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Review Article

A brief review on principle, preparation and properties of proniosomes: A provesicular drug delivery system

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ABSTRACT

This review paper is devoted to understand the concept, principle, preparation and properties of proniosomes, a provesicular drug delivery system. Broadly, a problem associated with traditional provesicular drug delivery system includes leaking, aggregation, vesicles sedimentation, fusion, sterilization and storage. Proniosomes are used to overcome the drawbacks associated with other vesicular drug delivery systems. It contains encapsulated drug, and shows a systemic and targeted delivery of poorly soluble drugs with increased bioavailability and decreased side effects. It is a water soluble pro-vesicular drug carrier which is coated noherefrn-ionic surfactant that upon hydration get converted niosoiomes. The present paper focuses on pros and cons of traditional vesicular drug delivery system and how proniosomes can overcome them. It describes the theory of structure, formation and mechanism of penetration and drug permeation there from.

Keywords: Provesicular; Proniosomes; In-vitro methods; Penetration; Drug permeation;

INTRODUCTION

There are many drug delivery systems available for the delivery of pharmaceutical drugs into the body. Depends on the biopharmaceutical class and problems associated with drugs, it has become necessary to develop suitable system for particular type of drugs. Over the last few years, many drug delivery systems such as tablets, mucoadhesive tablets, sustained released tablets, floating tablets, microemulsions, capsules, microcapsules, ethosomes, nanostructured hybrid vesicular system, proniosomal transdermal gels, jellies, etc have been investigated for delivery of various drugs [1-14]. Vesicular and pro-vesicular drug carriers are most efficient and approachable systems exhibits exceptional advantages such as over conventional dosage forms. These carriers may serve as reservoirs of a drug which are capable to deliver a therapeutic amount of drug to the targeted site in body. Poor solubility is a major physicochemical obstacle associated with many drugs and that can be overcome by developing a pro-vesicular drug delivery system. Novel drug delivery system plays important role to control the release of drug at a predetermined rate or by maintaining a relatively constant drug at the site of administration and presence of effective concentration of drug also

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reduces the undesirable side effects [15]. Encapsulation of a drug in the vesicles is one the best drug delivery system which helps to prolong drug duration in systemic circulation and decreases the toxicity by selective uptake.

TYPES OF VESICULAR DRUG DELIVERY SYSTEMS (VDDS)

Based on encapsulation technique, number of vesicular drug delivery systems have been developed. These are of following types [16-19].

Liposomes: These are vesicles made up of natural or synthetic phospholipid which enclose a wide variety of substances and drugs [20-22].

Niosomes: These are non-ionic surfactant-based liposomes having a bilayer which allows introduction of hydrophobic drugs in the non-polar region and the caging of hydrophilic drugs inside vesicles [22-25].

Virosomes: These are reconstituted viral coats consisting of unilamellar phospholipids membrane which allows the virosomes to fuse with target cells [26-27].

Transferosomes: These are ultra deformable vesicles designed for delivering higher concentrations of active substances to reach intact deeper regions of the skin after topical application thus suitable for controlled and potentially targeted drug delivery [28-29].

Proteasomes: These are protein complexes and are part of different mechanisms by which cells regulate the concentration of particular proteins and degrade misfold proteins because of the presence of ubiquitin conjugated to the targeted protein's lysine residue [30].

Sphingosomes: These are lipid vesicular drug delivery system mainly composed of sphingolipid and cholesterol. They are clinically used vesicles for chemotherapeutic agent, biological macromolecule and for diagnostics purpose [31-32].

Archaesome: These are liposomal vesicles made from several combinations of lipids that are bacterial ether lipids that include archaea. These lipids are unique and distinct in structure from the ester lipids found in Eukaryote and Bacteria [21].

Ethosomes: These are ethanolic liposomes. These are non-invasive delivery carriers that enable drugs to reach deep into the skin layers or the systemic circulation than conventional liposomes [33-34].

Disadvantages of vesicular drug delivery systems

Apart from above discussed advantages, these systems posses some of the following disadvantages [18-19].

- Short half-life of the dispersion and sedimentation.
- Aggregation, leakage, fusion and sedimentation problem.
- Production cost is high.
- Low solubility.
- Degradation by hydrolysis or oxidation.
- Physical and chemical stability issues at different pH.

To overcome the disadvantages associated with liposomes, niosomes and other vesicular drug delivery systems stipulated above, a proniosomal drug delivery system is one of the best and stable pro-vesicular drug delivery system. Proniosomes is latest approach in a field of novel drug delivery system. These are water soluble carrier particles coated with surfactant and can be hydrated by brief agitation in water to form niosomal dispersion [35-37]. They have capacity to entrap both hydrophilic and lipophilic drugs as it is bilayered compound as shown in (Fig. 1). Proniosomes are versatile vesicular drug delivery system due to ease of distribution, measuring capacity, transfer and have stability during the storage and sterilization. These are prepared by techniques such as coacervation phase separation, slurry method and spray drying [38]

Newer VDDS- Proniosomes: These are dry formulation of water soluble carrier particles coated with surfactants which upon rehydration get converted into niosomes. The system is capable of topical and systemic delivery of poorly soluble drugs [39-40].

