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UNLOCKING SKIN'S POTENTIAL: UTILIZE PRONIOSOMAL GEL FOR OPTIMAL DELIVERY

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ABSTRACT

Proniosomal gel is a novel drug delivery system that holds promising potential for enhancing the therapeutic efficacy of various pharmaceutical compounds. This review provides a comprehensive overview of the formulation, and applications of proniosomal gel in the field of pharmaceutical sciences. The paper begins by elucidating the concept of proniosomes, its types proniosomes in drug delivery and targeting and components of proniosomes. Also explaining about gels and its types has been explained such as Hydrogels, Organogels, Emulgels, Aerogels and xerogels, Bigels or bi (phasic) gels and proniosomal gels. The formulation strategies for proniosomal gel, including the selection of surfactants, lipids, and incorporation of active pharmaceutical ingredients (APIs), are discussed in detail. Method for the preparation of proniosomal gel are coacervation–phase separation technique''. Furthermore, the review explores the advantages and limitations of proniosomal gel in drug delivery.

INTRODUCTION

Proniosomes are a unique vesicular mechanism for topical and transdermal medication delivery.[1] Proniosomes address a number of drawbacks related to traditional dosage forms, namely issues with physical stability such leakage, fusing, and aggregation.[2] Proniosomes increase the therapeutic effects, lessen or eliminate side effects, and increase the efficacy of medications.[3] Proniosomes are utilized to avoid the unintended side effects of oral administration, first-pass hepatic metabolism, and gastrointestinal tract (GIT) incompatibility.

Proniosomes also lessen the need for frequent drug delivery, increase patient compliance, and prolong the duration of therapeutic drug levels.[4,5] The non-ionic bilayer structure of

proniosomes is composed of a hydrophobic outer layer and a hydrophilic interior layer. Niosomes that have lost moisture are called proniosomes. When proniosomes are applied to the skin, they are transformed into niosomes by the in-situ absorption of water. They then engage with the SC by strong hydrogen bonding, loosening and reversibly perturbing the extremely dense structure of lipid lamellae matrix and increasing the skin's permeability and fluidity. In contrast to other vesicular carrier systems, proniosomes exhibit greater stability.[6]

The proniosome is a potential product that is a dry granule that, when water is added, dissolves to generate niosome suspension. Proniosomes provide a number of benefits over niosomes, one of which is the reduction of physical instability issues such drug encapsulation aggregation, fusion, leakage, and hydrolysis. Furthermore, it facilitates transportation, distribution, storage, and dosage.[7] Comparing proniosomes to regular niosomes, they have demonstrated drug release performance that is either equivalent to or superior than the former. Proniosomes typically contain lecithin, alcohol (ethanol, methanol, isopropyl alcohol), and chloroform, as well as a variety of non-ionic surfactants such as span 20, 40, 60, 80, and 85, tween 20, 40, 60, and 80. The majority of surfactants have minimal aqueous solubility when employed to create non-ionic surfactant vesicles. But in the presence of cholesterol, readily soluble non-ionic surfactants like tween can form the micelles upon hydration.[8]

a) One possible effect of cholesterol concentration on the stability and permeability of vesicles is on proniosomal formulations.
b) When compared to formulations that solely contain lecithin, formulations that add cholesterol enhance the entrapment efficiency of medications.
c) The formulation of lecithin necessitates particular handling during preparation and storage, which reduces product stability and increases cost.

