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VESICULAR NIOSOMAL PATCH: A NOVEL ABSORPTION MODULATOR FOR TRANSDERMAL DELIVERY

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ABSTRACT

Niosomes are the vesicular carriers of non-ionic surfactants used in the drug delivery systems, as a tool to improve drug absorption. Niosomes has applications in oral, parenterals, topical and novel drug delivery for controlled and targeted delivery, such as in the treatment of cancer, as a carrier in haemoglobin, delivery of the peptide drugs through oral route, in treatment of Leishmaniasis, in ophthalmic delivery, in cosmetics and as a carrier in dermal drug delivery. Niosomes as transdermal drug delivery is a novel approach and the scientists working in the area of drug delivery system have turned their interest towards the same. The main aim of current review is to focus on niosome structure, composition, advantages, types of niosomes, methods of preparation, characterization, its application and also about its formulation, mechanism and characterization as transdermal drug delivery.

INTRODUCTION

Novel drug delivery carriers, especially vesicular niosomes have greater potential for transdermal route when compared to the other route of administration. Vesicular niosomes are novel drug delivery system, in which the vesicles formed by mixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media resulting in microscopic lamellar structures.[1] The various novel drug delivery system such as liposomes, microspheres, nanoparticles and other carriers have less advantages when compared with vesicular niosomes.

Niosomes increase the penetration of drug through the skin, which acts locally, systematically and sustained release of active components in which both hydrophilic and lipophilic drugs are entrapped either in aqueous layer or in vesicular membrane made of lipid material, which

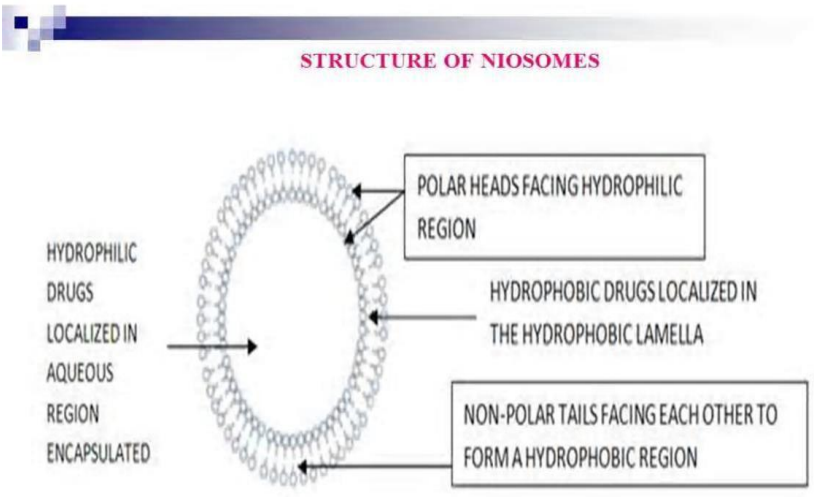
prolongs the circulation of entrapped drug.[2] Niosomes enhances the bioavailability of the encapsulated drug and provides better therapeutic activity in a controlled manner for prolonged duration of time.

Transdermal drug delivery system is a convenient route of administration and potential route for the local and systemic delivery of the drugs, in which the drug is passed through the skin to the systemic circulation. Strateum corneum is the main barrier layer for the permeation of drug, so to increase the flux through the skin membrane various penetration enhancement approaches are used. The penetration enhancement of drug through the skin is achieved by drug-vehicle based enhancement methods such as niosomes, liposomes and ion-pair for the transdermal drug delivery system.[3]

Transdermal drug delivery system offers many advantages over conventional methods of drug administration, such as reduced side effects, elimination of first pass metabolism, increase in therapeutic efficiency, frequency of administration is reduced and improved patient compliance.[4]

Niosomes are vesicular nanocarriers that are receivingmuch attention as potential transdermal drug delivery system because of its various properties such as penetration enhancement of drug, local depot for sustained release and a rate limiting membrane for the modulation of absorption of drug to the systemic circulation via the skin. Topically administered niosomes reduces the systemic absorption of drug while increasing the residence time of drugs in the strateum corneum and epidermis.[5]