ADVANTAGES OF PRONIOSOMES

Proniosomes have following important advantages [41].

- Low-cost materials are generally needed for formulation of proniosomes.
- Proniosomes eliminates physical stability problems such as aggregation, leaking of entrapped drug during long term storage, sedimentation and fusion associated with other vesicles on storage.
- They avoid the problems associated with chemical stability like hydrolysis of encapsulated drugs which limits the shelf life of the dispersion.
- Because of hydrophilic, amphiphilic and lipophilic infrastructure of proniosomes, they can easily accommodate drug molecules with a wide range of solubilities.

- They protect the drug from biological environment and restrict effects to target cells. Also improve the therapeutic performance of the drug molecules by delayed clearance from the circulation.
- The vesicles can be designed to release drug in controlled manner.
- They are osmotically active and also they increase the stability of entrapped drug.
- The non-ionic surfactants used for preparation of proniosomes are biodegradable, biocompatible and non-immunogenic.
- They enhance skin penetration of drugs and also improve oral bioavailability of poorly absorbed drugs.
- Sustained and controlled release of drugs can be achieved by using proniosomal formulation due to its depot pattern.
- They can be designed to reach the site of action by different routes like oral, parentral as well as topical and other site.
- Proniosomal carriers are useful to maintain therapeutic levels of drugs for a longer time, decrease frequency of administration and improve patient compliance.
- It does not require special conditions for handling and storage of surfactants.
- The shape, size, composition, and fluidity of proniosomes can be controlled when required.
- It shows uniformity of dose, minimum side effects and scale-up.

STRUCTURE OF PRONIOSOMES

Proniosomes is a microscopic bilayer, lamellar structured vesicle which is made up from non-ionic surface-active agents, cholesterol along with hydration by aqueous media [42]. The hydrophilic polar head of non-ionic surfactant is exposed to outside while the hydrophobic tail present inside to the opposite direction to form the bilayer structure shown in Fig. 1. Hence the proniosomes can easily hold both hydrophilic as well as hydrophobic drugs. The formation of unilamellar or multilamellar structure of proniosomes as a carrier is depends on the method of preparation [43].

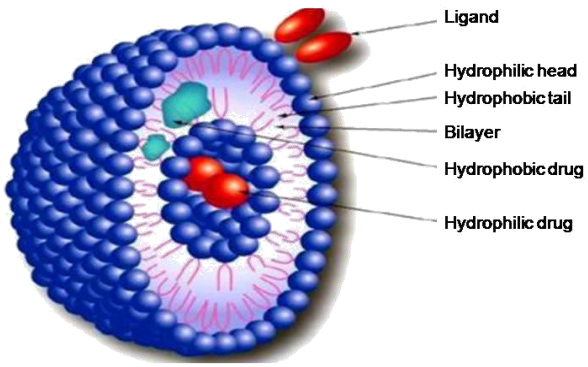

Fig. 1. Structure of proniosome [16].

STRUCTURE OF PRONIOSOMAL GEL

Proniosomal gel is the transparent, translucent or semisolid mass of proniosomes which shows the liquid crystalline phases of proniosomes in (Fig. 2).

(1) Hexagonal phase: In this compact cylindrical rods are arranged in hexagonal fashion.
(2) Lamellar phase: It shows sheets of surfactants arranged in bilayer form.
(3) Cubic phase: It consists of curved continuous lipid bilayer extending to three dimensions because of presence of limited solvent in it (Fig. 2) [35].

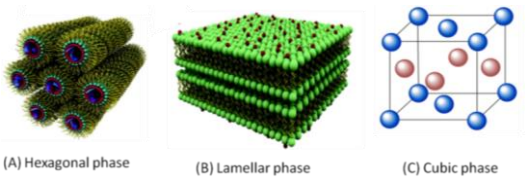

Fig. 2. Structure of liquid crystalline phases of proniosome.

FORMATION OF NIOSOMES FROM PRONIOSOMES

The proniosomes can be converted to niosomes with addition of the solvents like water or saline solution and drug with brief agitation at greater than the mean transition phase temperature of the surfactants (Fig. 3) [40-44].

$$T > Tm$$

Where, T = Temperature and Tm = Mean phase transition temperature.

