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REVIEW ARTICLE

Proniosomes : A Novel Provesicular Drug Delivery System

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ABSTRACT

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of traditional drug delivery systems and are able to deliver drug at the site of action and at predetermined rate which increases therapeutic efficacy, minimize adverse or side effects and increases bioavailability of the drug. Drug delivery system using colloidal particulate carriers such as liposomes and niosomes have distinct advantages over conventional dosage forms. However, remain a significant problems like instability in general application of liposomes and niosomes for drug delivery. Provesicular concept has evolved to resolve the stability issues pertaining to conventional vesicular system. Proniosome is an emerging trend in provesicular drug delivery system. These proniosomes minimize problems of niosomes physical stability such as aggregation, fusion, leaking and provide additional convenience in transportation, distribution, storage and dosing. Proniosomes are dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. The focus of this review is to bring out different aspects related to proniosomes preparation, characterization, entrapment efficiency, in vitro drug release, applications and merits.

KEYWORDS

Vesicular Drug Deliver, Niosomes, Proniosomes, Surfactant, Niosomes

INTRODUCTION

In recent years, continuous hard work has been done for development of novel drug delivery systems. Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of traditional drug delivery systems and are able to deliver drug at the site of action and at predetermined rate which increases therapeutic efficacy, minimize adverse or side effects and increases bioavailability of the drug. Many novel approaches emerged covering various routes of administration, to achieve their controlled or target drug delivery.

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Vesicular systems have been receiving a lot of interest as a carrier for advanced drug delivery. Encapsulation of the drug in vesicular structures is one such system, which can be expected to prolong the duration of the drug in systemic circulation, and to reduce the toxicity by selective up taking.

Drug delivery systems using colloidal particulate carriers such as liposomes or niosomes have proved to possess distinct advantages over conventional dosage forms because the particles can act as drug reservoirs, can carry both hydrophilic drugs by encapsulation or hydrophobic drugs by partitioning of these drugs into hydrophobic domains and modification of the particle composition or surface can adjust the drug release rate and/or the

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affinity for the target site. The vesicles in a dispersed aqueous system may suffer from some chemical problems associated with degradation by hydrolysis or oxidation as well as physical problems as sedimentation, aggregation, or fusion of liposomes during storage.[1]

The pro-vesicular concept has evolved to resolve the stability issues pertaining to the conventional vesicular systems i.e. liposomes and niosomes. Pro-vesicular systems are composed of water soluble porous powder as a carrier upon which one may load phospholipids/non-ionic surfactants and drugs dissolved in organic solvent. The resultant dry free-flowing granular product could be hydrated immediately before use and can avoid many of the problems associated with aqueous vesicular dispersions. The new emerging concept has demonstrated the potential of proliposomes/pro-niosomes in improving the oral bioavailability and permeation of drugs across the stratum corneum. Based on the investigations it is clear that pro-vesicular systems appear to be an alternate drug carrier for various routes of drug administration. It can avoid many of the problems associated with aqueous vesicular dispersions.[2] To overcome the limitations (especially chemical and physical stability) of vesicular drug delivery systems like liposomes, niosomes, transferosomes, and pharmacosomes, the pro-vesicular approach was introduced.

This includes-

A. Proliposomes

B. Pro-niosomes

C. Dry granular liposomes

D. Mixed micellar proliposomes

E. Pro-transferosomes

Niosomes are non-ionic surfactant vesicles that can entrap a solute in a manner analogous to liposomes. Niosomes possess an infrastructure consisting of hydrophilic and hydrophobic moieties together, and as a result, can accommodate drug molecules with a wide range of solubilities.[3] Although niosomes as drug carriers have shown advantages such as being cheap and chemically stable, they are associated with problems related to physical stability such as fusion, aggregation, sedimentation and leakage on storage[4]. All methods traditionally used for preparation of niosomes are time consuming and many involve specialized equipments.