Advantage of Proniosome

1. Preventing issues with physical stability such as leakage during storage, fusion, aggregation, and sedimentation.[9]
2. Preventing medication encapsulation from hydrolysing, which would shorten the dispersion's shelf life.[9]
3. Simple handling and storage.[9]
4. Easy scaling up, homogeneous dose storage, transportation, distribution, and sterilizing.[10]

5. Medication administration with less adverse effects and increased bioavailability.[10]
6. Hydrophilic and hydrophobic medicines are both entrapped.[11]
7. Due to depot formation, demonstrates regulated and prolonged drug release.[11]
8. Requires no immune system response and is biodegradable and biocompatible.[11]
9. The medication's niosomes size, content, shape, and fluidity can all be adjusted as needed.[11]

Types of Proniosomes

Proniosomes come in two varieties, depending on how they are prepared.

a) Dry Granular Proniosomes[12]

Sorbitol and maltodextrin are examples of water-soluble carriers that are covered with surfactant to create dry granular proniosomes. This results in a dry formulation with a thin film of surfactant covering every water-soluble particle.

Proniosomes are further classified as follows

Sorbitol-based proniosomes and maltodextrin-based proniosomes, based on the kind of carrier and production technique for dry granular form.

- **Sorbitol based proniosomes**

Sorbitol-based proniosomes are produced by coating sorbitol with a non-ionic surfactant, acting as a carrier. When hot water and agitation are added, niosomes are formed in a matter of minutes. Organic solvents are applied to sorbitol powder and then evaporated. Since sorbitol carrier dissolves in organic solvents, the procedure needs to be repeated until the required amount of surfactant coating is achieved. One advantage of sorbitol-based proniosomes is that their size distribution is homogeneous. This can be useful when the active ingredient is concerned about hydrolysis. The entrapment efficacy of this phosphorosome is only half of what it would be in the absence of the residual sorbitol.[13]

- **Maltodextrin Based Proniosomes**

Maltodextrin-based proniosomes are made by the fast slurry process. The amount of surfactant solution required to create proniosomes through the use of the slurry technique remains unchanged. Maltodextrin is a polysaccharide that dissolves in water and is used as a carrier material in formulation. A significant increase in surface area can be achieved by using hollow-blown maltodextrin particles. Because of their larger surface area, surfactant

coatings are thinner and facilitate faster rehydration. This formulation could be used to deliver hydrophobic and amphiphilic medications.

- **Liquid Crystalline Proniosomes**

Lipophilic chains of surfactants can undergo three transformations into the lyotropic liquid crystalline state—a disordered, liquid state—when they remain in contact with water (neat phase).[14] Lipids can be dissolved using one of three methods: adding the solvent that dissolves lipids, raising the temperature at the Kraft point (Tc), or using both. In an aqueous layer, bilayers are layered on top of one another to generate the neat phase, also known as the lamellar phase. In this kind of structure, polarized microscopes show birefringent features that resemble threads. Lamellar liquid crystals develop at kraft temperature when alcohol is present, and ternary lecithin, non-ionic surfactants, and monoglycerides produce proniosomes. The lamellar crystalline phase changes into niosome dispersion when there is an increase in water content. This lipid, ethanol, and water lamellar structure is conveniently utilized for transdermal drug delivery. The active medicinal ingredient is administered transdermally using the proniosomes gel and liquid crystalline proniosomes as reservoirs.[15]

Proniosomes in drug delivery and targeting

- **Dermal and transdermal delivery**

The majority of the human body is covered in skin, which is a very delicate tissue. The skin's primary job is to keep the body hydrated.[16] Certain chemicals cannot pass through the skin's selective penetration barrier and enter the body. The stratum corneum is the main component of skin and plays a crucial role in percutaneous absorption. In terms of percutaneous absorption, it is a rate-limiting barrier that exhibits strong penetration resistance.[17] Drugs are delivered to the precise place of action by means of drug carriers. Depending on the kind of drug carrier, either deep skin penetration or accumulation in the follicular appendages and stratum corneum occurs.[18] The benefits of dermal medication delivery include reduced systemic absorption, reduced adverse effects, and high concentrations contained at the site of action.