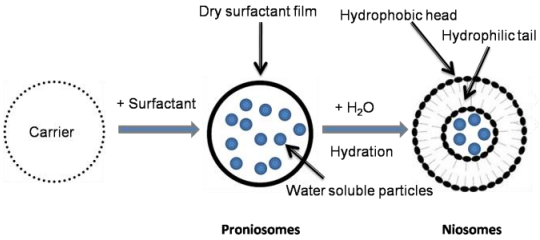

Fig. 3. Formation of niosomes from proniosomes [40].

MECHANISM OF VESICLE FORMATION IN PRONIOSOMES

Vesicle formation in proniosomes depends on the ability of non-ionic surfactant to form bilayer vesicles instead of micelles which depends on the following three parameters:

- Hydrophilic-lipophilic balance (HLB) values of the surfactant.
- Chemical structure of the components.
- Critical packing parameter (CPP).

Proniosomes have a tendency to form vesicles which are similar to niosomes. Critical packing parameter (CPP) can be defined as the relationship between the structure of surfactant including the size of hydrophilic head group and length of

hydrophobic alkyl radical chain is the ability to create vesicles. When the value of CPP is between 0.5 and 1, it indicates that the surfactant is likely to form vesicles. A CPP of value below 0.5 is said to give spherical micelles and a CPP of value above 1 should produce inverted micelles which on later stages give precipitation. Fundamentally, all spans have the same head group but different alkyl chain. As per study on vesicles, the entrapment efficiency of formulation increases with increase in alkyl chain length as follows:

Span 60(C18) > Span40(C16) > Span 20(C12) > Span 80(C18).

Spans 60 and 80 have the same head group, but differ in the alkyl chain ie; Span 80 have unsaturated alkyl chain.

MECHANISM OF DRUG PERMEATION FROM PRONIOSOMES THROUGH SKIN

Mechanism of drug transport through vesicles has rendered conflicting results. Proniosomes should be transformed into niosomes when come in contact with moisture present on the skin before the drug is released and permeates across the skin [45]. The lipophilic drugs get penetrate across it when vesicles come in contact with stratum corneum it aggregate, fuse and adhere to the surface of cell [46] as shown in (Fig. 4). There are several skin penetration mechanisms of vascular drug delivery systems. The topically applied molecule must first pass through the skin layers from SC and viable epidermis and dermis. Some of them may pass through the skin intact due to use of surfactants as penetration enhancers to penetrate the skin, as proniosomes and niosomes [37]. This can happen by one of three possible paths these are-

(i) The path of appendages,
(ii) Through the hair follicles,
(iii) Sweat glands.

The bilayer present in the vesicles which contains surfactants and phospholipids can act as a penetration enhancer and increases permeation power of many drugs. It also shows effect on vesicles to decrease stratum corneum barrier properties. Another possible mechanism is modifications in the structure of stratum corneum for the permeation of vesicle-encapsulated drugs [47].

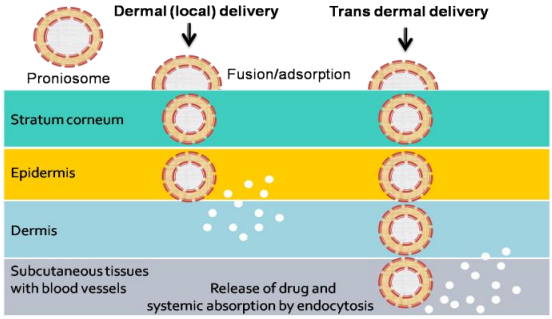

Fig 4: Mechanism of drug permeation of proniosomes

TYPES OF PRONIOSOMES

According to method of preparation of proniosomes are of two types:

Liquid crystalline proniosomes: When surfactant molecules come in contact with water in which lipophilic chains of surfactants are being transformed into hydrophilic liquid crystalline state and these types of proniosomes are mainly used for transdermal drug delivery. There are three methods by which the lipophilic chains of surfactants can be transformed into liquid crystalline state [39,42]. These methods are,

(i) Addition of solvents to dissolve the lipid
(ii) Increasing temperature at Kraft's point to forms lamellar liquid crystals.
(iii) Using both temperature and solvents.

Dry granular proniosomes: Dry granular proniosomes are dry powder in nature which involves the coating of water soluble carrier such as sorbitol and maltodextrin with surfactant resulting in the formation of a dry formulation in which each water soluble particle is covered with a thin film of surfactant. Based upon the carrier that is used in the preparation they are classify as follows [48-49].

1. ***Sorbitol based proniosomes*:** The sorbitol based proniosomes in which sorbitol is use as a carrier and are mainly prepared by spraying mixture of non-ionic surfactant and organic solvent onto the sorbitol powder and then evaporating the solvent to form dry formulations. Since the surfactant coating into the carrier is very thin which is achieved by repeated processing and hydration of this coating allows the mutilamellar vesicles to forms as the carrier dissolves. This is useful in case where active ingredient is susceptible to hydrolysis [50-51].