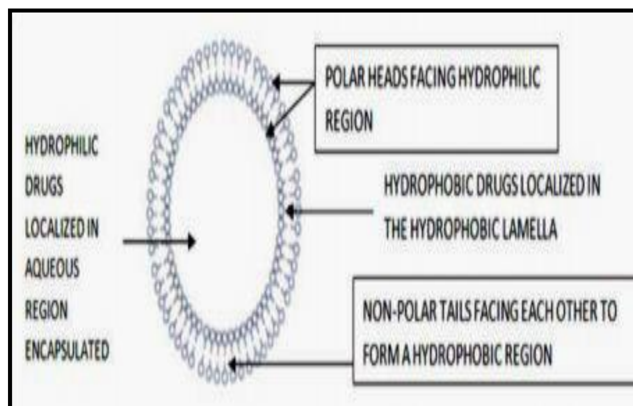

Figure 1: Representation of Niosomes

To overcome the Disadvantages associated with niosomes, proniosomes are prepared and reconstituted into niosomes.

Proniosomes

Proniosomes are dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. The resulting niosomes are very similar to conventional niosomes and more uniform in size.[4] The major barrier to transdermal delivery of drugs is stratum corneum. Vesicular delivery via skin is beneficial in that drugs, which permeate via skin and reaches systemic circulation. For transdermal delivery, proniosomes are the best vesicular system because they act as a drug reservoir for a prolonged period of time and increases skin permeation. The formulation of drugs into proniosomes also helps in better physical and chemical stability of the drug and the vesicular nature of the delivery system helps the drug to permeate through skin with an ease and helps in reaching systemic circulation and the target site without losing any drug activity and providing better therapeutic efficacy.

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Structure of Proniosomes

These are microscopic lamellar structure. They combine a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class, lipid and cholesterol followed by hydration in the aqueous media. The surfactant molecule direct themselves such that the hydrophilic end of the non- ionic surfactant orient outward, while the hydrophobic end are in the opposite direction to form the bilayer. Like liposomes proniosomes are also made of bilayer. In proniosomes this bilayer are made up of non-ionic surface active agent. On the basis of method of preparation proniosomes are unilamellar or multilamellar.

Conversion of Proniosomes into Niosomes

The hydration may occur either by the skin or by the addition of aqueous solvents. Proniosomes can entrap both hydrophilic as well as lipophilic drugs.

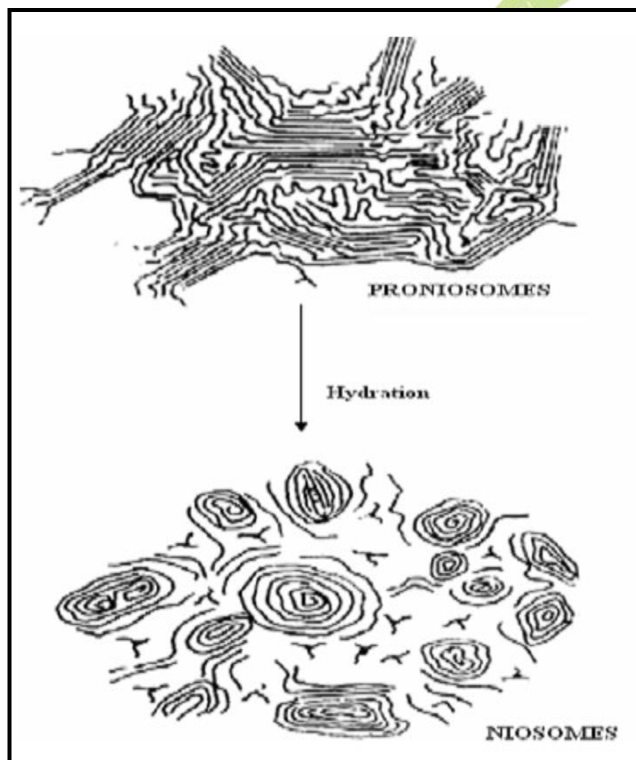

Figure 2: Schematic illustration of noisome formation

Advantages of Proniosomes Over Niosomes[5,6]

1. Avoiding problem of physical stability like aggregation, fusion, leaking.
2. Avoiding hydration of encapsulated drugs which is limiting the shelf-life of the dispersion.
3. Convenience of the transportation, distribution; storage and designing would be dry niosomes a promising industrial product.
4. Furthermore, unacceptable solvents are avoided in proniosomal formulations.
5. The storage makes proniosomes a versatile delivery system with potential for use with a wide range of active compounds.

