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A Review of Proniosomes Improve Transdermal Delivery of Drug

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ABSTRACT

Transdermal drug delivery has gained significant attention as a non-invasive therapeutic approach that bypasses gastrointestinal degradation and first-pass metabolism while providing sustained plasma concentrations and improved patient compliance. However, the major limitation of this route lies in the barrier function of the stratum corneum, which restricts the permeation of many drugs. To overcome this challenge, vesicular carriers such as liposomes and niosomes have been explored, but issues of stability, aggregation, and drug leakage often limit their clinical application. Proniosomal gels have emerged as an advanced alternative, offering enhanced stability, improved drug entrapment, and efficient reconstitution into niosomal vesicles upon hydration.These gels are composed of non-ionic surfactants, cholesterol, and stabilizers, incorporated into a semisolid base suitable for topical application. Their unique composition facilitates close interaction with skin lipids, thereby enhancing drug permeation while allowing sustained and controlled release. Proniosomal gels can accommodate both hydrophilic and lipophilic agents, making them highly versatile for a wide range of therapeutic applications, including hormone delivery, cardiovascular therapy, pain management, and dermatological disorders. Moreover, their ease of handling, cost-effectiveness, and patient-friendly nature further support their potential as promising carriers in transdermal systems.This review highlights the formulation strategies, mechanisms of skin permeation, therapeutic applications, and recent advancements in proniosomal gels for transdermal drug delivery. Emphasis is placed on their advantages over conventional carriers, challenges in clinical translation, and future perspectives in expanding their use for biopharmaceuticals and novel therapies. With continued research and optimization, proniosomal gels are expected to play a pivotal role in advancing transdermal drug delivery technologies.

Keywords: *Proniosomal gel, Transdermal drug delivery, Vesicular carriers, Skin permeation, Controlled release*

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1. INTRODUCTION

Transdermal drug delivery has emerged as a highly promising alternative to traditional routes such as oral and parenteral administration. This approach provides several advantages, including avoidance of gastrointestinal degradation, circumvention of hepatic first-pass metabolism, steady plasma concentration of drugs, and improved patient compliance due to its non-invasive nature. Over the last few decades, the transdermal route has attracted increasing attention for both systemic and localized therapy, particularly for chronic conditions requiring long-term administration of medications. Despite these benefits, effective delivery of drugs through the skin remains a challenge because the stratum corneum acts as a formidable barrier, limiting the permeation of most therapeutic molecules[1]. This challenge has stimulated extensive research into novel carrier systems designed to enhance drug transport across the skin and improve therapeutic outcomes.

Among the various strategies explored, vesicular drug delivery systems such as liposomes and niosomes have been extensively studied. These carriers offer unique advantages by encapsulating both hydrophilic and lipophilic drugs, protecting them from degradation, and promoting controlled release. However, liposomes often suffer from stability issues such as aggregation, fusion, and leakage of the encapsulated drug, which limit their practical application. Niosomes, which are vesicles composed of non-ionic surfactants and cholesterol, have been introduced as a more stable and cost-effective alternative. Yet, even niosomes encounter limitations during storage, as they are prone to physical instability, requiring special conditions to maintain their integrity[2]. To overcome these limitations, researchers have developed proniosomes, a precursor form of niosomes that can be converted into niosomes upon hydration.

Proniosomes are dry, free-flowing formulations prepared by coating water-soluble carriers with non-ionic surfactants, cholesterol, and stabilizers. When hydrated with aqueous fluids, these proniosomes readily form niosomal vesicles. This unique feature addresses many of the shortcomings of conventional vesicular systems by enhancing stability, improving handling, and reducing problems associated with leakage and fusion during storage. Proniosomes can also be formulated into gels, creating proniosomal gels, which are convenient, easy to administer, and particularly suitable for transdermal applications[3].

The proniosomal gel system combines the advantages of vesicular carriers with the patient-friendly nature of semisolid formulations. The gel base provides a uniform platform for application on the skin, while the proniosomal vesicles enhance penetration and allow for sustained drug release. One of the most significant advantages of proniosomal gels is their ability to encapsulate a wide range of therapeutic agents, including poorly soluble drugs, thereby improving their bioavailability. Additionally, proniosomal gels can be tailored by modifying the surfactant type, cholesterol ratio, or phospholipid content to optimize entrapment efficiency, vesicle size, and release kinetics. These characteristics make them versatile carriers adaptable for various therapeutic needs[1].

Another major advantage of proniosomal gels lies in their ability to overcome the skin barrier. The vesicular nature of the formulation facilitates closer interaction with the stratum corneum, leading to improved drug partitioning into the skin layers. Moreover, the non-ionic surfactants used in proniosomes act as penetration enhancers by fluidizing the lipid bilayers of the stratum corneum, thereby allowing higher drug flux. As a result, drugs that otherwise exhibit poor permeability through the skin can be delivered effectively in therapeutic concentrations. This mechanism has been demonstrated in several studies. For instance, optimized a proniosomal gel of lacidipine using factorial design and reported significantly enhanced transdermal delivery compared to conventional formulations[2].