Advantages of proniosomes as dermal and transdermal drug delivery

The transdermal route has a number of benefits, including

- Self-administration,
- non-invasiveness,

- avoiding hepatic metabolism first, which eventually boosts drug bioavailability,
- overcoming gastrointestinal degradation, and
- maintaining steady state plasma concentration.[19]

Disadvantages of proniosomes as dermal and transdermal drug delivery

Moreover, the transdermal method has many drawbacks, such as

- Limited drug penetration through the skin because of the stratum corneum, a major permeability barrier. Vesicular drug delivery systems have demonstrated themselves as a viable alternative to physical or chemical means of getting beyond skin barriers.[20]

COMPONENTS OF PRONIOSOMES

Surfactant: The surface-active agent, or surfactant, is often an organic molecule with an amphiphilic character. They can be used as emulsifiers, permeability enhancers, wetting agents, and solubilizers, among other things. The most often utilized non-ionic surfactants for vesicle production include fatty acid esters, alkyl ethers, alkyl amides, and alkyl esters.[21] The HLB value, which is a reliable measure of any surfactant's capacity to form vesicles, should be taken into consideration when choosing a surfactant. In addition to the surfactant's HLB values, other factors that influence the formation of bilayer vesicles rather than micelles include the component's chemical structure and the critical packing parameter. A surfactant's HLB value is crucial in regulating drug entrapment in the vesicle it creates. Any surfactant's capacity to form vesicles can be accurately determined by looking at its Hydrophilic Lipophilic Balance (HLB) number; a number between 4 and 8 was found to be compatible with vesicle formation.[22]

Carrier: While preparing proniosomes, the carrier allows for flexibility in the proportion of incorporated surfactant and other ingredients. Additionally, it improves loading efficiency by increasing surface area. To facilitate easy hydration, the carriers should be non-toxic, safe, and free-flowing. They should also have a low solubility in the loaded mixed solution.[23] Listed below are common carriers

a) Malodextrin.
b) Sorbitol.
c) Apply a dry lactose spray.
d) Monohydrate glucose.
e) Lactose monohydrate.

f) Stearate of sugar.

Solvent and Aqueous phase: Drug penetration rate and vesicle size are significantly impacted by the alcohol employed in proniosomes. Different alcohols generate different-sized vesicles, which are arranged as follows: Isopropanol > Butanol > Propanol > Ethanol. The aqueous phase employed in the process of creation of proniosomes is phosphate buffer 7.4, 0.1% glycerol, and hot water.[24]

Lecithin: The names given to them are typically based on where they come from; for example, soya lecithin is called after soya beans, whereas egg lecithin is named after egg yolks.[25] One of the main ingredients of lecithin is phosphatidylcholine. It serves a variety of crucial functions in the vesicular system, including.[26]

a) Enhancing penetration.
b) Preventing drug leakage.
c) A higher phase transition temperature (Tc) that increased the percentage of drug entrapment.

In comparison to egg lecithin, soya lecithin forms larger vesicles. However, when comparing the two based on their ability to penetrate, soya lecithin is a better option to choose because it contains unsaturated fatty acids like oleic and linoleic acid, while egg lecithin contains saturated fatty acids.[25]

Cholesterol: A naturally occurring steroid utilized as a membrane addition is cholesterol. Steroids are crucial membrane constituents that significantly alter the bilayer's stability, fluidity, and permeability when they are present. By adding molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic forces, it prevents aggregation.[25]

According to El-Laithy et al., entrapment efficiency (%) increases significantly as cholesterol content rises, but beyond a certain point, additional cholesterol increases cause a significant decline in entrapment efficiency. The higher entrapment efficiency indicates that the cholesterol is forming fewer leak vesicles by eliminating the gel to sol transition and functioning as the "vesicular cement" in the molecular cavities of the surfactant bilayer. Because of this, increasing stiffness reduces the drug's permeability and increases entrapment efficiency. On the other hand, the opposite happened when the amount of cholesterol was

elevated beyond a particular point. The drug may be removed from the bilayer and the structure of the vesicular membrane may be disrupted as a result of a cholesterol molecule competing with the drug for space within the bilayer. This could explain the drop in entrapment efficiency.[27]