Components of Proniosome

A. *Surfactants*

Surfactants are the surface active agent usually organic compounds that are amphiphilic in nature (having both hydrophobic and hydrophilic groups). They have variety of functions including acting as solubilizers, wetting agents, emulsifiers and permeability enhancers.[7] The most common non-ionic amphiphiles used for vesicle formation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids.

B. *Carrier Material*

The carrier when used in the proniosomes preparation permits the flexibility in the ratio of surfactant and other components that incorporated. In addition to this, it increases the surface area and hence efficient loading. The carriers should be safe and non-toxic, free flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration.[8,9]

C. *Membrane Stabilizer*

Cholesterol and lecithin are mainly used as membrane stabilizer. Steroids are important components of cell membrane and their presence in membrane brings about significance changes with regard to bilayer stability, fluidity and permeability. Cholesterol is a naturally occurring steroid used as membrane additive. It prevents aggregation by the inclusion of molecules that stabilize the system against the formation of aggregate by repulsive steric or electrostatic effects. It leads transition from the gel state to

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liquid phase in noisome system. Phosphatidylcholine is a major component of lecithin. It has low solubility in water and can form liposomes, bilayer sheets, micelles or lamellar structures depending on hydration and temperature. Depending upon the source from which they are obtained they are as named as egg lecithin and soya lecithin. It acts as stabilizing as well as penetration enhancer. It is found those vesicles composed of soya lecithin are of larger size than vesicle composed of egg lecithin probably due to the difference in the intrinsic composition.

D. Solvent and Aqueous Phase

Alcohol used in Proniosome has a great effect on vesicle size and drug permeation rate. Vesicles formed from different alcohols are of different size and they follow the order:

Ethanol > Propanol > Butanol > Isopropanol. Ethanol has greater solubility in water hence leads to formation of highest size of vesicles instead of isopropanol which forms smallest size of vesicle due to branched chain present. Phosphate buffer pH 7.4, 0.1% glycerol, hot water is used as aqueous phase in preparation of proniosomes.

E. Drug

The drug selection criteria could be based on the following assumptions.[10]

1. Low aqueous solubility of drugs.
2. High dosage frequency of drugs.
3. Short half life.
4. Controlled drug delivery suitable drugs.
5. Higher adverse drug reaction drugs.

Table 1: Commonly used materials for Proniosomal preparation

Class	Examples	Uses
Surfactant -Alkyl ethers and alkyl glyceryl ethers -Sorbitan fatty acid esters -Polyoxyethylene fatty acid esters	-Polyoxyethylene 4 lauryl ether (Brij30), Polyoxyethylene cetyl ethers (Brij 52, 56, 58), Polyoxyethylene stearyl ethers (Brij 72, 76) - Span 20, 40, 60, 80 - Tween 20, 40, 60, 80	To increase the drug flux rate across the skin
Carrier material	Maltodextrin, Sorbitol, Mannitol, Spray dried lactose, Glucose monohydrate, Lactose monohydrate, Sucrose stearate	-Penetration enhancer -Provides flexibility in surfactant and other component ratio -Altars the drug distribution
Membrane stabilizers	-Cholesterol -Soya and egg Lecithin	-To prevent leakage of drug from formulation -Skin permeation
Solvent	Ethanol, methanol, propanolol, isopranolol,	Skin permeation
Aqueous phase	Hot water, pH 7.4 buffer, 0.1 % glycerol	Entrapment efficiency

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Formulation Consideration

A. Selection of Surfactant

Surfactants can improve the solubility of some poorly soluble drugs. Selection of surfactants should be done on the basis of following;

HLB value which is a good indicator of the vesicle forming ability of any surfactant. It was found that the HLB value in between 4 and 8 are good candidate for vesicle formation as when hydrophilic surfactants are taken into account their high aqueous solubility on hydration do not allow them to attain a concentrated systems and it inhibits the free hydrated units to exist aggregates and coalesced to form lamellar structure. High HLB value results in reduction of surface free energy which allows forming vesicles of larger size. High HLB value results of span 40 and 60, results reduction in surface free energy which allows forming vesicles of larger size hence large area exposed to the dissolution medium and skin.[11]

Critical Packing Parameter (CPP) is a geometric expression relating to hydrocarbon chain length (l) and volume (v) and the interfacial area occupied by the head group.

$$CPP = v/ lc \times a$$

v = hydrophobic group volume

lc = critical hydrophobic group length

a = area of hydrophilic head group

A CPP between 0.5 and 1 indicates that the surfactant is likely to form vesicles. A CPP of below 0.5 which indicates a large contribution from the hydrophilic head group area is said to give spherical micelles and a CPP of above 1 indicates a large contribution from hydrophobic group volume should produce inverted micelles.

