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AN OVERVIEW OF PRONIOSOMES IN DRUG DELIVERY: A NOVEL APPROACH

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ABSTRACT
Proniosomes is an advanced vesicular drug delivery system that have emerged as a versatile solution for controlled and targeted drug release across various administration routes. As a precursor to niosomes, proniosomes are comprised of non-ionic surfactants and cholesterol, which enhance their ability to encapsulate a wide range of drug types, from hydrophilic to lipophilic compounds, making them highly adaptable across multiple routes of administration offering advantages in storage stability and ease of handling. This review delves into various methods of proniosome preparation—such as the slurry, coacervation-phase separation, and spray-coating methods—each of which enables formulation scalability and ensures consistency in drug delivery. Characterization techniques, including scanning electron microscopy, particle size analysis, and encapsulation efficiency assessment, further emphasize the robustness and versatility of proniosome-based system. Compared to traditional vesicular systems like liposomes, proniosomes present enhanced stability, bioavailability, and compatibility with both hydrophilic and lipophilic drugs, making them suitable for oral, topical, transdermal, ocular, pulmonary, and peptide delivery applications. Additionally, proniosomes overcome limitations such as aggregation, leakage, and short circulation times, providing a reliable drug delivery platform with potential in treating various diseases and improving therapeutic outcomes. The adaptability of proniosome formulations and their reduced toxicity highlight their promising role in advancing targeted drug delivery systems.

KEYWORDS: Proniosomes, Surfactants, Vesicle, Lipophilic.

INTRODUCTION[1,2]

Lately, there is no one drug delivery system that meets all the requirements, but efforts have been made through innovative methods. Several innovative methods have come up that encompass different administration routes in order to achieve controlled or targeted delivery. The main goal of innovative drug delivery is to maintain a consistent and efficient drug concentration in the body while minimizing side effects, and it also involves directing the drug action by targeting the drug delivery using drug carriers. One method that encapsulates the drug is vesicular drug delivery, which includes liposomes, niosomes, transferosomes, pharmacosomes, and provesicles like proniosomes and proliposomes. The particulate nature of liposomes and niosomes, which serve as a drug reservoir, gives them an advantage over other traditional dosage forms. A small number of adjustments can also be made to modify the pattern and drug release. Additionally, it was discovered that modified vesicles possessed characteristics that allowed medications to be effectively absorbed by the skin's deeper layers.

TYPES OF VESICULAR DRUG DELIVERY SYSTEMS

1. Liposomes
2. Virosomes
3. Niosomes
4. Transferosomes
5. Proteasomes
6. Sphingosomes
7. Archaesome
8. Ethosomes.

Liposomes

A bilayer of lipids makes up the artificially produced vesicle known as liposomes. These can be used to administer pharmaceutical medications and nutrients.

Biological membranes can be broken to create liposomes. Natural phospholipids make up their composition, and mixed lipid chains with surfactant qualities may also be present.[3,4]

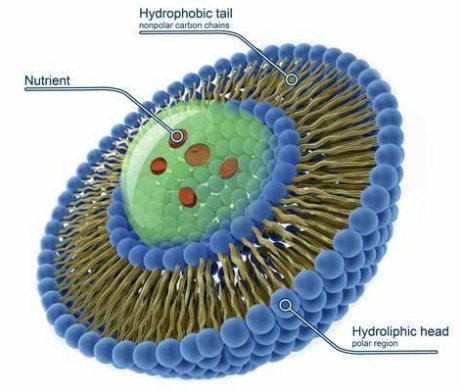


Figure 1: Structure of liposome.

Virosomes

The unilamellar phospholipid membrane, a mono- or bi-layer vesicle that contains virus-derived proteins to enable the virosomes to fuse with target cells, is the basis for virosomes, which are drug or vaccine delivery vehicles.[5]

Niosomes

Niosomes are liposomes based on non-ionic surfactants. The main excipient used in the formation of niosomes is cholesterol. It is also possible to use other excipients. Compared to earlier emulsion preparations, niosomes have a greater capacity for penetration. Although they have a bilayer and are structurally similar to liposomes, niosomes are more stable due to the materials used in their preparation, which gives them many more benefits than liposomes.[6,7]

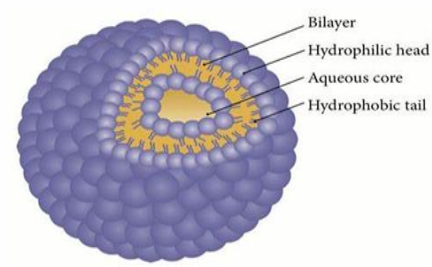


Figure 2: Structure of Niosome.

