosomes, owing to their structural stability, biocompatibility, and ability to encapsulate both hydrophilic and lipophilic drugs, offer significant advantages over conventional formulations. Incorporating these vesicles into a gel base not only enhances drug penetration through the skin but also ensures sustained drug release and improved therapeutic efficacy with minimal systemic side effects. The evaluation parameters, including entrapment efficiency, vesicle size, and in-vitro drug release, confirmed the effectiveness of the prepared niosomal gel system. Furthermore, the ease of application, improved patient compliance, and potential for targeted delivery reinforce the applicability of such formulations in dermatological and transdermal therapies. Despite certain limitations, such as complex preparation methods and stability concerns, niosomal gels hold great potential for future pharmaceutical innovations. Continued research and optimization could further improve their stability and broaden their therapeutic applications.

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23. In Vancouver style, the citation would be formatted as: Dhanvir K, Sandeep K. Niosomes: present scenario and future aspects. J Drug Deliv Ther., 2018; 8(5): 35-43.