Phase Transition Temperature (Tc) plays a vital role in the degree of entrapment, as the transition temperature of surfactants increase it leads to increase in the entrapment efficiency and decrease in the permeability. Spans with highest phase transition temperature provide the highest entrapment for the drug. The drug leaching from the vesicles can be reduced due to high phase transition temperature and low permeability.[11]

Spans are most widely used in the preparation of provesicles. Literature suggests that entrapment efficiency increases and it followed the trend Span 60 (C18) > Span 40 (C16) > Span 20 (C12) > Span 80 (C18). Spans 60 and 80 have the same head group, but difference lies in the alkyl chain of span 80 that is unsaturated. This might be the reason for the lower entrapment efficiency of the span 80 system.[12] Tween show slower penetration when compared to span formulation because; large size of vesicles and less lipophilic nature of tweens.

B. Cholesterol

Cholesterol is essential component of vesicles. Incorporation of cholesterol influences vesicle stability and permeability. Concentration of cholesterol plays an important role in entrapment of drug in vesicles. There are reports that entrapment efficiency increases with increasing cholesterol content but after certain limit further cholesterol increase results in significant decrease in entrapment efficiency. Reason revealed for this type of behavior is that cholesterol molecules accommodate itself as ‘‘vesicular cement’’ in the molecular cavities formed when surfactant monomers are assembled into bilayers to form niosomal membranes and this space filling action results in the increased rigidity, decreased permeability of cholesterol-containing membranes compared to cholesterol-free membranes and the improved entrapment efficiency. On further increase of cholesterol beyond certain concentration competes with the drug for the space within the bilayers, hence excluding the drug and can disrupt the regular linear structure of vesicular membranes.[13]

C. Solvents

Selection of alcohol is another important aspect as it greatly affects vesicle size and drug permeation rate. Literature revealed that as the solubility of alcohol in water increases the size increases and they follow the order.[11]

Ethanol > Propanol > Butanol > Iso-propanol

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It also effect the spontaneity of formation of niosomes, the formulations containing iso-propanol and butanol were formed more spontaneously than niosomes containing propanol and ethanol due to faster phase separation of iso-propanol and butanol due to their lower solubility in water.[14]

D. Aqueous Phase

Phosphate buffer (pH 7.4), 0.1% glycerol, hot water are generally used as aqueous phase in the preparation of proniosomal gels. Mokhtara et al. found that percentage encapsulation efficiency of flurbiprofen prepared by hydration of pro-niosomal gels of Span 60/cholesterol (9:1) was found to be greatly affected by the pH of the hydrating medium.

The fraction of flurbiprofen encapsulated was increased to about 1.5 times as the pH decreased from pH 8 to 5.5. The increase in the percentage encapsulation efficiency of flurbiprofen by decreasing the pH could be attributed to the presence of the ionisable carboxylic group in its chemical structure. Decreasing the pH could increase the proportions of the unionized species of flurbiprofen, which have higher partitioning to the bilayer lipid phase compared to the ionized species.[15] Reason suggested by Ammara et al. for such type of behavior is that the type of aqueous medium might influence the tactness of proniosomes, thus, affecting their entrapment efficiency.[16]

E. Total Lipid Concentration

The percentage encapsulation efficiency of flurbiprofen was increased as the lipid concentration was increased from 25 to 200mol/ml, respectively. The increase in percentage encapsulation efficiency of flurbiprofen as a function of total lipid concentration was linear.

On the other hand, the amount of flurbioprofen entrapped was decreased on increasing the lipid concentration from 25 to 200mol/ml, respectively. This leads to the fact that the fraction of lipid taking part in encapsulation decreases as the concentration of lipid increases.