Gels: A semisolid formulation that has an exterior solvent phase, is hydrophobic or hydrophilic, and is immobilized inside the gaps that a three-dimensional network structure provides is referred to as a gel. Gels are special materials that have an elastic and rigid nature.[28] They are used in food technology, biomaterials, cosmetics, and medicine.[29] Furthermore, the majority component of gels is a solid matrix, with a fluid solvent making up the remainder.[30] Generally, to create a homogenous dispersion, a gelling ingredient like xanthan gum or carbomer is dissolved in purified water. Because of their high-water content, gels allow for a better solubility of pharmaceuticals and ease drug migration through the vesicle, in contrast to creams and ointments. Gels can also help transport drugs through the skin and keep a large amount of trans epidermal water, which hydrates the skin.[31]

Based on the characteristics of their liquid phase, gels can generally be classified into two categories. Hydrogels contain water, whereas organogels (oleogels) contain an organic solvent. Other gel types, like proniosomal gels, emulgels, bigels, and aerogels, have been reported in recent research for the cutaneous delivery of a medication. With regard to transdermal drug administration on skin, the purpose of this study was to present the most recent developments and terminology of gel systems (such as proniosome gels, emulgels, bigels, and aerogels).

Hydrogels: Hydrogels are defined as gels made from an aqueous dispersion medium gelled with an appropriate hydrophilic gelling agent. Large amounts of water can be absorbed by hydrogels, which are three-dimensional networks of hydrophilic polymers.[32] Prior research has examined hydrophilic polymers as gelling agents, including sodium alginate, carbopol, and hydroxypropyl methylcellulose (HPMC).[33] Crosslinks, which give hydrogels their networked structure and physical stability, can be created chemically or physically. Hydrogen bonds, Van der Waals interactions, entanglements, and crystallites are examples of these physical crosslinks. "Reversible" or "physical" hydrogels are those that are created when physical crosslinks are generated.[30] On the other hand, networks of covalently connected crosslinks generate the hydrogels known as "chemical" or "permanent" gels.[29] Diffusion and chemical stimulation are two different ways that drugs can be released from hydrogels.

Movement across the polymer matrix or the hydrogel's bulk erosion control diffusion. Chemically triggered gels efficiently open their pores to release the medication that has been captured by swelling in response to external stimuli such as pH and temperature or by enzymatic action.[34] Only sick tissues can benefit from the focused medication release provided by this kind of mechanism. Drug release via chemical stimulation has found more applicability for oral drug administration and can provide control for selective therapy, whereas drug release by diffusion is more prevalent for localized and non-specific drug release. The use of hydrogels in the biomedical sciences, such as cell encapsulation, tissue repair, and controlled drug administration, has expanded recently due to advancements in hydrogel technologies. To meet the growing demands of the pharmaceutical and medical areas, numerous innovative hydrogel-based delivery matrices have been developed and produced.[32]

Advantages

1. Easily prepared.
2. Inexpensive.
3. Degradable by Nature.
4. Basic building block for numerous more gel forms, including bigels, emulgels, and liposomal gels.
5. Versatile, many substances can be integrated.

Disadvantages

1. Hydrogels may have problems with mechanical strength.
2. The hydrophilic nature of transdermal medication distribution can provide challenges.
3. Adding lipophilic substances to hydrogels is difficult.
4. Hydrogels based on polysaccharides may get contaminated by microorganisms.