STRUCTURE OF NIOSOME



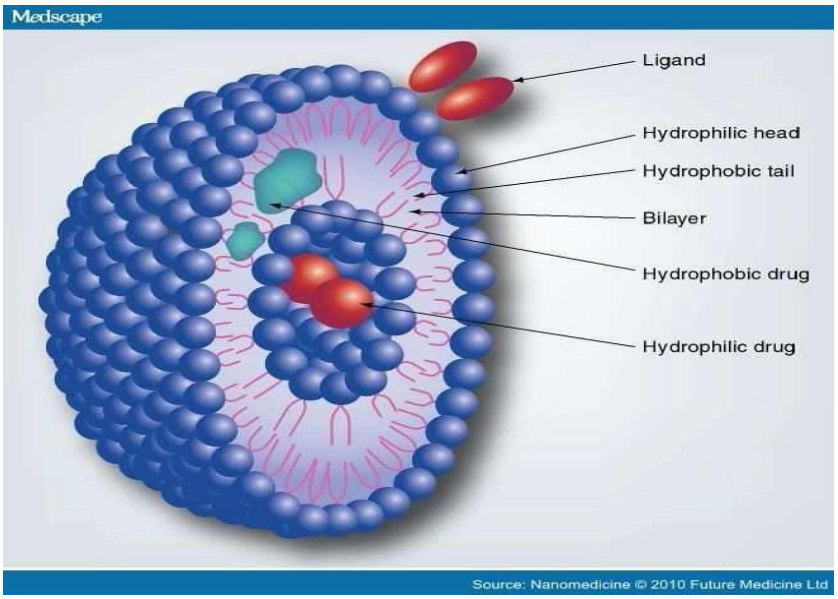


Figure 2: Diagrammatic representation of drug loaded niosomes.

COMPOSITION OF NIOSOMES

Cholesterol

Cholesterol is a waxy steroid metabolite which is found in the cell membrane. Membrane stabilizing activity and decrease in the leakiness of membrane is achieved by incorporating cholesterol into bilayer composition of niosome. Cholesterol provides proper shape and conformation to the niosomal preparations and increases the rigidity upon mixing with non-ionic surfactant.[6]

Non-ionic surfactant

As they are polymeric nanocarriers, non-ionic surfactants play wide role in controlled, sustained, targeted and continuous drug delivery system. They don't have any charge group in their hydrophilic heads, so in the solutions hydrophilic heads are opposite to aqueous solutions and hydrophilic tails are opposite to organic solutions resulting in formation of structures. Due to this property, niosomes formed in aqueous dispersions are by self-assembly of non-ionic surfactants.[7]

ADVANTAGES OF NIOSOMES[8]

i. Niosomes have better patient compliance when compared to oily dosage form as the vesicle suspension being water based vehicle in niosomes.

ii. By altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration, the vesicle characteristics can be controlled.

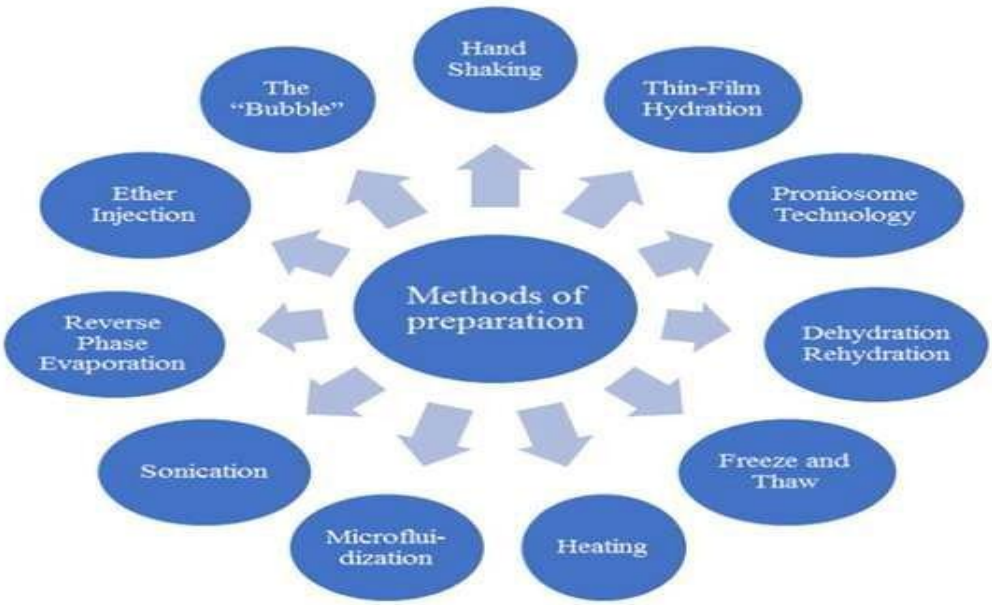
iii. They can release the drug in sustained/controlled manner.
iv. Niosomes possess stable structure even in emulsion form.
v. Niosomes enhances the oral bioavailability of poorly soluble drugs.
vi. Drugs undergoing enzyme metabolism can be protected by the niosome formulation.
vii. Niosomes are osmotically stable and active and improves the stability of entrapped drug.
viii. Niosomes can enhance the permeation of drugs through the skin.
ix. They are biodegradable and non-immunogenic.
x. They can entrap lipophilic drugs into vesicular bilayer membranes and hydrophilic drugs in aqueous compartments.
xi. They have low toxicity and high compatibility with biological systems because of their non-ionic nature.
xii. Because of the functional groups on their hydrophilic heads, their surface formation and modification is very easy.
xiii. Access to raw materials is convenient.