The therapeutic potential of proniosomal gels has been explored across a variety of drug classes. Cardiovascular drugs, hormones, analgesics, and anti-inflammatory agents are among the many categories studied for proniosomal delivery. Their ability to provide controlled and sustained release makes them suitable for chronic conditions such as hypertension, diabetes, and hormonal disorders. Moreover, proniosomal gels offer an attractive alternative for patients who face challenges with oral administration, such as elderly individuals, pediatric patients, or those with gastrointestinal disorders. By minimizing dosing frequency and enhancing compliance, these systems contribute to improved therapeutic outcomes[3].

From a formulation perspective, proniosomal gels are relatively simple to prepare, cost-effective, and scalable for industrial production. The choice of surfactant plays a critical role in determining the physicochemical properties of the vesicles, such as size, entrapment efficiency, and release profile. Similarly, cholesterol acts as a membrane stabilizer, providing rigidity to the bilayer structure and minimizing drug leakage. Optimization of these components allows formulators to design proniosomal gels suited for specific drugs and therapeutic objectives. Additionally, proniosomes are more stable during storage compared to conventional vesicular systems, eliminating the need for strict refrigeration conditions[1].

Recent advancements in proniosomal technology have further expanded their potential. Researchers are now exploring proniosomal gels for the delivery of macromolecules, peptides, and even vaccines, which are traditionally difficult to administer through the skin. Innovative approaches such as the incorporation of natural oils, co-surfactants, or novel gel bases have also been investigated to enhance permeation and patient acceptability. These advancements highlight the versatility of proniosomal gels and their growing significance in the field of drug delivery.

Materials and their actions involved in preparation of Proniosomes

Lipids: Lipids are indispensable excipients in proniosomal formulations, where they function as stabilizers, modulators of vesicle properties, and enhancers of drug entrapment. Among the commonly used lipids, cholesterol and phospholipids such as lecithin are frequently incorporated due to their ability to impart structural integrity and biocompatibility[4]

Surfactants: Surfactants are the core excipients in proniosome formulations, as they act as vesicle-forming agents and critically influence the physicochemical and functional properties of the system. Additionally, enhance the drug solubilization by incorporating both hydrophobic and hydrophilic molecules into the vesicle structure. Their amphiphilic nature not only stabilizes the bilayer but also facilitates interaction with biological membranes, improving penetration and therapeutic effectiveness. Non-ionic surfactants, such as sorbitan esters (Span) and polysorbates (Tween), and cremophore RH-40 are most frequently employed due to their favorable safety profile, biocompatibility, and ability to self-assemble into stable bilayers[5].

Table no.1: Different surfactants and its properties used in preparation of proniosomes

Sr. no.	Name of surfactant	Synonyms	Description
1	Sorbitan Monolaurate	Span 20	HLB value = 8.6, Transition temperature = 16^0C, Not able to form gel at room temperature at lower conc. of cholesterol, Required 20-30% molar percentage of cholesterol to start formation of gel[6].
2	Sodium Monopalmitate	Span 40	The drug leaching from the vesicles composed of Span-40 is down, because of its high phase transition temperature 47.8^0C, HLB value = 6.7[7,8,9,10].
3	Sodium Monosterate	Span 60	Span 60 proportion increase (lower HLB 4.7) ibuprofen causes improved efficiency of encapsulation, Transition temperature = 52.9^0C[11,12].
4	Sodium Mono-oleate	Span 80	HLB = 4.2, Transition temperature = -12^0C improve permeation, ensure stability of proniosome formulation of Acelofenac[13].
5	Polyoxyl hydrogenated 40 Castor oil	Cremophore RH-40	Sosor Bebek (Kalanchoe pinnata (Lam.) Per.) Leaf Extract combination with Carbopol show that the incorporation of Cremophore RH 40 improves the encapsulation efficiency and biocompatibility of the gels[14, 15].
6	Brij 30	Polyethylene glycol dodecyl ether	HLB = 9, Transition temperature = 16^0C, it have high surface to volume ratio improve % EE, reduce surface free energy produce small vesicles which improves penetration and produce sustained and controlled effect of drug[16].
7	Brij 58	Polyoxyethylene (20) cetyl ether	It has less polyoxyethylene groups and more flexible linear chains since there aren't any double bonds, which reduces hydration and increases the protection of the hydrophobic core. HLB value = 15.7, TT= 38-42^0C[17].

Solvents: Solvents play a crucial role in the preparation of proniosomes by facilitating the solubilization and uniform mixing of surfactants, lipids, and drugs before hydration. In most methods, volatile organic solvents such as ethanol, isopropanol, or chloroform are used to dissolve formulation components. Upon hydration or solvent evaporation, these mixtures transform into a dry, free-flowing proniosomal powder or gel that readily converts into niosomal vesicles when exposed to aqueous media.

The choice of solvent influences several critical characteristics of proniosomes, including vesicle size, entrapment efficiency, and stability. For instance, isopropanol is often preferred for topical proniosomes because of its moderate polarity, which ensures adequate solubilization of both hydrophilic and lipophilic components while minimizing toxicity risks. Ethanol has also been widely used due to its rapid evaporation and safety profile, whereas chloroform, despite its excellent solubilizing capacity, is less favored because of residual toxicity concerns[18].