F. Drug Concentration

The main factor in the consideration is the influence of an amphiphilic drug on vesicle formation. When drug was encapsulated in niosomes, aggregation occurred and was overcome by the addition of a steric stabilizer. When more drugs is added the increase in its encapsulation could be the result of saturation of the medium. This suggests that the solubility of certain poorly soluble drugs can be increased by formulation in niosomes but only up to a certain limit above which drug precipitation will occur. Increasing flurbiprofen concentration from 25 to 75mg/mmol lipids in the Pro-niosomes prepared from Span 60/cholesterol (9:1) showed an increase in both percentage encapsulation efficiency and the amount of drug encapsulated per mol total lipids upon hydration and formation of niosomes.

G. Charge of the Lipids

Incorporation of either dicetyl phosphate (DCP) which induces negative charge or stearylamine (SA) which induces positive charge decreased the percentage encapsulation efficiency of flurbiprofen into niosomal vesicles.

H. Hydration Medium

Phosphate buffer having various pH"s are most widely used hydration medium for preparation of proniosome derived niosomes. The solubility of drug being encapsulated determines the actual pH of hydration medium. The temperature of hydration also plays an important role in governing the self assembly of non-ionic surfactant into vesicles and affects their shape and size. In case of proniosomal gel preparation, the hydrating temperature used to make niosomes should usually be above the gel to liquid phase transition temperature of the system.[12,17,18] The proniosome derived niosomes are very similar to conventional niosomes and more uniform in size.

Types of Proniosomes

Depending on the method of preparation, the proniosomes exists in two forms;

A) Dry Granular Proniosome

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According to the type of carrier these are again divided as

a) Sorbitol based proniosomes

b) Maltodextrin based proniosomes

Sorbitol based proniosomes is a dry formulation that involves sorbitol as a carrier. These are made by spraying surfactants mixture prepared in organic solvent on to the sorbitol powder and then evaporating the solvent. It is useful in case where the active ingredient is susceptible to hydrolysis.

Maltodextrin based proniosomes prepared by slurry method. Maltodextrin is a polysaccharide easily soluble in water and it is used as carrier material in formulation. Since its morphology is preserved, hollow blown maltodextrin particles can be used for significant gain in surface area. The higher surface area results in thinner surfactant coating, which makes the rehydration process efficient. Time required for this process is independent of the ratio of surfactant solution.

B) Liquid Crystalline Proniosomes

When the surfactant molecule are kept in contact with water, there are three ways through which lipophilic chains of surfactant can be transformed into a disordered, liquid state called lyotropic liquid crystalline state. These three ways are

- Increasing temperature at kraft point (Tc),
- Addition of solvent which dissolve lipids,
- Use of both temperature and solvent.

The liquid crystalline proniosomes and proniosomal gel act as reservoir for transdermal delivery of drug.[19,20]

Method of Preparation of Proniosomes

A. Slurry Method

Proniosomes can be prepared by addition of the carrier and the entire surfactant solution in a round bottomed flask which is fitted to rotary flash evaporator and vacuum was applied to form a dry and free flowing powder. Finally, the formulation should be stored in tightly closed container under refrigeration in light. The time required for proniosome production is independent of the ratio of surfactant solution to carrier material and appears to be stable. This method is advantageous because due to uniform coating on carrier it protects the active ingredients and surfactants from hydrolysis and oxidation. Along with that the higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient.[19, 21]

Advantages

1. Maltodextrin is a polysaccharide simply soluble in water and it is used as carrier material in formulation, it was easily coat the maltodextrin particles by simply accumulation of surfactant in organic solvent to dry maltodextrin.[22]
2. Due to uniform coating on carrier it protects the active ingredients and surfactants from hydrolysis and oxidation etc.
3. The superior surface area results in a thinner surface coating, which makes the rehydration development more efficient.[15]

Disadvantages

1. Method is time consuming and involves specialized equipment with vaccum and nitrogen gas.
2. The thin film approach allows only for a predetermined lot sizes so material often wasted so minute quantities or small dose batch can be tedious one.

B. Slow Spray Coating Method

This method involves preparation of proniosomes by spraying surfactant in organic solvent onto the carrier and then evaporating the solvent. It is necessary to repeat the process until the desired surfactant loading has been achieved, because the carrier is soluble in the organic solvent.