Transferosomes

An artificial vesicle called a transferosome carrier is made to function as a cell vesicle or an exocytosing cell, making it appropriate for controlled and possibly targeted drug delivery.[8]

Proteasomes

Proteases are cytoplasmic organelles that break down endogenous proteins. They are made up of an acylindric core particle that is connected to two regulatory particles at either end. Proteases can identify proteins that need to be destroyed because they contain ubiquitin conjugated to the lysine residue of the targeted protein.[9]

Sphingosomes

Sphingosomes are bilayered vesicles made up primarily of synthetic or natural sphingolipid, with an aqueous volume completely encased in a membrane lipid bilayer. The main problems with vesicle systems (liposomes, niosomes), including their decreased stability, short in vivo circulation time, and poor tumor loading efficacy in cancer treatment, are resolved by sphingosomes. Clinically, sphingosomes are employed as delivery systems for biological macromolecules, chemotherapeutic agents, and diagnostics. Because sphingosomes can vary in size and composition, several varieties have been created.[10]

Archaesome

The polar ether lipids of Archaea are used to make liposomes known as archaeosomes. The structure of these lipids differs from that of the ester lipids present in bacteria and eukarya.*a*.[11]

Ethosomes

Soft, pliable vesicles designed for improved active agent delivery are called ethersomes. It has been demonstrated that ethosomes' physicochemical properties enable this vesicular carrier to carry active ingredients into the deeper layers of the skin more effectively than traditional liposomes through the stratum corneum.[12]

PRONIOSOMES

Since the early 1980s, proniosomes have drawn a lot of interest from researchers due to their potential as drug targeting agents and drug carriers, which offer a number of benefits without the drawbacks of traditional drug forms. Niosomes are water-soluble carrier particles that, when briefly stirred in hot aqueous media, dry to form a niosomal dispersion. Proniosomes are the name given to this dehydrated product. The resultant niosomes have greater size uniformity and are highly correlated with conventional niosomes. The proniosomal method lessens the issues with a free-flowing, dry product that is more stable during sterilization and storage. The proniosomes' ease of distribution, measurement, transfer, and storage makes them a flexible delivery system.[3] Proniosomes were investigated as potential substitutes for liposomes and other carrier systems in the entrapment of hydrophilic and hydrophobic, polar and nonpolar medications. Proniosomes have the added benefits of low toxicity due to their non-ionic nature and the absence of special conditions and precautions needed for formulation and preparation. Furthermore, it is the straightforward technique for producing proniosomes on a regular and large scale without the use of unwantedsolvents. Stability is a major concern in the development of any formulation, though, and proniosomes have benefits as drug carriers, including cost effectiveness and chemical stability when compared

to liposomes. Additionally, they reduce physical stability issues like aggregation, sedimentation, fusion, and leakage during storage. Dry niosomes, also known as proniosomes, are a promising industrial product because of all these benefits.

TYPES OF PRONIOSOMES[13,14]

Dry granular proniosomes

a) Sorbitol based proniosomes

The dry formulation includes sorbitol as a carrier and is coated with non-ionic surfactant using water through a simple agitation method.

b) Maltodextrin based proniosomes

Maltodextrin based proniosomes were prepared by fast slurry method.

Liquid crystalline proniosomes

The proniosomes of this kind serve as reservoirs for delivering drugs transdermally. A plastic sheet is present in the transdermal patch along with a backing layer. The gel is evenly distributed on the sheet.

MATERIALS[15,16,17]

Surfactants

The surfactant selection was based on their HLB value, as the hydrophilic lipophilic balance (HLB) serves as a reliable indicator of a surfactant's ability to form vesicles. Surfactants with HLB values falling between 4 and 8 were found to be suitable for vesicle formation. Additionally, it has been noted that hydrophilic surfactants, due to their high aqueous solubility upon hydration, do not form concentrated systems, allowing free hydrated units to aggregate and coalesce into a lamellar structure. Even though polysorbate 20, a water-soluble detergent, has an HLB number of 16.7, it can still form niosomes in the presence of cholesterol. It is important to note that the degree of entrapment is influenced by the HLB of a surfactant. The entrapment of drugs in vesicles is influenced by the transition temperature of surfactants. Surfactants with the highest phase transition temperature result in the greatest drug entrapment, and vice versa. Vesicles produced by Span 40 and Span 60 are larger in size and have higher drug entrapment. The high phase transition temperature and low permeability of these surfactants reduce drug leaching from the vesicles. The higher HLB value of Span 40 and Span 60 leads to a reduction in surface free energy, allowing for the formation of larger vesicles, which exposes a larger area to the dissolution medium and skin. The skin permeation profile of the formulation containing Span 60 and Span 40 shows no significant difference, attributed to their higher phase transition temperature which results in lower permeability. Tween exhibits relatively low encapsulation efficiency compared to Span. The structure of surfactants affects the geometry of the vesicles they form, as determined by critical packing parameters. The geometry of the vesicles formed can be predicted based on the critical packing parameters of the surfactants, defined using the following equation.