Gelling agent: Gelling agents are critical excipients in proniosomal gel formulations as they provide the desired semi-solid consistency, improve stability, and enhance patient compliance. By forming a three-dimensional polymeric network, gelling agents entrap proniosomal vesicles, thereby preventing aggregation and ensuring uniform distribution of drug throughout the gel matrix[19, 20]. It influence drug release kinetics. By restricting the mobility of vesicles within the matrix, they provide a sustained release pattern and prolong the residence time of the formulation at the application site. This is especially valuable for topical and mucosal drug delivery, where prolonged contact enhances therapeutic effect[21, 22].

Mechanism of Proniosome permeation through the skin

Proniosomes enhance skin permeation of drugs through a multifaceted mechanism that involves both physicochemical and biological interactions with the stratum corneum. Upon hydration, proniosomes form niosomes capable of encapsulating both hydrophilic and lipophilic drugs. Their vesicular nature and nanoscale dimensions allow them to overcome the rigid barrier of the stratum corneum and facilitate controlled drug diffusion[23].

One of the primary mechanisms involves lipid bilayer disruption. Non-ionic surfactants present in proniosomes interact with skin lipids, increasing fluidity of the stratum corneum and thereby reducing its resistance to penetration[24]. This effect is further supported by the presence of phospholipids, such as lecithin, which can integrate into skin membranes, enhance hydration, and create flexible vesicles that promote deeper penetration[25].

Another pathway involves vesicle adsorption and fusion at the skin surface, which enables direct transfer of drug molecules into cutaneous lipid domains[22].

2. PREPARATION OF PRONIOSOME

Coacervation Phase Separation Method and Its Modified Approach

Among the techniques available for vesicular drug delivery systems, the **coacervation phase separation method** is one of the most extensively employed for the preparation of proniosomes. The principle of this method lies in the separation of a polymer–surfactant–lipid solution into two distinct liquid phases: a dense coacervate phase and a dilute equilibrium phase. When a drug is incorporated into this system, it becomes entrapped within the coacervate, which on hydration gives rise to stable niosomal vesicles. Typically, volatile organic solvents such as ethanol, isopropanol, or chloroform are used to dissolve surfactants and lipids. Upon gradual addition of an aqueous phase and solvent removal, the mixture transitions into a proniosomal state capable of rehydration into nanosized vesicles. This approach offers the advantages of high entrapment efficiency and compatibility with both hydrophilic and lipophilic drug molecules[26].

Despite its simplicity and reproducibility, the conventional coacervation method presents certain limitations, including vesicle aggregation, instability during storage, and concerns regarding residual solvent toxicity. To overcome these challenges, the modified coacervation phase separation method was introduced. This technique incorporates stabilizers such as carbopol, cellulose derivatives, or natural gums to improve rheological properties and prevent vesicle fusion, thereby ensuring better physical stability). Furthermore, the replacement of toxic solvents with safer alternatives like isopropanol enhances the biocompatibility of the final formulation. Recent studies have confirmed that proniosomes prepared via the modified approach exhibit improved stability, controlled vesicle size distribution, and sustained release patterns. For example, amphotericin B–loaded proniosomal gels prepared by this technique demonstrated enhanced stability and prolonged drug release compared to the conventional method[27].

Collectively, the coacervation phase separation method remains a versatile and efficient approach for proniosome preparation, while its modified version offers distinct advantages in terms of safety, stability, and scalability, making it particularly suitable for modern topical formulations in conditions such as skin cancer and fungal infections.

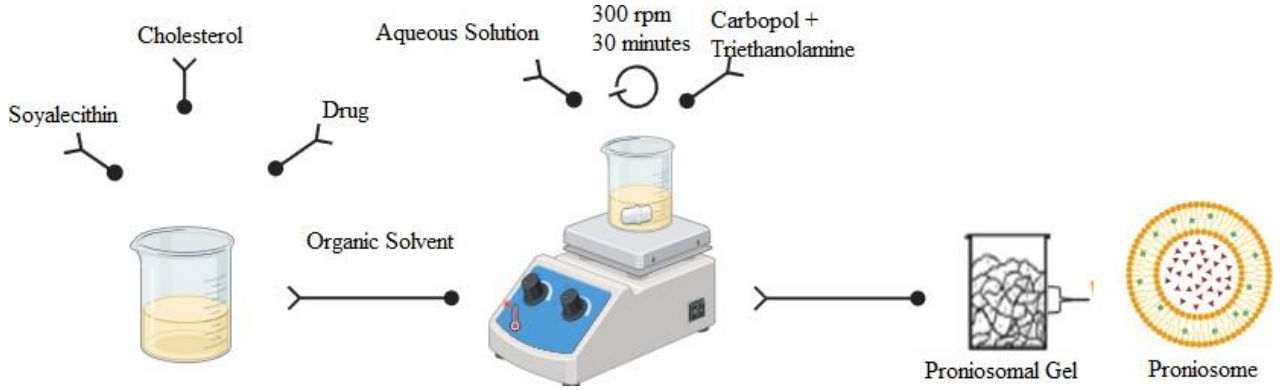

Fig. no.1 :Coacervation and Modified Coacervation Phase Separation Method (Prepared by Biorender).