The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves. The resulting niosomes have uniform size distribution similar to those produced by conventional methods. The main advantage of this method is to provide a means to formulate

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hydrophobic drugs in a lipid suspension with or without problem with instability of the suspension or susceptibility of active ingredient to hydrolysis. This method was reported to be tedious since the sorbitol carrier is soluble in the solvent used to deposit the surfactant. It is also found to interfere with the encapsulation of certain drugs.[19, 21]

Advantages

1. Simple method suitable for hydrophobic drug without concerns of instability or susceptibility of active pharmaceutical ingredient to hydrolysis.[23]

Disadvantages

1. If the coating of surfactant solution was applied too quickly, the sorbitol particles would degrade and sample becomes viscous slurry.[24]

2. Sorbitol is found to interfere with encapsulation efficiency of drug.

3. This method was reported to be tedious since the sorbitol carrier for formulating proniosomes is soluble in the solvent used to deposit the surfactant.[25]

C. Co-Acervation Phase Separation Method

Proniosomal gels can be prepared by this method which comprises of surfactant, lipid and drug in a wide mouthed glass vial along with small amount of alcohol in it.

The mixture is warmed over water bath at 60-70^0 C for 5min until the surfactant mixture is dissolved completely. Then the aqueous phase is added to the above vial and warmed still a clear solution is formed which is then converted into proniosomal gel on cooling.[19] After hydration of proniosomes they are converted to uniformly sized niosomes.

Advantages

1. Method is easy and without time consumable so it does essential specialized equipment.

2. Specially adopted for gel preparation.[26]

3. Little quantities or small dose formulation can be prepared on lab scale.

Characterization of Proniosomes

A. Vesicle Morphology

Vesicle morphology involves the measurement of size and shape of proniosomal vesicles. Size of proniosomal vesicles can be measured by dynamic light scattering method in two conditions: without agitation and with agitation. Hydration without agitation results in largest vesicle size.

B. Shape and Surface Morphology

Surface morphology means roundness, smoothness and formation of aggregation. It is studied by scanning electron microscopy, optical microscopy, transmission electron microscopy.[27]

C. Scanning Electron Microscopy

The proniosomes are sprinkled onto the double-sided tape that is to be affixed on aluminum stubs. The aluminum stub is placed in the vacuum chamber of a scanning electron microscope. The samples are observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 tor, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).[28]

D. Optical Microscopy

The niosomes are mounted on glass slides and viewed under a microscope with magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.[29]

E. Transmission Electron Microscopy

The morphology of hydrated niosome dispersion is determined using transmission electron microscopy. A drop of niosome dispersion is diluted 10-fold using deionized water. A drop of diluted niosome dispersion is applied to a carbon coated 300 mesh copper grid and is left for 1 min to allow some of the niosomes to adhere to the carbon substrate. The remaining dispersion is removed by adsorbing the drop with the corner of a piece of filter paper. After twice rinsing the grid (deionized water for 3-5 s) a drop of 2% aqueous solution of uranyl acetate is applied for

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1 s. The remaining solution is removed by absorbing the liquid with the tip of a piece of filter paper and the sample is air dried. The sample is observed at 80 kv.

F. Angle of Repose

The angle of repose of dry proniosomes powder is measured by a funnel method. The proniosomes powder is poured into a funnel which is fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.[30]

G. Rate of Hydration

Neubaur's chamber.

H. Drug Content

Drug can be quantified by a modified HPLC method or UV method.

I. Encapsulation Efficiency

The encapsulation efficiency of proniosomes is determined after separation of the unentrapped drug.

Separation of Unentrapped Drug is Done by the Following Techniques

(a) Dialysis

The aqueous niosomal dispersion is dialyzed tubing against suitable dissolution medium at room temperature then samples are withdrawn from the medium at suitable time interval centrifuged and analyzed for drug content using UV spectroscopy.[29]

(b) Gel filtration

The free drug is removed by gel filtration of niosomal dispersion through a sephadex G50 column and separated with suitable mobile phase and analyzed with analytical techniques.[30]

(c) Centrifugation

The niosomal suspension is centrifuged and the surfactant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug.[31]