2. Maltodextrin based proniosomes: Maltodextrin is a carrier material in formulation of maltodextrin based proniosomes. They are polysaccharides easily soluble in water and are prepared by fast slurry method. It has potential application in delivery of hydrophilic or amphiphilic drugs. The formulations of maltodextrin based proniosomes are better to have hollow particle with high surface area results in thinner surfactant coating which is suitable for rehydration process [52-55].

COMPONENTS OF PRONIOSOMES

Proniosomes consist of various ingredients like non-ionic surfactants formed as lamellar vesicles, cholesterol membrane stabilizer, solvent, other components may be added to improve properties of the proniosomes as described below.

Surfactants: These are the surface active agents. These are the main structural components of proniosomes occur amphiphilic in nature and are

used to prepare vesicles due to many benefits with respect to stability, compatibility, and toxicity, compared to their anionic, amphoteric, or cationic counterparts [56-57]. Non-ionic surfactants possess high interfacial activity as well as polar and nonpolar segments. They are generally less toxic, less irritating to cellular surfaces and tend to maintain near physiological ph in solution. Also they act as wetting agents, solubilizers, emulsifiers, and permeability enhancers. They are also strong p-glycoprotein inhibitors. Different types of surfactant are available as shown in Table 1.

Table 1: Non-ionic surfactants used in preparation of proniosomes with their properties [16,25]

Sr.No.	***Surfactant***	***Synonyms***	***Properties***
1.	*Sorbitan monolaurate*	*Span 20,* *Sorbitan mono dodecanoate*	*Tc: 16°C* *Density: 1.032 g/mL at 25°C (L)* *Flash point: >230°F* *HLB value: 8.6*
2.	*Sorbitan monopalmitate*	*Span 40*	*Tc: 42°C* *Flash point: 113°C* *Melting point: 46-47°C* *HLB value: 6.7*
3.	*Sorbitan monostearate sorbitan*	*Span 60,* *monooctadecanoate*	*Tc: 53°C* *Flash point: >110°C* *Melting point: 54-57°C* *HLB value: 4.7*
4.	*Sorbitan monooleate*	*Span 80,* *sorbitan* *(Z)-mono-9-octadecenoate*	*Tc: −12°C* *Flash point: >110°C* *Density: 0.986* *HLB value: 4.3*
5.	*Polyoxyethylene sorbitan monolaurate*	*Tween 20*	*Density: 1.106* *Aq. solubility: 100 g/L* *Boiling point: 100°C* *HLB value: 16.7*
6.	*Polyoxyethylene sorbitan monopalmitate*	*Tween 40*	*Density: 1.05* *Aq. solubility: 100 g/L* *Boiling point: 0.1°C* *HLB value: 15.6*
7.	*Polyoxyethylene sorbitan monostearate*	*Tween 60*	*Density: 1.081* *Aq. solubility: 100 g/L* *HLB value: 14.9*
8.	*Polyoxyethylene sorbitan monooleate*	*Tween 80*	*Density: 1.064* *Aq. solubility: 5-10 g/100 mL at 23°C* *Flash point: >110°C* *HLB value: 15.0*

*Tc- Phase transition temperature, HLB- Hydrophilic Lipophilic Balance, Aq.-Aqueous

Selection of a surfactant for bilayer formation of vesicle in proniosomes depends on HLB value of the surfactant, the chemical structure of the components, and the CPP value of surfactant [58].

(i) HLB value: The HLB value of a surfactant is important to control the drug entrapment of the vesicle. HLB value in between 4 and 8 was reported to be compatible with vesicles formation by proniosomes. A suitable HLB value of surfactant is 8.6 offers vesicles with the highest entrapment efficiency. Entrapment efficiency is depend on HLB value, if EE decreases the HLB value also decreases from 8.6 to 1.7. Due to larger size of vesicles and less lipophilic nature of tween The encapsulation efficiency of tween is relatively low as compared to span [57]. Spans have high phase transition temperature, hence are selected for vesicle formulation due to good encapsulation efficiency, less leakage of drug [59].

(ii) Critical packing parameter (CPP): The type of vesicles formed can depend on the basis of the CPP of a surfactant and the entrapment efficiency with stearyl (C18) chains show higher than those with lauryl (C12) chains [59-60].

(iii) Phase transition temperature: It is important for degree of drug 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 and vice versa [61].