Organogels: Organogels also referred to as oleogels are gels that use oil or non-polar liquids as a dispersion medium. A thermoreversible, three-dimensional gel network containing organic liquid is known as an organogel. Organogelators are liquid solvents that are ensnared in a three-dimensional network created by low-molecular-weight components or oil-soluble polymers, giving rise to solid-like systems resembling solids.[35] Hydrogels and organogels are similar in that they both develop through weak interactions like hydrogen bonds and van der Waals forces.[36] Numerous culinary oils, including cod liver oil, sweet almond oil, and olive oil (as a liquid phase), as well as numerous organic solvents, including benzene and

hexane[23] as well as numerous waxes, such as sugarcane, carnauba, rice bran, and candelilla wax have been looked into as potential organogelators for lipophilic compound transdermal drug delivery vehicle.[37] The capacity of organogelators to create a crystalline network to entrap bulk oils at low concentrations (510% wt.) may be the reason for the increased interest in organogels. Numerous heterogeneous systems are stabilized and given the appropriate texture by organogels.[35] Because of their lipophilic character, organogels can improve drug penetration through the stratum corneum in addition to being easily prepared.

Permeation enhancers include several common organogel constituents such fatty acids, surfactants, glycols, essential oils, and terpenes. Since several fatty acid moieties are believed to form distinct domains that are highly permeable routes and aid in fatty acid penetration into the stratum corneum's lipid bilayer, they are referred to as penetration enhancers. Particularly when it comes to hydrophilic active agents, components like surfactants and phoshpolipids enter into the stratum corneum and promote tissue hydration, which in turn increases drug permeation. Furthermore, the oils utilized in organogels are safe to use in the development of lipophilic chemical drug delivery systems. Because of their ability to solubilize substances with varying physiochemical properties, as well as their biocompatibility,[38] thermodynamic stability, thermoreversible nature, resistance to microbial contamination, and insensitivity to moisture, lecithin organogels-phospholipids derived from egg yolks-have garnered attention recently for the transdermal delivery of drugs.

Advantages

1. Simplicity in preparation.
2. Cheaper.
3. Shows enhanced mechanical strength as a result of the organogelators.
4. Greater skin permeability.
5. Adaptable to temperature changes.
6. Unaffected by microbial contamination.

Disadvantages

1. Suitable for lipophilic medications.
2. Heat may affect stability unless certain chemicals, like lecithin, are added.
3. The greasy feel of cosmetics may be an irritating aspect.
4. Difficult to wash.

Emulgels: A blend of an emulsion and a gel is called an emulgel. Gels offer many benefits, but the administration of hydrophobic medications has long been a source of worry. Emulgels, which have been employed for hydrophobic drug delivery, were developed in order to get around this restriction.[39] An emulgel is created when a traditional emulsion has a gelling ingredient present in the water phase. Drug delivery has been accomplished through the use of both water-in-oil (w/o) and oil-in-water (o/w) emulsions. Emulgels are good for the skin because of their thixotrophicity, greaselessness, spreadability, removability, emollient qualities, long shelf life, and attractive appearance. Furthermore, emulgels are highly favored by patients due to their ability to combine the benefits of gels and emulsions. Microemulsions exhibit acceptable physical characteristics, medication release, and low skin irritation. They also lower the stratum corneum's diffusion barrier.[40] Moreover, emulgels have demonstrated their promise as a great carrier for skin care products that offer UVA/UVB radiation protection. Microemulsion-based gels (MBGs) have attracted a lot of attention lately as a possible topical drug delivery system for skin.[41] Since these gels are made of emulsions (oil and surfactant), they can be categorized as emulgels; yet, because of the smaller particle sizes, they are more stable than emulgels. Gelatin is created when a gelling ingredient is dissolved in a heated w/o or o/w microemulsion and subsequently chilled. Microemulsions have several benefits, one of which is their thermodynamic stability. Consequently, topical transdermal medication administration using gels based on microemulsions may be a promising approach. Furthermore, topical drug distribution on skin has been studied for MBGs using surfactants such as polyglyceryl-6 dioleate and PEG-8 capric glycerides and gelling agents such as xanthan gum and carbopol.[40]

Advantages

1. Preparation is simple and inexpensive.
2. Long shelf life, thickening, greaseless, spreadable, detachable, emollient, non-staining, water-soluble, transparent, and aesthetically pleasant.
3. Emulgels are useful for pharmacological controlled releases.