Determination of Entrapment Efficiency of Proniosomes

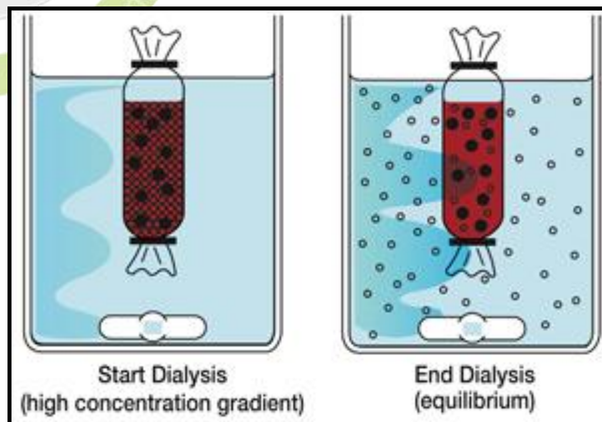
The vesicles obtained after removal of unentraped drug by dialysis is then resuspended in 30% v/v of PEG 200 and 1 ml of 0.1% v/v triton x-100 solution was added to solubilize vesicles the resulted clear solution is then filtered and analyzed for drug content. The percentage of drug entrapped is calculated by using the following formula[30]:

Percent Entrapment = Amount of drug entrapped/total × 100

J. In-Vitro Methods for Assessment of Drug Release from Proniosomes

(a) Dialysis Tubing

This apparatus has prewashed dialysis tubing, which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using suitable method (UV spectroscopy, HPLC etc.). The maintenance of sink condition is essential.[33]

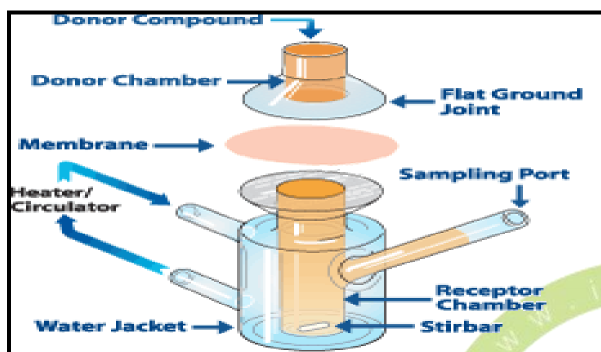


(b) Reverse Dialysis

In this technique a number of small dialysis tubes containing 1 ml of dissolution medium are placed. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method; however the rapid release cannot be quantified using this method.[33]

(c) Franz Diffusion Cell

The in-vitro studies can be performed by using Franz diffusion cell. Proniosomes are placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The proniosomes is then dialyzed against suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable method (UV spectroscopy, HPLC etc.). The maintenance of sink condition is essential.[34]



L. Zeta Potential Analysis

Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted proniosomes derived niosome dispersion is determined using zeta potential analyzer based on Electrophorectic light scattering and laser Doppler Velocimetery method. The temperature is set at 25°C. Charge on vesicles and their mean zeta potential values with standard deviation of 5 measurements are obtained directly from the measurement.[35]

M. Stability Studies

Stability studies are carried out by storing the prepared proniosomes at various temperature conditions like refrigeration (2°-8°C), room temperature (25°± 0.5°C) and elevated temperature (45°C ± 0.5°C) from a period of one month to three months. Drug content and variation in the average vesicle diameter are periodically monitored. ICH guidelines suggests stability studies for dry proniosomes powder meant for reconstitution should be studied for accelerated stability at 75% relative humidity as per international climatic zones and climatic conditions.[29,14,36]

Applications of Proneosomes[37]

A. Drug Targeting

One of the most useful aspects of proniosomes is their ability to target drugs. Proniosomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelium system (RES) preferentially takes up proniosomes vesicles. The uptake of proniosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosomes for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize the liver and spleen. This localization of the drugs can also be used for treating parasitic infections of the liver. Proniosomes can also be utilized for targeting drugs to organs other than the RES.

B. Anti-Neoplastic Treatment

Most antineoplastic drugs cause severe side effects. Proniosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs.

C. Treatment of Leishmaniasis

Leishmanasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Commonly prescribed drugs for the treatment are derivatives of antimony (antimonials), which in higher concentrations can cause cardiac, liver and kidney damage.

D. Delivery of Peptide Drugs

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of proniosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in-vitro study, oral delivery of a Vasopressin derivative entrapped in proniosomes showed that entrapment of the drug significantly increased the stability of the peptide.