Cholesterol: Cholesterol is a naturally occurring steroidal component of proniosomal vesicle used as

membrane stabilizer. It enhances the stability of vesicles and prevents aggregation by the inclusion of molecules due to repulsive steric or electrostatic effects. It is an essential component functioning as the "vesicular cement" of the surfactant monomers when they are assembled into the bilayer of the niosomal membrane. An increase in the concentration of cholesterol there is a significant increase in entrapment efficiency, but increase in concentration of cholesterol the effect will saturates. Then, any further cholesterol added shows decrease in the entrapment efficiency due to the competition between cholesterol and drugs to fill the bilayer [62-65].

Due to rigid steroid ring cholesterol provides rigidity to the proniosomal bilayer and makes it stable also enhances the entrapment efficiency of proniosomes. An increasing cholesterol content in the ratio of cholesterol: lecithin: sucrose laurate from 10:180:180 to 20:180:180 significantly increased entrapment efficiency from 74.25% to 85.37%. However, a further increase to 30:180:180 ratio significantly decreased entrapment efficiency to 79.91% due excessive increase in ratio of component [66].

Lecithin: Lecithin is a phospholipid and acts as a membrane stabilizer in the formulation of proniosomes. Lecithin composed from acetone insoluble phosphatides which consist of phosphatidylcholine, phosphatidyl ethanolamine combined with other substances like triglycerides, fatty acids, and carbohydrates. Lecithin is one type of phosphatidylcholine obtained from source of origin, named as soya lecithin which is from soya beans, and egg lecithin, which is from egg yolk [67-69]. It plays a number of important roles in vesicular drug delivery such as,

(i) It acts as permeation enhancers.
(ii) Prevents the leakage of drug from vesicles.
(iii) Lecithin increases entrapment efficiency due to high phase transition temperature.
(iv) It leads to form smaller size vesicles due to increase in hydrophobicity.
(v) Penetration capability of soya lecithin is a better as it contains the saturated fatty acid.
(vi) Lecithin provides stability, but to a lesser extent as compared to cholesterol [70].

Solvent: Alcohol shows its great influence on vesicle size and permeability of the drug. Vesicles formed from different alcohols have different size. Solvent like alcohol can act as penetration enhancer. It also affects the spontaneity of the formation of niosomes from proniosomes. Ethanol gives the greater size of vesicle due to high aqueous solubility and lowest size is due to branched chain present in it [71-73].
The major influence of vesicle size and the rate of permeation depends on the type of alcohol used in formulation: Ethanol >Propanol >Butanol >Isopropanol. Ethanol may cause the reduction of lipid polar head interactions within the membrane, thereby increasing the permeation through skin [39,74].

Aqueous phase: Phosphate buffer pH 7.4, glycerol 0.1%, and distilled water are mainly used in the aqueous phase in preparation proniosomes. pH of the hydrating medium also play an important role in entrapment efficiency and particle size of proniosomes [53,75]. According to literature, it was found that the pH of the hydrating medium shows variation in entrapment efficiency. As the pH decreased from pH 8 to 5.5 there is an increase in the fraction of drug encapsulated [75-77].

Carriers: The carriers play effective role in the preparation of proniosomes to carry the drugs. The carriers should be stable, non-toxic, free flowing, have poor solubility in the loaded mixture solution, but good solubility in water for ease of hydration and it increases the surface area, and enhance drug loading capacity. Coating with sorbitol, glucose or lactose monohydrate is quite difficult but, which upon application brings about viscous slurry samples. On other side maltodextrin provides a flexible ratio between surfactants and other incorporated components, therefore, it is used as an effective carrier in proniosomes [54,62]. There are few examples of carriers used for formulation of proniosomes these are enlisted below in Table 2.

Table 2: Carriers used for preparation of proniosomes [78]

Sr.No.	***Carrier used***
1.	*Maltodextrin*
2.	*Mannitol*
3.	*Sorbitol*
4.	*Sprayed lactose*
5.	*Glucose monohydrate*
6.	*Lactose monohydrate*
7.	*Sucrose stearate*

Miscellaneous components: There are some other components that can be used in the preparation of proniosomes.

1. *Dicetyl Phosphate (DCP):* It imparts negative charge to the vesicles containing bilayer. It is reported that drug release was maximum for the proniosomes containing DCP due to charge present in the DCP containing bilayer, which is responsible for an increase in the curvature and decrease vesicle size [73].

2. *Stearylamine (SA):* This imparts a positive charge to the vesicle. SA decreases the entrapment efficiency of vesicle [62,79].
3. *Solulan:* Solulan C24 a poly-24 oxyethylene cholesteryl ether, is added to formulations to give homogeneous nature and devoid of aggregates [80].

Oleic acid: It may provide negative charge to the vesicles, and reduces both zeta potential and particle size [45,81].

Drug: The drug selection criteria should be based on the following characteristics-

(i) Low aqueous solubility of drugs.
(ii) High dosage frequency of drugs.
(iii) Controlled drug delivery of suitable drugs.
(iv) Short half life.
(v) Drugs having higher adverse drug reactions [42,54].