Disadvantages

1. Bubbles appearing while preparing the emulgel.
2. Surfactant presence may irritate skin.

Aerogels and xerogels: Given that silica makes up both aerogels and xerogels, they are also referred to as inorganic gels. Research has been done on the possible applications of xerogels

and aerogels as drug delivery systems.[42] Studies on regulated subcutaneous medication administration have been conducted with silica gels.[43] The potential of silica xerogels as a drug delivery device or disc[44] has been assessed in their evaluation as drug delivery implants. Conversely, silica aerogels have been studied for topical medication administration; still, additional characterisation and research are required to assess their potential. Although they go through different drying processes, both aerogels and xerogels are made of silica and are produced using the sol-gel method. When a wet silica gel is dried at room pressure, it shrinks considerably and becomes a solid substance called xerogel, which has relatively small pores. The resulting aerogel maintains its exceptionally porous structure and shrinking is prevented through supercritical drying. Aerogels have a more customizable surface area and pore size, and their structure is more flexible.[45] Additionally, the drug solubility and bioavailability of aerogels are thought to be better regulated than that of xerogels due to the addition of different functional groups that alter the release kinetics of the aerogels.[43] Hydrophilic aerogels have the potential to produce a very rapid drug release, which is especially useful for medications that are not very soluble in water.[46] This effect stems from the collapse of the hydrophilic aerogel structure in aqueous solutions as a result of the pores' internal surface tension. Xerogels do not exhibit a collapse in structure, in contrast to aerogels. A novel approach to cutaneous medication administration is offered by hydrophilic silica aerogels. Drugs are present inside the extremely porous matrix in a non-crystalline form thanks to the drug loading process, which involves adsorption from supercritical gases and homogenous drug distribution at the molecular level inside the aerogel matrix. Drug release, penetration, and stability of semisolid formulations have all been found to be enhanced by the use of a drug-loaded aerogel matrix.[43]

Advantages

1. Aerogels, as alternative to xerogels, can be modified for extended medication delivery.
2. Extremely steady
3. Low thermal conductivity and steady temperature
4. Large drug-carrying surface area.
5. For regulated medication delivery, xerogels and aerogels can both be utilized.

Disadvantages

1. Expensive method.
2. Difficulties in the biodegradation of xerogels and pure silica aerogels.

Bigels or bi (phasic) gels: Aqueous (hydrogels) and lipophilic (organogels) systems are combined to create bigels, which are topical formulations. The properties of both gels are present in bigel formulations, including the capacity to chill the skin, improve stratum corneum moisture, moisturize, distribute readily, and wash away with water. The stable oleogel and hydrogel combinations known as bigels are free of emulsion stabilizers and surfactants.[47] Aqueous and lipophilic systems are mixed at a high shear rate, or revolutions per minute, to create these homogeneous preparations. Bigels are not the same as creams or emulgels in that they don't contain an emulsifier or surfactant. In bigels, combining two gel systems can result in a synergistic effect like as improved stratum corneum hydration and medication penetration as a result of both the oil phase and the water phase.[48] Hydrogels and oleogels share the same mode of action when it comes to medication penetration through skin. The medicine can pass through the stratum corneum and have a topical and transdermal effect on skin thanks to the hydrogel's traditional dispersion, the lipophilic nature of oils, and the addition of fatty acids as penetration enhancers. The pharmaceutical and cosmetic sectors may utilize bigels as a topical medication delivery medium on skin since they combine the benefits and features of hydrogels and organogels. Bigels have been investigated using carbopol hydrogels and oleogels made from sweet almond oil and liquid paraffin.[48]

Advantages

1. Hydrogels and oleogels work synergistically.
2. No emulsifier,
3. Easy to prepare,
4. Skin irritation not brought on by surfactants,
5. It is possible to administer both hydrophilic and lipophilic medicines via the skin.