Slurry Method

Among the different strategies for proniosome production, the slurry method is one of the most extensively described in literature due to its simplicity and adaptability. In this process, surfactants, lipids, and the drug are first dissolved in a minimal volume of a volatile organic solvent such as ethanol or chloroform. This solution is then added to a water-soluble carrier like sorbitol or maltodextrin to form a slurry. The mixture is subsequently dried under controlled conditions, leading to uniform deposition of the surfactant–lipid layer over the carrier particles. When hydrated with an aqueous medium, the

dry-coated carriers readily form niosomal vesicles. This technique is advantageous because it offers high drug entrapment efficiency, reproducibility, and protection of thermolabile drugs, while also ensuring better stability compared to conventional niosomal suspensions[2].

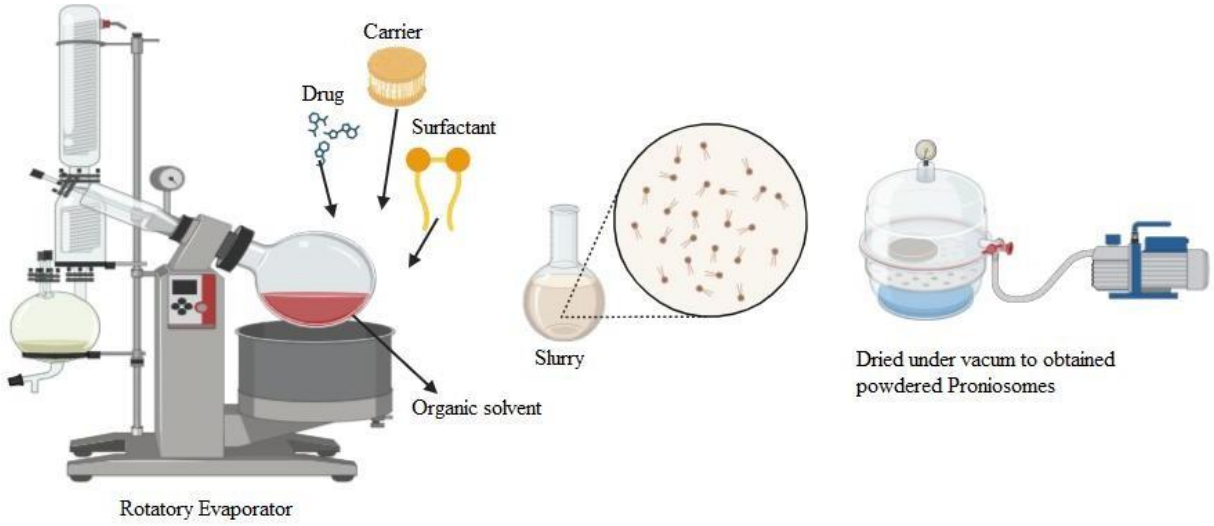

Fig no:-2 Slurry Method (generated by Biorender).

Spray Congealing method

The spray congealing method is a solvent-free approach that provides a more industrially feasible alternative. Here, the molten mixture of surfactant, lipid, and active drug is atomized into a cooling chamber, where rapid solidification produces fine proniosomal powder. Since the process does not rely on organic solvents, it circumvents issues of residual toxicity, making it more biocompatible. Additionally, spray congealing yields free-flowing particles with narrow size distribution, enhancing both stability and handling. This method is particularly suitable for large-scale production, offering better scalability and reproducibility than solvent-based approaches. Moreover, the absence of residual solvents makes it attractive for regulatory compliance and safer therapeutic applications[18].

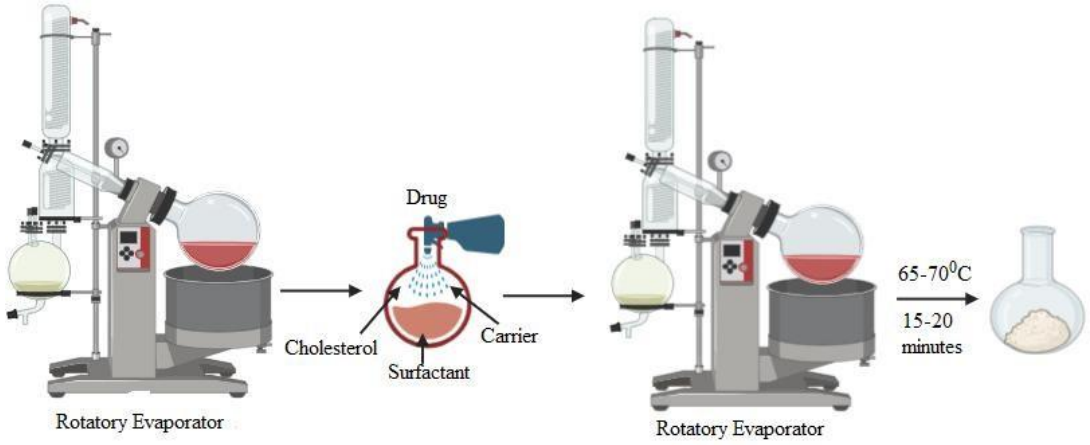

Fig no: - 3 Slow Spray Coating Method (generated by biorender)