Some examples of drug with proniosomal carrier formulations are shown below in Table 3.

Table 3: Proniosomes as carrier of various drug molecules

Drug	Category	Method of preparation	Purpose/reason	Ref.
Ritonavir	Anti-viral, HIV treatment	Modified coacervation method	To improve stability of formulation and sustain release of drug	35
Risperidone	Anti-psychotic drug	Coacervation phase separation method	To increase bioavailability because it has low systemic absorption (orally)	58
Carvedilol	Anti-hypertensive (b-blocker)	Coacervation phase separation method	To improve entrapment efficiency and bioavailability	80
Ofloxacin	Anti-biotic (broad spectrum)	Slurry method	To enhance sustain release of drug	87
Tolnaftate	Antifungal	Coacervation phase separation method	To increase duration of action &improve systemic absorption	91
Celecoxib	Anti-inflammatory, analgesic, anti- pyretic	Modified coacervation method	To reduce 1st pass metabolism and enhance bioavailability	92
Isoniazid	Anti-tubercular drug. Anti-bacterial	Coacervation phase separation method	To improve therapeutic efficacy .and reduces side effects	93
Olmesartan medoximil	Anti-hypertensive	Slurry method	To enhance the bioavailability due to their poor water solubility orally (26%)	94
Glimepiride	Hypo-glycemic activity	Coacervation phase separation method	To improve its therapeutic efficacy	95
Cefuroxime axetil	Anti-biotic (2nd generation)	Slurry method	To enhance bioavailability	96
Clotrimazole	Anti-fungal (Imidazole)	Coacervation phase separation method	To enhance solubility	97
Acyclovir	Anti-viral	Coacervation phase separation method	To facilitate sustain release of drug and improve bioavailability	98
Lovastatin	Hyper cholesterolemia	Coacervation phase separation method	To reduce risk of cardiovascular diseases	99
Irinotecan	Anti-cancer drug	Slurry method	To treat colon cancer and reduces severe adverse effect	100
Bromocriptine	Anti-parkinsonism	Coacervation phase separation method	To treat pituitary tumour, infertility, menstrual disorder	101
Candesartan cilexetil	Anti-hypertensive	Slurry method	Improve oral bioavailability	102

METHODS OF PREPARATION OF PRONIOSOMES

Proniosomes are prepared from many ingredients like non-ionic surfactants, coating material, carriers, membrane stabilizer, solvent and are prepared by following methods [82-83].

1. Coacervation phase separation method
2. Modified coacervation
3. Handshaking method
4. Slurry method
5. Slow spray coating method

Schematic representation of method of preparation of proniosomes is shown in Fig. 5.

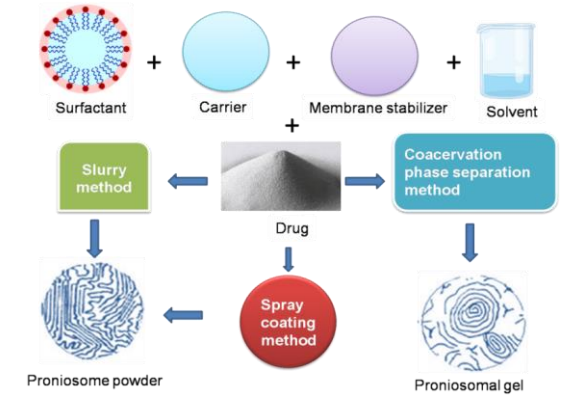

Fig. 5. Materials and method used for preparation of proniosomes [35]

Coacervation phase separation (CPS) method: This method is mainly used for preparation of proniosomal gel. In this method cholesterol, surfactant, phosphatidyl choline, drug and suitable alcohol are added to avoid micelle formation in a wide-mouthed glass vial. All the ingredients are mixed thoroughly with the help of glass rod and then covered the mouth of vial with a lid to prevent the loss of solvent. Warmed at 60-70°C on water bath until all ingredients dissolved completely. After this hydrate it with limited amount of aqueous phase (Dil. glycerol solution, phosphate buffer, isotonic buffer solution, or saline solution) and continue the heating for a few minutes on water bath to form clear solution, which on cooling converts into a transparent and translucent solution or white creamy proniosomal gel (Fig. 6). Niosomes are formed by hydrating the proniosomal gel with a little amount of aqueous medium [37-39].