$$CPP = \frac{V}{LC * AO}$$

CPP ≤ 0.5 micelles form
CPP= 0.5 – 1 spherical vesicles form
CPP = 1 ≥ inverted vesicles form
V– Hydrophobic group volume lc = the critical hydrophobic group length, ao= the area of hydrophilic head group. Span 60 is the good surfactant because it has CPP value between 0.5 and 1.

Stabilizers

Cholesterol

Cholesterol is a vital component of vesicles, and its presence enhances the stability and permeability of the vesicles. The concentration of cholesterol plays a crucial role in trapping drugs within the vesicles. Studies have shown that the efficiency of drug entrapment increases with higher levels of cholesterol and with the use of Span 60, which has a higher transition temperature. However, it has been observed that excessively high cholesterol content can actually decrease the entrapment of drugs within the vesicles. This may be attributed to the fact that beyond a certain threshold, cholesterol starts to disrupt the regular bilayer structure, leading to a loss in drug entrapment.

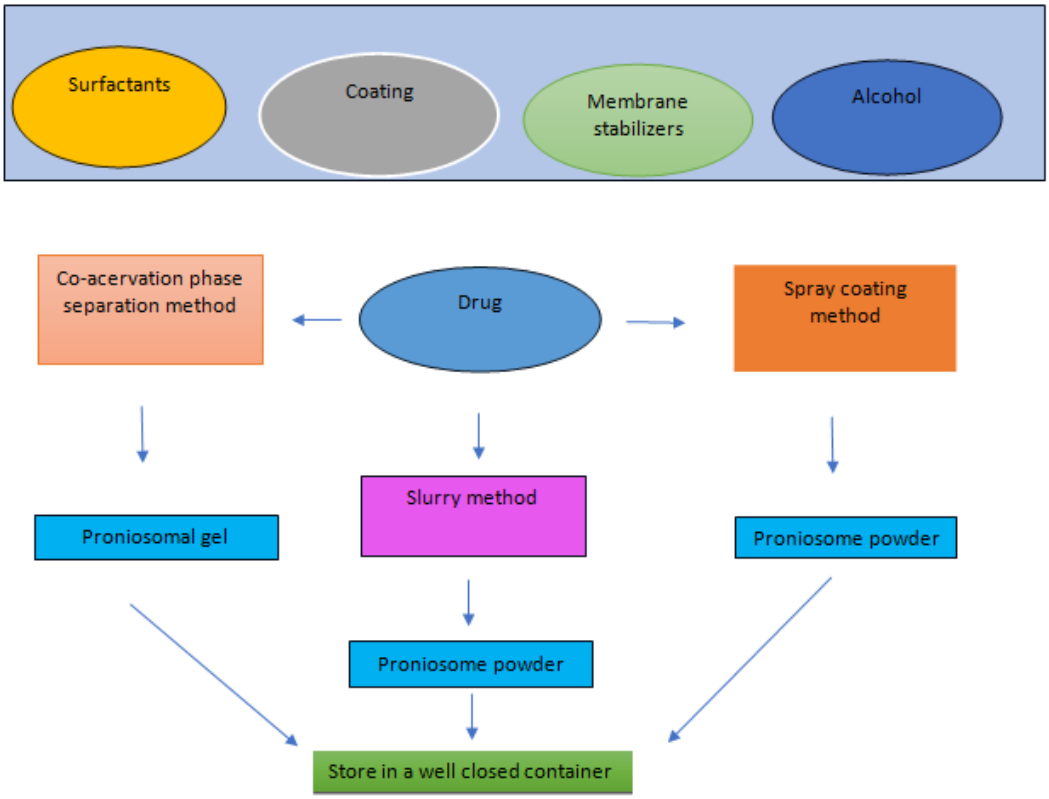
Lecithin

Lecithin contributes to stability, but to a lesser extent when compared to cholesterol.