Types of Niosomes[9]

Niosomes can be divided into three groups on the basis of their vesicles size:

(i) Small Unilamellar Vesicles (SUV, Size is 025-0.05 μm)
(ii) Multilamellar Vesicles (MLV, Size is >0.05 μm)
(iii) Large Unilamellar Vesicles (LUV, Size is >0.10 μm).

Method of preparation



Thin film hydration technique

Cholesterol and surfactant are weighed accurately and dissolved in suitable solvent in 100ml round bottom flask. Exactly weighed amount of drug is added to the solvent mixture. The solvent mixture will be separated from liquid phase by flash evaporation at 60^0C to obtain a thin film on the wall of the flask at a rotation speed of 150rpm. Further by applying vaccum, complete elimination of remaining solvent is done. For the formation of niosomes, the dry lipid film is hydrated with 5ml phosphate buffer saline of pH 7.4 at a temperature of 60^0C for one hour.[10]

Ether injection method

Niosome formation is carried out by slowly introducing diethyl ether in a solution of surfactant into warm water maintained at 60^0C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Niosomes are formed by vaporization of ether.[11]

Trans-membrane pH gradient drug uptake process (Remote loading)

Surfactant and cholesterol are dissolved in chloroform. To obtain a thin film on the wall of the round-bottom flask evaporation of solvent is carried under reduced pressure. By using vortex mixing the film is hydrated with 300 Mm citric acid (pH 4.0). The multilamellar vesicles are frozen and thawed three times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to produce the desired multilamellar vesicles.[12]

Reverse phase evaporation technique (REV)

In this method, ether and chloroform are mixed in which cholesterol and surfactant are dissolved. The drug in aqueous phase is added to this and the resulting two phases are sonicated at 4-5°C. After addition of a small amount of phosphate buffer saline the clear gel is formed which is further sonicated. Under low pressure at 40°C the organic phase is removed. This results in viscous niosome suspension, further to yield niosomes this is diluted with phosphate-buffered saline and heated in a water bath at 60°C for 10 min.[12]

Sonication

The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in a scintillation vial. The mixture is probe sonicated at 60°C for 3 minutes to produce small and

uniform in size niosomes.[13]

Micro-fluidization

Recently small multi lamellar vesicles are prepared by using this technique. The fluid is pumped at a very high pressure (10,000 psi) through a 5 pm screen using a microfluidizer. Then it is forced along with defined micro channels, which leads to collision of two streams of fluid together at right angles, which results in efficient transfer of energy. The lipids can be introduced into the fluidizer. The recycling of collected fluid collected carried out through the pump until spherical vesicles are obtained. This method resulted in niosomes with greater uniformity and small size which shows better reproducibility.[14]

The bubble method

It is one of the novel technique in which liposomes and niosomes can be prepared by one step without the use of organic solvents. The temperature is controlled by a bubbling unit which consists of round-bottomed flask with three necks positioned in water bath. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. In 7.4pH buffer, cholesterol and surfactant are dispersed together at 70°C. Then dispersion mixed for 15 seconds using high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.[15]

Extrusion method

In this method, niosomes can be prepared by using a chemically defined non -ionic surfactant C16G2 by extrusion through a polycarbonate membrane. These studies not only demonstrate the effect of number of extrusion on vesicles size but also the effect of size on encapsulation of drug.[16]