Table no.2: Previously research study of Proniosomal gel

Sr. No.	Year of Publication	Incorporated drug	Preparation method	Therapeutic Category	Reason of Preparation	Reference
1	2023	Carvedilol	CPM	Antihypertensive	Carvedilol, particularly its R-enantiomer, has demonstrated significant potential in preventing skin carcinogenesis through various mechanisms, including anti-inflammatory effects and enhanced skin penetration when formulated in Proniosomes.	28
2	2023	Doxorubicin	CPM	Anti-neoplastic	This innovative drug delivery system aims for enhancing doxorubicin's therapeutic efficacy while reducing side effects through targeted delivery mechanism	29
3	2024	Ofloxacin	CPM	Antibiotic	Improve permeation of drug, antibacterial activity and otic tolerance through in vitro, ex vivo, and microbiological evaluations.	18
4	2024	Enalapril maleate	CPM	Antihypertensive	This innovative drug delivery system utilizes a coacervation technique to optimize the formulation, resulting in improved drug entrapment and permeation characteristics.	30
5	2021	Gossypin	CPM	Antioxidant and Anti-inflammatory	This innovative approach highlights the potential of proniosomal gels in enhancing drug stability, permeability, and localized action, making them a promising option for treating melanoma.	31
6	2021	Progesterone	CPM	Contraceptive agent	Proniosomal gels are prepared using non-ionic surfactants, lecithin, cholesterol, and ethanol, aiming to improve drug stability and permeability for effective transdermal delivery.	32
7	2020	Clozapine	CPM	Antipsychotic agent	Lozapine, a BCS Class II drug, has low bioavailability (27%) as well as frequent dosing requirements, leading to adverse drug reactions.Proniosomal gel in vitro release, ex vivo permeation, as well as gel properties, showcasing its potential to improve drug stability, permeability, and controlled release.	33
8	2017	Risperidone	CPM	Antipsychotic agent	The formulations provided a sustained release of risperidone, reducing peak plasma concentration while increasing the area under the curve (AUC), which is beneficial for managing schizophrenia	34
9	2021	Atrovastatin calcium	CPM	Calcium channel blocker	The gel demonstrated superior skin permeation and controlled drug release compared to conventional formulations. And it have a potential to alleviate statin-induced hepatotoxicity.	35
10	2018	Lovastatin	CPM	Calcium channel blocker	Incorporating hydrated proniosomes into a Carbopol matrix enhanced the gel's stability and viscosity, making it suitable for transdermal application.	36
11	2023	Acitretin	CPM	Anti-inflammatory	Reduce irritation of psoriasis patient and improve the therapeutic efficacy of drug.	37

12	2023	Oxybutynin chloride	CPM	Antispasmodic agent	Oxybutynin chloride, an antimuscarinic agent, often causes side effects like dry mouth and dizziness when administered orally. Proniosomal gels minimized systemic side effects by bypassing first-pass metabolism. It showed significant improvements in bladder morphology and reduced urinary frequency	38
13	2019	Ethinyl estradiol and Levonorgestrel	CPM	Contraceptive agent	Proniosomal gel achieve sustained drug release, improved skin permeation, and enhanced stability	39
14	2016	Glimepiride	CPM	Antidiabetic agent	Proniosomal formulations provided sustained drug release, sustaining therapeutic levels for a long time. enhancing treatment results and patient compliance for the control of diabetes.	40
15	2023	Resveratrol	CPM	Antioxidative agent	The gel demonstrated better bioavailability compared to conventional formulations. Superior skin penetration was observed, ensuring effective transdermal delivery.	41
16	2021	5-fluorouracil	CPM	Antineoplastic agent	Proniosomal gel formulations demonstrated improved skin penetration and sustained drug release compared to conventional methods.	22
17	2022	Tapentadol HCl	CPM	Analgesic	This innovative approach highlights the potential of proniosomal gels in providing effective pain management while minimizing systemic side effects.	42
18	2016	Ritonavir	CPM	Antiviral agent	Improve the bioavailability of drug.	43
19	2020	Televacin	CPM	Antibiotic	This innovative approach highlights the potential of proniosomal gels in improving the therapeutic efficacy of antibiotics for topical applications.	44
20	2018	Itraconazole	CPM	Antifungal	The research aims to enhance patient compliance, reduce drug dosage, and minimize side effects like liver and kidney damage associated with oral administration.	45

3. EVALUATION PARAMETERS

Entrapment efficiency

Entrapment efficiency (EE%) is a critical parameter in evaluating proniosomal formulations, as it reflects the proportion of drug successfully incorporated into the vesicles relative to the total amount used. A high entrapment efficiency ensures improved therapeutic performance, prolonged drug release, and reduced dosing frequency.