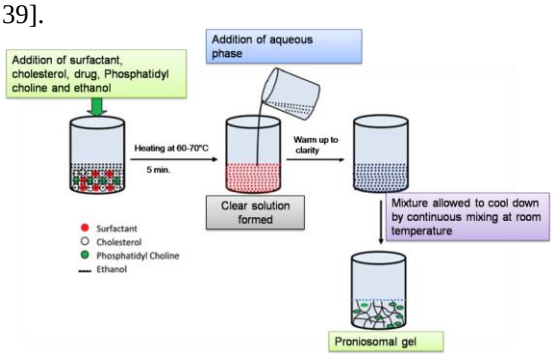

Fig. 6. Coacervation phase separation method [39].

Advantages CPS method [49,85]

- *(i)* Specialized method for preparation of gel.
- *(ii)* Specialized instrument is not required.
- *(iii)* Easy to prepare little quantity or small dose formulation on lab scale.
- *(iv)* Easy and time saving method.

Modified coacervation: In this method mix drug, cholesterol, lecithin, and surfactant with solvent in a wide mouth glass tube. Covered open-end of the glass vial with a lid and warmed it in a water bath at 65±3°C for 5 min. Then ad pH 7.4 phosphate buffers in it and heated mixture for 2 min in the water bath until the clear solution obtained. After this the mixture was allowed to cool at room temperature until the dispersion will be converted to proniosomal gel [15,86].

Handshaking method: In this method the vesicles forming ingredients such as cholesterol and surfactants are dissolved in organic solvent like methanol or chloroform in a round bottom flask. The solvent get evaporates at room temperature in the rotary evaporator and deposited a thin layer of solid mixture on the walls of the round bottomed flask. Multi-lamellar niosomes can be formed by rehydration of surfactant film with the aqueous phase at 0-60°C with little agitation [53].

Slurry method: In Slurry method, proniosomes can be prepared by addition of weighed quantity of surfactants and cholesterol in suitable solvent. The resultant solution was transferred into a round bottom flask which is fitted to a rotary flask evaporator at 50-60 rpm under reduced pressure of 600 mmHg at a temperature of 45 ± 20^0C containing drug and maltodextrin or lecithin. Then vacuum is applied to form a dry and free-flowing powder. If additional surfactant solution can be added it form slurry. The flask was removed from the evaporator and kept under vacuum overnight [63]. Proniosomal dry powder is formed as shown below in Fig. 7(c). These proniosomes dry powder mixed with a suitable gelling agent to get the proniosomal gel [88-89] (Fig. 7).

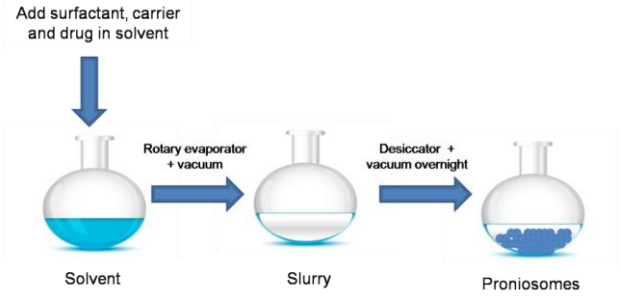

Fig. 7. Slurry method [26].

Advantages of slurry method

- *(i)* It protects the active ingredients and surfactants from hydrolysis and oxidation.
- *(ii)* The higher surface area form thinner surfactant coating makes the rehydration process more efficient.
- *(iii)* Carrier material is easily to coat the carrier particles by simply adding surfactant in organic solvents to dry carrier particles [39].

Disadvantages of slurry method

(i) The method is time-consuming.
(ii) This process required specialized equipment with vacuum and nitrogen gas.
(iii) Preparation of small dose batch can be tedious one [39].

Slow spray coating method: In slow spray coating method, proniosomes are prepared by spraying surfactant and drug in organic solvents onto the carrier and then evaporating the remaining solvent for preparation of proniosomes. Attached a 100 ml round bottom flask containing desired amount of combination of surfactants, cholesterol, and diacetyl phosphate as a carrier material to the rotary evaporator and then spray sequential aliquots onto carrier's surface at a controlled rate of application [75]. By continuous spraying of aliquots onto the carrier's the flask has to be transferred to a water bath of 65-70°C for 15-20 min in water bath. Continue the same evaporation process till to get free-flowing proniosomal powder. Rotates the flask after the addition of the final aliquots under vacuum until powder becomes completely dry. Repeat the process until the surfactant loading reaches to desired level. Then get very thin surfactant coating carrier and hydration of this coating allows carrier dissolves.

The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar structure of vesicles to form as the carrier dissolves. The material is further dried in a desiccators under vacuum overnight. It gives a dry, free flowing proniosomal powder (Fig. 8) [39].