CHARACTERIZATION OF NIOSOMES

Size and Morphology

The vesicle size and morphology of niosomes can be determined by using different methods such as Dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), freeze fracture replication electron microscopy (FF-TEM) and cryotransmission electron microscopy (cryo-TEM). DLS provides information the particle size and homogeneity of the solution simultaneously. A single sharp peak in the DLS profile implies existence of a single population of scatterers. The PI less than 0.3 corresponds to a homogenous population for colloidal systems. The characterization of morphology of niosomes can be done

by using microscopic approaches.[17]

Zeta Potential

Zeta sizer and DLS instruments are used to determine the surface zeta potential of niosomes. The surface charge plays an important role in the behavior of niosomes. The charged niosomes are more stable against aggregation when compared to uncharged vesicles.[17]

Size distribution, Polydispersity index

Laser beam is used for mean surface diameter, size distribution and mass distribution of niosomes. Polydispersity index is a measure of the different sizes of molecules or particles in a mixture. Monodisperse is a collection of objects or uniform objects have the same size, shape, or mass. Polydisperse or non-uniform is a sample of objects that have an inconsistent size, shape and mass distribution. Polydispersity index is determined by Dynamic light scattering method.[18]

Entrapment efficiency

As described above after preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation or gel filtration and/ or complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 is done for the estimation of the drug remained entrapped in niosomes and then analysing the resultant solution by appropriate assay method for the drug. Where, Entrapment efficiency (EF) can be defined by[19]:

Entrapment efficiency (EF) = (Amount entrapped/ total amount) x100.

Membrane rigidity and homogeneity

Bio-degradation and bio-distribution of niosomes are affected by the rigidity of the membrane. The rigidity of niosomal suspension is determined by fluorescence probe as a function of temperature. The membrane homogeneity is determined by P-NMR, differential scanning calorimetry (DSC), Fourier transform-infra red spectroscopy (FTIR) and fluorescence resonance energy transfer (FRET).[20]

***In-vitro* drug release study[21]**

a) Dialysis

The *in-vitro* release rate study can be done by using dialysis tube. A dialysis sac is washed and soaked in distilled water. In the bag the suspension of vesicles are to be pipetted into it which is made up of the tubing and then its sealed and placed in 250 ml beaker containing 200ml of

buffer solution with constant shaking at 25°C or 37°C. The buffer is then analysed at various time intervals, for the drug content by an appropriate assay method.

b) Reverse dialysis

In this technique, niosomes are placed in a number of small dialysis tubes containing 1 ml of dissolution medium and the niosomes are then displaced from the dissolution medium.

c) Franz diffusion cell

In this method cellophane membrane is used as the dialysis membrane. The dialysis of niosomes takes place through a cellophane membrane against suitable dissolution medium at room temperature. The samples are withdrawn at suitable time intervals and analysed for drug content.

Stability

The stability of niosomes is carried out to the optimized batch which has to be store in airtight sealed vials. These are maintained at different temperatures i.e., (40c, 250c, 450c). Surface characteristics and percentage drug retained in niosomes are determined. Samples are to be taken at regular intervals of time (0,1,2,and 3months)observed for colour change, surface characteristics and tested for the percentage drug retained after being hydrated to form niosomes and analysed by suitable analytical methods(UV spectroscopy, HPLC methods etc).[22]

Applications of niosomes[23]

- Niosomes have been used for studying the nature of the immune response provoked by antigens.
- Niosomal system can be used as diagnostic agents.
- It is used as Drug Targeting.
- It is used as Anti-neoplastic Treatment i.e. Cancer Disease.
- It is used as Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
- It is used act as Delivery of Peptide Drugs.
- It is used in Studying Immune Response.
- Niosomes as Carriers for Haemoglobin.
- Transdermal Drug Delivery Systems Utilizing Niosomes.
- It is used in ophthalmic drug delivery.

Other Applications: Niosomes can also be utilized for sustained drug release and localized

drug action to greatly increase the safety and efficacy of many drugs. Toxic drugs which need higher doses can possibly be delivered safely using niosomal encapsulation.