The determination of EE% in proniosomes generally involves separation of the unentrapped (free) drug from the vesicle-associated drug, followed by quantification. Soliman et al. (2016) employed centrifugation, a widely accepted method, where the hydrated proniosomal dispersion is subjected to high-speed centrifugation. This process causes the niosomal vesicles, which contain the entrapped drug, to sediment, while the free drug remains in the supernatant. The supernatant is carefully collected, and the amount of unentrapped drug is quantified using suitable analytical techniques such as UV–visible spectrophotometry or high-performance liquid chromatography (HPLC**)**. The entrapped drug content is then calculated by subtracting the free drug from the total amount initially added[2].

The entrapment efficiency is usually expressed as a percentage using the following equation:

EE%=(Total drug−Free drug)/Total drug×100

Vesicle size determination

Vesicle size is one of the most crucial physicochemical parameters influencing the performance of proniosomal formulations, as it directly affects drug entrapment, stability, skin permeation, and release kinetics. Accurate characterization of vesicle size and its distribution provides insight into the quality and reproducibility of the developed system. vesicle size is typically determined using dynamic light scattering (DLS**)**, also known as photon correlation spectroscopy. This method measures fluctuations in the intensity of scattered light caused by Brownian motion of the vesicles when dispersed in a medium. From these fluctuations, the hydrodynamic diameter and polydispersity index (PDI) are calculated, which reflect the average vesicle size and uniformity of the dispersion, respectively. A low PDI (<0.3) indicates a homogenous population of vesicles, which is desirable for consistent drug delivery performance[46].

Surface Morphological Study of vesicles

Surface morphology is an essential parameter in the characterization of proniosomal vesicles, as it provides critical insights into their structural integrity, uniformity, and suitability for drug delivery. The morphology of vesicles influences not only drug encapsulation and release behavior but also their interaction with the skin barrier, which is particularly relevant for topical applications. Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are the most widely used, as they provide high-resolution images that reveal the shape, surface texture, and lamellarity of the vesicles. TEM allows visualization of vesicles at the nanoscale, demonstrating whether the vesicles are spherical and uniformly distributed, while SEM provides three-dimensional images of the vesicular surface, confirming smoothness or the presence of irregularities[47].

In-vitro diffusion study

In-vitro diffusion studies serve as the preliminary method to evaluate the release characteristics of proniosomal formulations. Using Franz diffusion cells, a synthetic barrier such as cellophane or dialysis membrane is employed to separate the donor and receptor compartments. The proniosomal gel is applied to the donor side, while the receptor chamber contains a suitable buffer, typically phosphate-buffered saline, maintained at 37 ± 0.5 °C to simulate physiological conditions. At fixed time intervals, aliquots are withdrawn from the receptor compartment and analyzed for drug content. This procedure provides valuable information regarding the release kinetics of the formulation, helping to determine whether the system follows zero-order, first-order, or diffusion-controlled release mechanisms. In-vitro studies thus establish the fundamental release behavior of proniosomes before proceeding to more complex biological models.

Ex-vivo diffusion study

Ex-vivo diffusion studies extend the evaluation by incorporating biological membranes such as excised animal skin or human cadaver skin. This approach provides insights into how the proniosomal formulation interacts with the natural barrier properties of the stratum corneum and viable epidermis. Using Franz diffusion cells, the excised skin is mounted between the donor and receptor compartments, with the proniosomal gel applied to the surface. Samples are collected over time from the receptor phase and analyzed for drug concentration. Key permeation parameters, including steady-state flux, permeability coefficient, and lag time, are calculated to assess the ability of proniosomes to enhance transdermal transport. Ex-vivo studies are particularly important as they bridge the gap between in-vitro release data and in-vivo therapeutic outcomes, offering a more realistic prediction of drug penetration across the skin[48].

Determination of Viscosity of proniosomal gel

The viscosity of proniosomal gels is a critical parameter that directly influences their spreadability, stability, and drug release behavior. Measurement is generally performed using a Brookfield viscometer, which operates on the principle of rotational resistance. In this method, the gel sample is placed in a sample container, and an appropriate spindle is immersed in the formulation. The spindle rotates at a predetermined speed, and the resistance encountered by the spindle during rotation is translated into viscosity values, expressed in centipoise (cPs).

To ensure reliability, measurements are usually taken at controlled temperatures (25 ± 1 °C) and at varying shear rates to observe rheological behavior. Proniosomal gels often display non-Newtonian, shear-thinning characteristics, which is advantageous for topical application since viscosity decreases upon spreading but recovers after application, providing better retention at the site. Evaluating viscosity not only helps in characterizing the gel's flow properties but also provides insight into the consistency and stability of the system during storage and use[49].

Spreadability testing

Spreadability is an essential parameter in evaluating the topical performance of proniosomal gels, as it reflects the ease with which the formulation can be applied over the skin surface. An ideal gel should spread smoothly with minimal effort while ensuring uniform application and adequate patient compliance.The testing is generally carried out using a parallel

plate method. In this approach, a small amount of gel is placed between

two glass plates, and a specific weight is applied to the upper plate for a fixed duration. The extent of spreading, usually measured in terms of diameter or area covered, is recorded. This technique provides a quantitative measure of the gel's spreadability, which is influenced by viscosity, gelling agent concentration, and overall formulation composition.

Proniosomal gels typically demonstrate moderate to high spreadability, ensuring effective coverage of the target site. Optimized spreadability not only improves patient acceptability but also plays a role in enhancing drug permeation by facilitating closer contact between the gel and skin surface[50].