Disadvantages

1. Lack of an emulsifying agent makes phase separation difficult to control,
2. subject to little research,
3. Not thermoreversible since stability may be problematic at higher temperatures.

Proniosomal gel

Proniosomes are vesicular systems composed of cholesterol, additional additives, and non-ionic based surfactants. Semisolid liquid crystal gel, are made by hydrating the surfactant with the least quantity of water to form a gel after dissolving it in a little amount of an appropriate solvent, in this case, ethanol is used. These structures are liquid crystalline

compact niosome hybrids that can be applied topically or transdermally and instantly transform into niosomes upon hydration. Proniosomal gels are typically found in semisolid gel textures that are transparent, translucent, or white. This allows them to maintain their physical stability while being stored and transported.[49] Proniosomal hydrogels have also been described in relation to their possible application as transdermal medication delivery systems.[50]

Because they require moisture to produce niosomal capillaries prior to drug release and epidermal penetration, promiosomes are often referred to as "dry niosomes".[51] Proniosomes are manufactured similarly to niosomes, but they are not separated; instead, all preparation steps—such as adding a gelling agent and a surfactant—are carried out concurrently, and the final product is dispersed in a warm water bath. The dispersion is thereafter allowed to cool to room temperature in order to form a proniosomal gel.[52]

Additionally, proniosomes offer a special vesicle with the potential for transdermal drug administration and are hydrated by agitation in hot water.[53] Proniosomal hydrogels are also thought to be more successful than niosomal hydrogels because the former can get over a lot of niosome-related physical stability issues, like aggregation, sedimentation, destruction by hydrolysis, and fusion.[54] Proniosomal gels also improve medication penetration across the skin barrier, which may make them more successful in transdermal drug delivery. In addition to their ability to diffuse throughout the stratum corneum, niosomes can also interact with it and cling to its surface, resulting in a drug's high thermodynamic activity gradient at the vesicle-stratum corneum surface. This phenomenon serves as the catalyst for the penetration of lipophilic drugs into the stratum corneum.[55] Niosomes have the potential to alter the structure of the stratum corneum, thereby increasing the permeability and looseness of the intercellular lipid barrier.[56] Niosomes are an extremely useful vesicular system for topical and transdermal delivery, as they act as a drug reservoir for an extended duration and improve skin penetration, as demonstrated by research on estradiol-loaded niosomes that were made with cholesterol included, which facilitated estradiol transdermal penetration.[56]

Advantages of Proniosomal gel

The drug and cosmetic delivery systems known as liposomes and proniosomes have been found to have numerous drawbacks concerning preparation, storage, sterilization, and other related issues. The drawbacks of liposomes and niosomes are listed below and can be circumvented by using proniosomes.

- Liposomes and niosomes are dispersed aqueous systems that have a problem of degradation by hydrolysis or oxidation.
- Niosomes and liposomes need particular care and storage.
- On storage, sedimentation, aggregation, or fusion are frequently observed.
- The natural phospholipid purity in liposomes varies as well.
- Difficulties with scaling up, uniform dosage storage, transportation, distribution, and sterilizing.
- The lipid/surfactant coating on the walls not fully hydrating throughout the hydration process.[57]

Disadvantages

1. Proniosomes combine, settle, and break down through fusion and hydrolysis.
2. Expensive.[57]

Material and procedure for making proniosomal gel

Table I: lists the components needed to make proniosomal gel.[58]

Sr. No.	Ingredients used	Example	Use
1	Surfactants (Non-ionic)	Spans, Tweens	To boost the rate of penetration
2	Cholesterol		To enhance vesicle stability
3	Lecithin		Penetration Booster
4	Solvents	Ethanol, methanol	For surfactant-drug solubilization.