Transdermal Drug Delivery

Preparing vesicles would be a versatile technique for enhancing the topical penetration of pure drugs through skin barrier, Stratum corneum. To diffuse through this barrier particles mainly depend on its size and viscoelastic properties.[24] The major drawback of transdermal drug delivery is slow penetration of the drug, which can be achieved by incorporating the drug in niosome form thereby increasing the penetration rate.[15] For the modulation of systemic absorption of drugs topical niosomes serve as a solubilization matrix, local depot for sustained release of dermally active compounds, penetration enhancers or as rate-limiting membrane barrier[23]

Mechanism of Niosomal Skin Delivery[25]

- The mechanism followed by the niosomes for transdermal drug delivery is:
- Diffusion through stratum corneum layer.
- The amount of water present in the skin is important for this mechanism.
- The lipophilic drugs cross the stratum corneum by aggregation, fusion and adhesion.
- The niosomes looses the cells of stratum corneum which increases the permeation of drugs.
- The non-ionic surfactant enhances the permeation and this leads to improved drug permeation through skin.

Niosomes as Carrier in Dermal Drug Delivery[25]

Topical formulations of niosomes which are developed recently are mentioned below:

- For local anaesthesia action.
- For the treatment of Psoriasis.
- Hyperpigmentation.
- NSAID'S.
- For the treatment of Acne.

Application of niosomes in transdermal drug delivery[19]

Those drugs have slow penetration of medicament through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Topical niosomes may serve as

solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

Preparation of niosomal patch[26]

The prepared niosomes can further formulated as transdermal patch by using following components:

- Polymer matrix/ Drug reservoir
- Permeation enhancers
- Pressure sensitive adhesive (PSA)
- Backing laminate
- Release liner
- Other excipients like plasticizers and solvents

CHARACTERIZATION OF NIOSOMAL PATCH

Thickness

The thickness of patches is measured by using micrometer (Mitutoyo Co., Japan) or Vernier calliper at three different places and mean values were calculated.[27]

Folding Endurance

This is determined by repeatedly folding one patch at the same place till it brake. The number of times the patch could be folded at the same place without breaking/cracking will give the value of folding endurance[28]

Weight uniformity

Before testing weight uniformity the patches are dried at 60°c for 4hrs. The specific area of patch is cut into different parts and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.[29]

Percentage moisture absorption[29]

Initially weigh the prepared patches and keep it in dessicator at room temperature for 24hrs. And then these are taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in desiccators until a constant weight is achieved. % moisture uptake is calculated as given below.

% moisture uptake = Final weight – Initial weight X 100 Initial weight

Percentage moisture loss[30]

The formulated patches are weighed individually and kept in a desiccators containing anhydrous calcium chloride at room temperature for 24 hours. After the 24 hours the patches are weighed at a specific time interval until the constant weight is obtained. The percentage moisture loss is calculated by using following formulae:

Percentage moisture loss = (Initial wt - final wt)/initial wt) X 10

Drug Content

Dissolve the suitable area of patch in a specified volume of solvent. Filter the solution through a filter medium and analyse for the drug content by suitable techniques(UV or HPLC technique). Take the average of three samples.[31]

Weight Uniformity

Dry the prepared patches at 60°C for 4 hrs before testing. Cut the specific area of patch in different and weigh the parts in digital balance. Calculate the average weight and standard deviation from the individual weights.[31]

Swellability[31]

Weigh 3.14 cm^2 of patch and keep it in a petri dish containing 10 ml of double distilled water and allow to imbibe. Determine the weight of patch at a specific time interval. The degree of swelling (S) is calculated using the formula,

$$S\ (\%) = Wt - Wo/Wo \times 100$$

Where, S is percent swelling

Wt is the weight of patch at time t and Wo is the weight of patch at time zero.

***In-vitro* drug release studies**

In-vitro drug release of transdermal patch can be carried out using Franz diffusion cell. Which is made up of two compartments i.e. donor and receptor compartment. Volume of the receptor compartment is 5-12ml and effective surface area of 1-5cm^2. Stirr the diffusion buffer continuously at 600rpm by a magnetic stirrer. Maintain the temperature in the bulk of the solution is by circulating thermostated water through a water jacket that is present in the receptor compartment. Analyse the drug content using suitable method, maintain the sink condition if it is essential.[32]

CONCLUSION

Vesicular niosomes of suitable active components formulated as transdermal drug delivery system may be a promising Drug Delivery System. Transdermal delivery of niosomes is also found to have effective localization of drugs, which are reasonably non-toxic and stable. They can also act as controlled release and targeted drug delivery system as it is capable of loading both hydrophilic and hydrophobic drugs. Niosomes are found to be cost effective and are more stable when compared to liposomes. The main requirement in formulation of niosomes is selection of surfactant, as it plays an important role in the formation of vesicles, its stability and toxicity of the formulations.

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