P^H determination of Proniosomal gel

The pH evaluation of proniosomal gels is a critical step in their characterization, as it directly affects skin compatibility, drug stability, and overall patient acceptability. Since the formulation is intended for topical delivery, the pH should ideally fall within the physiological skin range (approximately 5.0–7.0) to prevent irritation or barrier disruption.

The determination is generally carried out by dispersing a specified amount of the gel in distilled water and allowing equilibration before measurement with a calibrated digital pH meter. This method ensures accurate assessment of the surface hydrogen ion concentration and provides an indication of whether the formulation is suitable for dermal application[51].

Drug Content

Drug content analysis is a fundamental quality control parameter in the evaluation of proniosomal gels, as it ensures uniform distribution of the active pharmaceutical ingredient (API) throughout the formulation. This parameter directly influences therapeutic efficacy and dose reproducibility.

The procedure generally involves accurately weighing a specific amount of the gel and dissolving it in a suitable solvent system, such as phosphate buffer or methanol, to ensure complete extraction of the entrapped drug. The solution is then subjected to spectrophotometric or chromatographic analysis, where the absorbance or peak area is compared against a standard calibration curve of the pure drug[52].

4. THERAPEUTIC USES

Localized drug delivery

Proniosomal gels have emerged as a promising platform for localized drug delivery, particularly in the management of site-specific conditions such as periodontal diseases, skin infections, and localized inflammatory disorders. Their unique vesicular structure allows them to encapsulate both hydrophilic and lipophilic drugs, while the gel matrix facilitates prolonged residence time at the site of application.

Doxycycline-loaded proniosomal gel for periodontal treatment, where the formulation ensured sustained drug release, effective penetration into gingival crevicular fluid, and targeted antimicrobial activity. Such findings underscore the relevance of proniosomal gels as localized delivery systems, offering improved therapeutic efficacy, reduced dosing frequency, and patient compliance compared to conventional topical preparations[53].

Cardiological application

Proniosomal gels have shown significant promise in the field of cardiovascular therapeutics, particularly for drugs with poor oral bioavailability, short half-life, or extensive first-pass metabolism. Their ability to provide sustained release and enhance transdermal drug delivery makes them suitable for managing chronic conditions such as hypertension and ischemic heart disease.

One notable example is the development of atenolol-loaded proniosomal gel for transdermal application. Atenolol, a widely used β-blocker, suffers from low oral bioavailability due to first-pass metabolism, necessitating frequent dosing to maintain therapeutic levels[54].

Management of Diabetic condition

Diabetes mellitus requires long-term therapy, often involving drugs with limitations such as low oral bioavailability, short half-life, and gastrointestinal side effects. Metformin hydrochloride, the most widely prescribed oral antidiabetic agent, is associated with poor absorption and gastrointestinal intolerance when administered orally. To overcome these drawbacks, transdermal delivery via proniosomal formulations has been explored as an alternative strategy.

Proniosomes offer several advantages in diabetes management, particularly by enabling sustained and controlled release of antidiabetic agents. Researcher developed a transdermal patch containing metformin-loaded proniosomes, which demonstrated enhanced permeation through the skin barrier compared to conventional formulations. The vesicular nature of proniosomes improved drug entrapment and facilitated passage across the stratum corneum, while the patch design

ensured prolonged contact time, leading to steady and sustained plasma drug concentrations[55].

Effective Enzyme Delivery

The therapeutic application of enzymes in topical and transdermal therapy is often restricted by their large molecular size, instability, and poor permeability through the skin barrier. Conventional formulations fail to maintain enzyme activity and limit their effective delivery to the target site. Vesicular carriers such as proniosomes and niosomes provide a promising strategy to overcome these limitations by encapsulating enzymes within a stable, biocompatible vesicular matrix.

Researchers investigated the delivery of serratiopeptidase using a niosomal gel system, demonstrating significant potential in enhancing enzyme stability and facilitating controlled release at the site of application. Incorporating the enzyme into vesicular carriers protected it from degradation while improving penetration through the stratum corneum. Furthermore, the gel base provided ease of application, prolonged residence time, and better patient acceptability.

The ability of proniosomal and niosomal formulations to safeguard enzymatic activity while improving skin permeation broadens their scope for therapeutic enzyme delivery. Such systems can be tailored for localized treatment of inflammatory conditions, wound healing, and other enzyme-mediated therapies where conventional delivery routes remain ineffective.

Thus, enzyme-loaded proniosomal gels represent an innovative approach to topical biotherapeutics, offering enhanced stability, sustained release, and improved therapeutic efficacy compared to conventional formulations[56].