E. Uses in Studying Immune Response

Proniosomes are used in studying immune response due to their immunological selectivity, low toxicity and greater stability. Proniosomes

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are being used to study the nature of the immune response provoked by antigens.

F. Niosomes as Carriers for Haemoglobin

Proniosomes can be used as carriers for haemoglobin within the blood. The proniosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anaemic patients.

G. Transdermal Drug Delivery Systems

One of the most useful aspects of proniosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing proniosomal technology is widely used in cosmetics; In fact, it was one of the first uses of the niosomes. Topical use of proniosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to un-entrapped drug. Recently, transdermal vaccines utilizing proniosomal technology is also being researched. The proniosome (along with liposomes and transferomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in proniosomes allows only a weak immune response, and thus more research to be done in this field.

H. Sustained Release

Sustained release action of proniosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via proniosomal encapsulation.

I. Localized Drug Action

Drug delivery through proniosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration.

Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects e.g. Antimonials encapsulated within proniosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity. The evolution of proniosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has promise in cancer chemotherapy and anti-leishmanial therapy.

J. Cosmetics or Cosmeceuticals

Proniosome gel can be used as-an effective delivery systems for cosmetics and Cosmeceuticals due to their unique properties. For applying therapeutic and cosmetic agents onto or through skin requires a non toxic, dermatologically acceptable carrier, which not only control the release of the agent for prolong action but also enhances the penetration to the skin layer. Proniosomes gel formulation shows advantages in controlled drug delivery improved bioavailability, reduced side effects and entrapment of both hydrophilic and hydrophobic drugs.

Table 2: Provesicular systems studied for transdermal applications

Sr. no.	Drug	Category	Carriers used	Result
1	Flubiprofen[38]	NSAIDS	Span(20,40,60, 80),absolute ethanol, cholesterol	The drug release rate from Cholesterol free proniosomes was found to be high.
2	Fursemide[36]	Antihypertensi ve	Span 40, lecithin	Enhanced bioavailability and skin permeation of drug.
3	Levonorgestr el[32]	Anti contraceptive	Span 40, alcohol, cholesterol, Lecithin	The study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrel for effective contraceptive.

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4	Estradiol[24]	Steroidal hormone	Span, tween, lecithin, cholesterol	The non ionic surfactants in proniosomal formulations help in increasing the drug permeation across the skin.
5	Ketorolac[39]	NSAIDS	Span 60, ethanol, cholesterol, lecithin	The drug entrapment was high within the lipid bilayers of vesicles.
6	Chlorphenira mine maleate[40]	Anti-histamine	Span 40, alcohol, cholesterol, lecithin	Span 40 proniosomes showed optimum stability, loading efficiency, particle size and suitable release kinetics for transdermal delivery of drug.
7	Losartan potassium[41]	Anti-hypertensive	Span(20,40,60,80), tween(20,40,60), cholesterol	Enhanced bioavailability and skin permeation of drug.
8	Captopril[14]	Anti-hypertensive	Surfactants, cholesterol, lecithin, alcohol	Prolonged release of captopril
9	Perindopril acetate[42]	Anti-hypertensive	Surfactants, cholesterol, lecithin, alcohol	Release of drug for the extended period of time.
10	Ibuprofen[43]	Antiarthritic	Maltodextrin,Cholesterol, HPMC , span-60	Drug release for extended period of time
11	Gugulipid[44]	potent hypolipidemic, antimicrobial, anthelmintic, anti-inflammatory, antiarthritic, antioxidant	Surfactants, cholesterol, lecithin, alcohol	Enhanced bioavailability and solubility
12	Picroxicam[45]	NSAIDS	Span 60, ethanol, cholesterol, lecithin	Span 60 based lecithin vesicle showed increased drug delivery from lipid vesicles
13	Celecoxib[46]	Cyclooxygenase inhibitor	Spans, cholesterol, lecithin, methanol, ethanol	Enhanced bioavailability of celecoxib

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14	Tenoxicam[47]	NSAIDS	Tween 20, spans, cholesterol, alcohol	Lecithin free proniosomal gel shows highest stability and entrapment efficiency.
15	Haloperidol[48]	Neuroleptic drug	Surfactants, alcohol, cholesterol	Incorporation of single surfactant can increase drug permeation across the skin as compare to mixture of surfactants.

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