Methods

Proniosomal gel preparation "coacervation–phase separation technique"

The procedure described by Vora et al. and adjusted by Ibrahim et al. can be used to make the proniosomal gel. The right amount of cholesterol was combined with precisely weighed surface active agents and placed into glass vials. The surfactant or surfactant/cholesterol mixtures were mixed with absolute ethanol (a modest amount sufficient to solubilize the lipids; roughly half the weight of total lipids). The vials were then tightly sealed, warmed in a water bath (55–60ºC), and shaken until the lipids were completely dissolved. The distilled water was heated to 55–60 degrees Celsius and added to each of the generated transparent hot lipid solutions in small amounts (approximately 40% of the total solvent added). The lipid solution was then warmed in the water bath for 3–5 minutes until a clear or translucent solution was produced. When the mixtures cooled to room temperature, observers looked for

the production of two-phase liquids, translucent, transparent, or white, creamy proniosomal gels.[59]

Drug loading into proniosomal gel formulations

If lipid-soluble, the medication might be added to the non-ionic surfactant/cholesterol mixture and dissolved with the help of 100% ethanol while heated at 50–60ºC in a water bath. As per the drug's physicochemical properties[60], it could be added to the heated lipid solution after being dissolved in alcohol or distilled water and allowed to cool down to a gel form. It's crucial to remember that the drug shouldn't precipitate into the gel phase and didn't cause turbidity or precipitated crystals in liquid preparations prior to gelation.

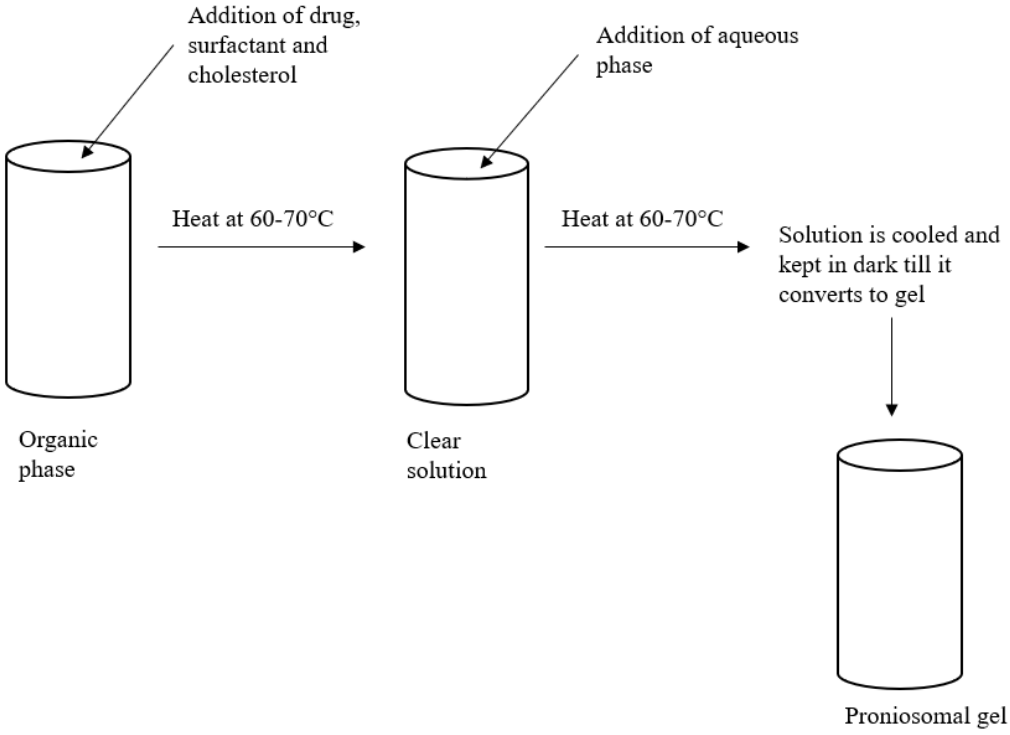

Fig. 1: Represents the steps involved in the preparation of proniosomal gel.[58]

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