Maltodextrin

Maltodextrin's use as a carrier in proniosomes preparation allows for flexibility in incorporating the ratio of surfactant and other components. Solid cake-like mass is formed by coating sorbitol.

METHOD OF PREPARATION OF PRONIOSOMES[18,21]



Slurry method

A slurry is prepared in a round bottom flask, typically using solvents and maltodextrin as a carrier. To obtain the free-flowing powder of proniosomes, apply vacuum during the slurry process. Start by placing a round bottom flask containing the carrier (maltodextrin, lecithin) on a rotary evaporator set to 50-60 rpm at a temperature of 45-47 °C to evaporate the solvent. To obtain the dry, free-flowing product, reduce the pressure to 600 mm Hg and retrieve the dry formulation. Store the product in a tightly closed container under refrigeration.

Coacervation phase separation

A specified quantity of surfactants, cholesterol, and lecithin was combined with a solvent in stopper glass vials, with a stopper used to prevent solvent loss. The mixture was then heated and stirred using a glass rod until all ingredients were fully mixed. Following this, small amounts of buffer solutions were added to the prepared mixture, and it was heated again on a water bath for 10 minutes. A clear solution was then obtained, which was left at room temperature for 24 hours. After 24 hours, the clear solution transformed into proniosomal gel.

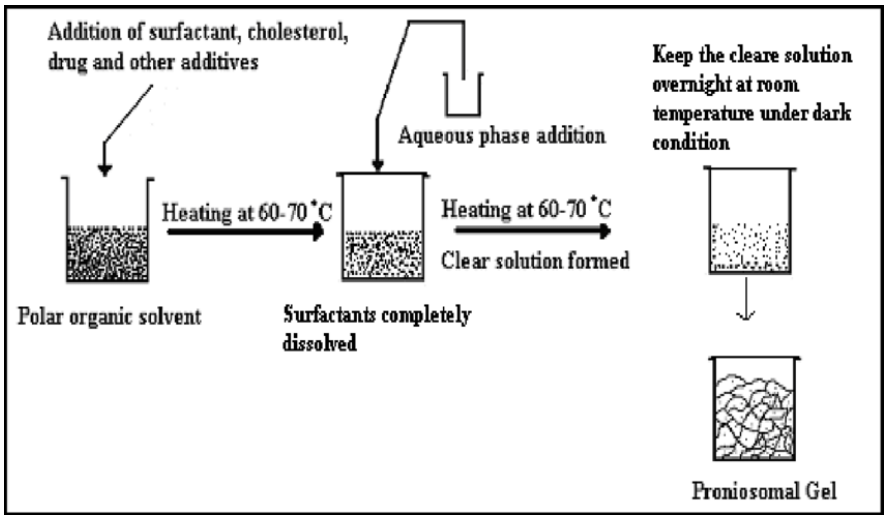


Figure 3: Paragraph outline.

Spray coating method

The carrier is placed in a round bottom flask and connected to a rotary evaporator. A mixture is then created using the necessary amount of cholesterol and surfactant, which is sprayed onto the carrier. The evaporator is then evacuated and placed in a rotating flask, maintaining a temperature of 65-70°C under vacuum for 15-20 minutes. The evaporation process continues, and all surfactants are added until the dry powder of proniosomes is prepared.

AFFECTORS ON THE PRONIOSOME FORMULATION[22,24]

The properties of proniosomes are influenced by a number of formulation and processing parametes. The length of the surfactant chain, cholesterol levels, drug concentration, total lipid concentration, lipid charge, dispersion medium pH, and kind of alcohol employed in the preparation are some of these.

1. Surfactant chain length

Proniosome preparation often involves the use of Spans, which have similar head groups but varying alkyl chain lengths. Longer alkyl chains are associated with higher entrapment efficiency, with Span 60 (C18) > Span 40 (C16) > Span 20 (C12) > Span 80 (C18) following this trend. Although Span 60 and Span 80 share the same head groups, Span 80's unsaturated alkyl chain results in lower entrapment efficiency. The introduction of double bonds into the paraffin chains significantly enhances permeability, which may explain the reduced entrapment efficiency of the Span 80 formulation.

2. Cholesterol content

The percentage of encapsulation efficiency can be affected by changes in cholesterol levels, which can be influenced by the type of surfactant or its concentration in the formula.

3. pH of the hydration medium

The pH of the hydrating medium significantly impacted the percentage encapsulation efficiency of proniosomes prepared from Span /cholesterol proniosomal gels.