Hormonal Delivery

Transdermal systems have been widely investigated for hormonal delivery due to their ability to bypass hepatic first-pass metabolism, maintain steady plasma concentrations, and improve compliance in long-term therapies. Hormonal agents, such as contraceptive steroids, are particularly suitable for this route since they require sustained systemic availability at therapeutic levels. However, their low solubility and poor permeability through the stratum corneum limit their transdermal efficiency. To overcome these challenges, vesicular carriers such as proniosomes have been explored as promising vehicles for hormone delivery. Proniosomal gels are advantageous for the delivery of contraceptive hormones like levonorgestrel, as they enhance skin permeation while providing controlled release over extended periods. A proniosome-based transdermal system was formulated to deliver levonorgestrel effectively for contraception. The system demonstrated improved entrapment efficiency and stability compared to conventional niosomes, while also enhancing the permeability of the hormone through the skin. The vesicular system acted both as a reservoir for the drug and as a penetration enhancer by interacting with the stratum corneum lipids, thereby facilitating transdermal transport[57].

Topical Delivery of Drug

Proniosomal gels are composed of non-ionic surfactants, cholesterol, and phospholipids, which upon hydration, form niosomal vesicles capable of encapsulating both hydrophilic and lipophilic drugs. When applied topically, these vesicles act as penetration enhancers by interacting with stratum corneum lipids, disrupting their rigid structure, and allowing drug molecules to diffuse more efficiently. In addition, the gel base ensures prolonged residence time on the skin, leading to sustained drug release and improved therapeutic outcomes.

Researchers developed a proniosomal gel formulation containing ethinylestradiol and levonorgestrel for antifertility treatment. The formulation demonstrated enhanced entrapment efficiency, optimal vesicle size, and improved stability compared to conventional delivery systems. Importantly, in vitro and ex vivo evaluations confirmed higher drug permeation and prolonged release, highlighting the potential of proniosomal gels to provide controlled systemic delivery of hormonal agents via the topical route[38].

The use of proniosomal gels for topical delivery is not limited to contraceptive agents. Their ability to enhance solubility and permeability makes them applicable to a wide range of therapeutic areas, including pain management, dermatological treatments, and hormone replacement therapies. Furthermore, their stability during storage and ease of reconstitution make them a practical alternative to conventional vesicular systems, which are often hindered by issues such as aggregation and drug leakage.

Overall, proniosomal gels represent a versatile and effective platform for topical drug delivery. By combining the benefits of vesicular carriers with the convenience of gel formulations, they not only overcome the limitations of traditional systems but also open new avenues for the delivery of drugs that are otherwise poorly absorbed through the skin. Continued research and optimization of these systems are expected to further expand their clinical applications.

5. CONCLUSION

Proniosomal gels have emerged as an innovative and efficient approach for enhancing transdermal drug delivery. By combining the advantages of vesicular systems with the convenience and stability of gel formulations, they successfully address many of the limitations associated with conventional drug delivery methods. Their ability to encapsulate both hydrophilic and lipophilic agents, improve skin permeation, and provide sustained release makes them a versatile platform for a wide range of therapeutic applications.

The structural composition of proniosomes, particularly the use of non-ionic surfactants and cholesterol, contributes to their stability and efficiency in overcoming the stratum corneum barrier. Moreover, their ease of storage, reconstitution, and patient-friendly application enhance their suitability for long-term therapy. Evidence from various studies demonstrates that proniosomal gels significantly improve drug entrapment, permeability, and bioavailability, supporting their potential as an alternative to oral or invasive delivery systems.

Despite these advantages, further investigations are required to standardize formulation strategies, evaluate large-scale production feasibility, and confirm their long-term safety through extensive clinical studies. With continued research and optimization, proniosomal gels hold great promise in advancing transdermal delivery technologies, offering improved therapeutic efficacy and patient compliance across diverse treatment areas.

6. FUTURE PERSPECTIVES

Although proniosomal gels have shown considerable potential in improving transdermal drug delivery, several opportunities remain for further development. Future research should focus on the optimization of formulation parameters, including surfactant type, cholesterol concentration, and vesicle size, to achieve consistent performance across diverse drug categories. Advances in nanotechnology and materials science may enable the design of hybrid proniosomal systems with improved stability, controlled release, and targeted delivery.

Another area of exploration lies in expanding the therapeutic scope of proniosomal gels. While significant work has been carried out in the delivery of hormones, anti-inflammatory agents, and cardiovascular drugs, there is scope for investigating their role in the delivery of peptides, proteins, vaccines, and other biopharmaceuticals that are otherwise difficult to administer via the transdermal route. Incorporation of natural oils or bioactive excipients may further enhance skin permeation while improving biocompatibility.

From a translational perspective, large-scale manufacturing and regulatory validation are essential to bring proniosomal gels closer to clinical application. Stability studies under real-world conditions, along with extensive in vivo and clinical evaluations, will help establish their safety, efficacy, and reproducibility. In addition, integrating proniosomal gel systems with advanced drug delivery platforms such as microneedles, iontophoresis, or patches may provide synergistic benefits in enhancing drug permeation and patient adherence.

Overall, the future of proniosomal gels lies in their continued refinement and diversification. With multidisciplinary research efforts, they hold strong potential to evolve into mainstream transdermal delivery systems, ultimately improving therapeutic outcomes and patient quality of life.

Author contribution

Megha Gandhi: Conceptualization, Writing – review & editing, **Ramesh Parmar:** Resources, Writing – original draft.

Conflict of Interest

Authors declare that none of the data available in this publication has been allegedly influenced by any known conflicting financial interests or personal relationships.

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