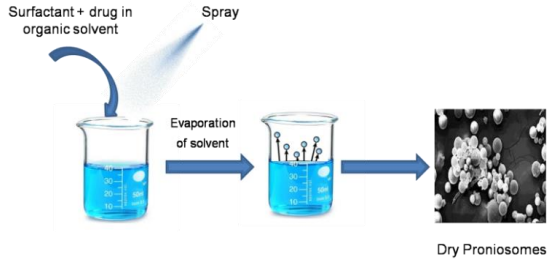

Fig. 8. Slow spray coating method

Advantages of slow spray coating method

(i) This is simple method
(ii) Suitable for hydrophobic drug [86].

Disadvantages of slow spray coating method

(i) If the coating of surfactant solution was applied too fast, the sorbitol particles would degrade and sample form viscous slurry.
(ii) This method was time consuming since the sorbitol carrier for formulating proniosomes is soluble in the solvent used to deposit the surfactant.
(iii) Carrier may interfere with the encapsulation efficiency of the drug [87].

FORMULATION CONSIDERATIONS

It is very important to understand the role of basic components of proniosomes before formulation. There are some factors which may affect significantly the physical nature of proniosomes [62-64].

Selection of surfactant: Selection of surfactants should be depend on the basis of HLB value. Mainly non-ionic surfactant and HLB value is good indicator of the vesicle forming ability of surfactant and it can improve the solubility of some poorly soluble drugs. It plays a key role in controlling drug entrapment into the vesicle it forms and also having good stability, compatibility and toxicity aspects. The formation of bilayer vesicles instead of micelles formation is also depends upon the chemical structure of component, the critical packing parameter and the phase transition temperature (Tc) of the surfactant [53,62,100].

Cholesterol concentration: Cholesterol stabilizes cell membrane and is required for the cell membrane permeability and fluidity, rigidity and also % encapsulation efficiency. Cholesterol along with the addition of surfactant forms homogenous niosome thus it usually included in a 1:1 molar ratio in most formulations as it is known to abolish the gel to fluid phase formation of niosome systems resulting in niosomes that are less leaky. The amount of cholesterol for formation of stable vesicle to be added depends on the HLB value of the surfactants [45-47].

Hydration medium: Phosphate buffer having various pH are mostly used hydration medium for preparation of proniosomes. The temperature of hydration 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 [102]. The proniosomes derived niosomes are very similar to conventional niosomes and more uniform in size (Fig. 9).

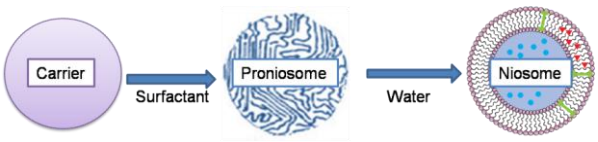

Fig. 9. Formation of niosome from proniosome

Nature of encapsulated drug: The main factor in the consideration of proniosomal formulation is the influence of an amphiphilic nature of drug on vesicle formation. When drug was encapsulated in

niosomes, aggregation occurred and it overcome by the addition of a steric stabilizer [60]. This suggests that the solubility of some poorly soluble drugs can be increased by formulation of niosomes but only up to a certain limit above which drug precipitation may occur, so the formulation of proniosomes is an advanced drug delivery which stabilises the vesicles. Increase in drug concentration showed an increase in both percentage encapsulation efficiency and the amount of drug encapsulated per mole total lipids upon hydration and formation of niosomes [62,102].

FUTURE SCOPE

Studies on proniosomal formulations reveal that it has become a useful dosage form for drug permeation into the skin and other route, particularly due to their simple, manufacturing process and capacity to modulate drug delivery across the skin. In cosmetic formulation and transdermal delivery, the use of proniosomes may lead to sustained operation, increased absorption, along with many applications. There is a great need for exploring the proniosomal vesicular delivery systems for cosmetics, herbal actives, nutraceuticals and other synthetic formulations.

CONCLUSION

Proniosomes are an efficient and promising drug carrier acquiring a lot of interest due to its controlled and sustained release action with enhanced physical and chemical stability, good bioavailability of poorly soluble drugs, reduced drug toxic effects compare to other vesicular drug delivery systems. They do not required special conditions for their handling, protection, storage and industrial manufacturing. With different structural characteristics, they can be prepared and configured for specific routes of administration. Transdermal delivery of drugs is very efficient by this system due to decreased toxicity and penetration enhancing effect of surfactants in the field of cosmetics, nutraceuticals, targeting, ophthalmic, topical, parenteral, vaccine, etc. This carrier mechanism has enormous opportunities in dermatology for the treatment of skin disorders such as melanoma, psoriasis, bacterial and fungal infections. Thus, it concludes that proniosomal vesicular system is very effective for delivering drugs and also for targeting numerous therapeutically active drug molecules. They provide better potential treatment than conventional drug delivery systems. More clinic trials and studies should be carried out in this field to know the precise potential of this novel drug delivery system to reap its unparallel benefits.

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