4. Total lipid concentration

The higher the lipid concentration, the greater the percentage encapsulation efficiency of drug. The relationship between percentage encapsulation efficiency of drug and total lipid concentration was found to be linear.

5. Charge of the lipids

Dictyl phosphate (DCP) and stearylamine (SA), which pr ovide positive and negative charges, respectively, reduce d the percentage encapsulation efficiency of drug into niosomal vesicles.

CHARACTERIZATION OF PRONIOSOMES[25,30]

1. Measurement of angle of repose

Two methods can be used to measure the angle of repose.

- **For the Funnel Method**

A funnel is placed 2 cm above the surface, and the proniosomal powder is poured through it to form a cone. The angle of repose is then calculated using the height (h) and the diameter (r/2) of the base.

- **In the Cylinder Method,**

similar to the Funnel Method, the proniosomal powder is poured into a cylinder with an outlet orifice positioned above the surface, and the powder flows down to form a cone. The angle of repose was furthercalculated by measuring the height (h) of the cone and the diameter (r/2) of the base.[18]

$$\text{Angle of repose } (\square) = \text{Tan}^{-1} (h/r)$$

2. Scanning electron microscopy (SEM)

The size of the particles in proniosomes is extremely important. The SEM was used to examine the surface characteristics such as roundness, smoothness, and the formation of aggregates, as well as the size distribution of proniosomes. To conduct this study, the proniosomal powder was evenly spread on a double-sided tape affixed to aluminum stubs, and then placed in the vacuum chamber of the SEM (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were then observed for morphological characterization using a gaseous secondary electron detector under specific conditions (working pressure of 0.8 torr, acceleration voltage of 30kv.

3. Optical microscopy

The niosomes were placed on a glass slide and examined using an optical microscope (Medilux - 207 RII, Kyowa-E1 etner, Ambala, India). The microscope had a magnification of X 1200 for observing the morphology. A digital single lens reflex (SLR) camera was used to capture the photomicrograph of the preparation from the microscope.

4. Measurement of vesicle size

Niosomal dispersions are thinned approximately 100 times in the identical solution utilized for their creation. Before measuring the vesicle size, the sample was thoroughly mixed. The Laser diffraction particle size Analyzer, Sympatec, Germany, was used to determine the vesicle size, with an apparatus comprising a He-Ne laser beam of 632.8 nm focused with a minimum power of 5 mW using a Fourier lens (R-5) towards a point at the center of a multielement detector and a small volume sample holding cell (Su cell). The average particle size of proniosome-derived niosomes was roughly 6×10-6 m, whereas the traditional niosomes contained about 14×10-6 m.

5. Entrapment efficiency

The unentrapped drug can be separated using different methods. For dialysis, the niosomal dispersion is placed in dialysis tubing and dialyzed against a suitable dissolution medium at room temperature. Samples are collected at regular intervals, centrifuged, and then tested for drug content.

- **In the case of centrifugation**,

the niosomal suspension obtained from proniosomes is centrifuged, and the supernatant is separated. The resulting pellet is washed and then resuspended to obtain drug-free vesicles.

- **Gel filtration**

Gel filtration involves separating the free drug from the niosomal dispersion using a sephadex G-50 column. The separated drug is then eluted with an appropriate mobile phase and analyzed.

The entrapped drug can be separated by completely disrupting the vesicles using 50% n-propanol or 0.1% Triton X-100. The resulting solution is then analyzed using the appropriate method.

$$Percent\ drug\ entrapment = \frac{Total\ drug - diffuse\ drug}{Total\ drug}\ \%$$

6. In vitro Drug Release

The release of proniosomal drug was assessed through various methods, including Franz cell diffusion, dialysis, reverse dialysis, USP dissolution apparatus Type-1, and molecular porous membrane tubing. Drug release from the suspension can occur through desorption from the vesicle surface, drug diffusion from the bilayered membrane, or a combination of both desorption and diffusion mechanisms.

7. Rate of Hydration

The spontaneity of niosome formation depends on the number of niosomes created after hydrating proniosomes for approximately 15 minutes. Proniosomes are evenly spread in a small stoppered glass tube. 1ml of saline solution (0.154M Nacl) is added and left undisturbed. After 15-20 minutes, a small sample is taken and placed on Neubaur's chamber. The number of niosomes formed from proniosomes is then counted.[18]

8. Stability studies

The stability of proniosomes is determined by storing the prepared proniosomes at different temperature conditions, including refrigeration temperature (2-8°C), room temperature (25 ± 0.5°C), and elevated temperature (45 ± 0.5°C) for 1-3 months. Monitoring includes checking the drug content and observing any changes in the average vesicle diameter over time.

According to ICH guidelines, stability studies for dry proniosomes powders intended for reconstitution should undergo accelerated stability testing at 40°C/75% RH to align with international climatic zones and conditions. After a specific storage period, the product's appearance, color, assay, pH, particulate matter, sterility, preservative content, and pyrogenicity should be evaluated.

APPLICATION OF PRONIOSOMES[31,38]

Oral Drug Delivery: Proniosomes have great promise for delivering drugs orally, as they can improve bioavailability, provide sustained release, and enhance patient compliance. When formulated for oral administration, proniosomes can contain both hydrophilic and hydrophobic drugs, safeguarding them from enzymatic breakdown and facilitating absorption in the gastrointestinal tract. They can be developed as immediate-release, controlled-release, or targeted delivery systems, allowing for versatility in drug release timing and site-specific targeting.

Topical Drug Delivery: Proniosomes play a role in improving the penetration of drugs into the skin, aiding drug deposition, and enhancing the effectiveness of topical drug delivery in various dermatological conditions. They are capable of encapsulating drugs for treating infections, inflammation, and skin disorders, making them suitable for delivering both lipophilic and hydrophilic drugs topically. Proniosomes have the advantages of improved stability, prolonged release of drugs, and reduced skin irritation.

Transdermal Drug Delivery: Proniosomes are becoming increasingly popular as carriers for transdermal drug delivery, aiding in the effective permeation of drugs through the skin barrier. Formulations of transdermal proniosomes improve drug solubility, permeability, and retention in the skin, leading to sustained release and a prolonged therapeutic effect. Proniosomes have benefits such as enhanced skin penetration, decreased systemic exposure, and improved patient compliance, making them suitable for delivering drugs with low skin permeability through the skin.

Ocular Drug Delivery: Proniosomes are used in ocular drug delivery to enhance drug bioavailability, extend ocular residence time, and improve therapeutic effectiveness. Ocular proniosomes formulations can contain drugs for treating various ocular diseases and conditions, such as glaucoma, cataracts, and ocular infections. Proniosomes provide benefits like increased corneal penetration, minimized drug loss from tear dilution, and enhanced patient comfort, making them suitable for delivering both hydrophilic and lipophilic drugs to the eye.

Pulmonary Drug Delivery: Proniosomes find applications in delivering drugs directly to the lungs for rapid onset of action and localized therapeutic effect in pulmonary drug delivery. Pulmonary proniosomes formulations can encapsulate drugs aimed at treating respiratory diseases and conditions like asthma, chronic obstructive pulmonary disease (COPD), and lung

infections. Proniosomes offer benefits such as improved drug solubility, enhanced lung deposition, and reduced systemic side effects, making them appropriate for delivering both small molecules and biologics to the lungs.

Delivery Of Peptide Drug: Peptides and proteins break down when taken orally. Niosomes protect the peptides from being broken down in the gastrointestinal tract. Vasopressin derivative complexed with niosomes also demonstrated increased stability.

Hormonal therapy: Proniosomes are used to deliver levonorgestrel, the emergency contraceptive, through hormonal therapy. The system underwent testing for particle size, encapsulation efficiency, safety, in vivo and in vitro studies. The test method for pregestational activity was also conducted, which included endometrial testing and inhibition of corpora lutea development.

CONCLUSION

Proniosomes have emerged as a highly versatile and promising platform for drug delivery, offering benefits such as improved and targeted delivery, formulation flexibility, and the ability to overcome many of the challenges faced by traditional drug delivery systems. Various techniques, including coacervation and phase separation, slurry methods, and spray drying, are employed to prepare proniosomes, each with its own set of advantages and challenges. This drug delivery system holds great potential for effectively delivering amphiphilic drugs while avoiding common issues seen in aqueous niosome dispersions, such as physical instability, aggregation, fusion, and leakage. Proniosomes have garnered significant interest for transdermal drug delivery due to their non-toxic nature, the penetration-enhancing effects of surfactants, and their ability to modify drug release profiles. They offer a wide range of applications across different administration routes, including oral, transdermal, ocular, and pulmonary, providing tailored solutions to meet specific therapeutic needs. Based on these observations, it can be concluded that the concept of entrapping drugs in proniosomes to improve targeting to specific tissue sites is widely recognized and accepted by researchers and academics.

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