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ENHANCEMENT OF TRANSDERMAL DELIVERY OF AN ANTIDIABETIC DRUG VIA PRONIOSOMAL GEL ENTRAPMENT

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ABSTRACT

Conventional drug delivery systems frequently fail to provide optimal therapeutic outcomes due to poor bioavailability, fluctuating plasma drug concentrations, systemic adverse effects, and reduced patient compliance. To address these limitations, novel vesicular drug delivery systems have been extensively explored. Among them, Proniosomal gel has emerged as a promising transdermal delivery system owing to its superior stability, enhanced skin permeation, and sustained drug release properties. Proniosomes are dry, non-ionic surfactant-based formulations that readily transform into niosomes upon hydration, allowing effective encapsulation of both hydrophilic and lipophilic drugs. This review highlights the formulation aspects, structural characteristics, mechanism of action, preparation techniques, evaluation parameters, and therapeutic applications of Proniosomal gels. The influence of formulation variables such as surfactant type, cholesterol content, lipid charge, hydration pH, and total lipid concentration is also discussed. By overcoming the stratum corneum barrier, Proniosomal gels offer a patient-friendly and efficient approach for transdermal drug delivery, particularly in the management of chronic diseases such as diabetes mellitus.

KEYWORDS: Proniosomal gel; Transdermal drug delivery system; Vesicular systems; Skin permeation; Sustained release.

INTRODUCTION

Although no single drug delivery method has been able to satisfy all the requirements in recent years, efforts have been made to solve this through creative solutions. Numerous cutting-edge techniques covering a variety of administration routes have emerged to achieve either targeted or controlled distribution. Reducing side effects and preserving a stable and efficient drug level in the body are the fundamental objectives of novel drug delivery. Additionally, it targets drug distribution and localizes drug activity via drug carriers.[1]

Vesicular drug delivery techniques that employ colloidal particle carriers, such as liposomes or niosomes, have definite benefits over traditional dosage forms. Proniosomal gels are structurally similar to liposomes and niosomes, despite the fact that the ingredients employed to create them make them more stable and offer numerous advantages. Both liposomes and niosomes possess a bilayer.[2]

A number of issues with conventional dosage forms, including as low water solubility, poor bioavailability, poor membrane permeability, changing plasma concentration, adverse effects, low patient compliance, and ultimately low patient efficacy, can be avoided using these systems.[3]

Therapeutic medications are administered to and via the skin using proniosomal gel, a semi-solid, liquid crystalline gel. Because of its low water content, it has a gel-like texture and is composed of non-ionic surfactants, alcohol, lipids, and an aqueous phase. Proniosomal gels are stable during storage and transportation and are frequently transparent, translucent, or white in colour.[4]

TRANSDERMAL DRUG DELIVERY

The delivery of active chemicals through the skin for systemic distribution is known as transdermal administration. To get consistent therapeutic levels of the medicine, transdermal drug delivery is an alternative to the traditional oral and parental routes. Proniosomes provide a flexible vesicle drug delivery approach that may be used for transdermal medication delivery. This could occur if proniosomes hydrate with skin water after topical administration under occlusive conditions to create niosomes.[5]

STRUCTURE OF PRONIOSOMES

A combination of liquid crystal phases, including lamellar, cubic, and hexagonal shapes, make up the semisolid gel-like formations known as proniosomes. They usually have microscopic-sized lamellar structures. Non-ionic surfactants and cholesterol are used to create proniosomes. The non-ionic surfactant forms a bilayer with its hydrophilic and hydrophobic parts oriented outward and inward, respectively. When medications are incorporated, hydrophobic pharmaceuticals are embedded in the proniosome bilayer, whereas hydrophilic drugs are contained within the vesicles' watery core. Depending on how they are prepared, proniosomes can be either unilamellar or multilamellar.[6]

They are made up of a surfactant bilayer in which the hydrophobic chains face one another and the hydrophilic ends are orientatedtoward the vesicle's surface and interior. Because of this structure, hydrophilic medications can be contained in the aqueous core while hydrophobic medications are integrated into the lipid bilayer.[7]

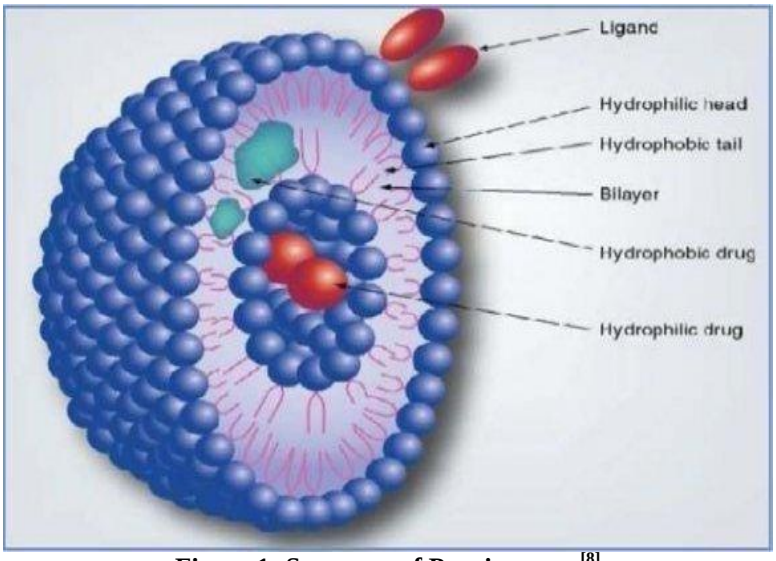

Figure 1: Structure of Proniosomes.[8]

PRONIOSOMAL GEL

Proniosomes are vesicular drug delivery systems made up of several additives, cholesterol, and non-ionic surfactants. These are anhydrous or dry formulations made by applying non-ionic surfactants to a carrier.[6]

Non-ionic surfactants make up the semi-solid, liquid crystalline composition known as proniosomal gel. It can be made by dissolving the surfactant in a little amount of an appropriate solvent and a tiny amount of aqueous phase.[9]

These structures are compact, liquid crystalline hybrids of niosomes that can be applied topically or transdermally or easily transformed into niosomes when hydrated. Proniosomal gels typically have a transparent, translucent, or white semisolid appearance and offer superior physical stability while being transported and stored. [10]

ADVANTAGES OF PRONIOSOMAL GEL[11]

1. **Enhanced Drug Delivery:** Proniosomal gels have the potential to enhance medication delivery via the skin. Both hydrophilic and lipophilic medications can be encapsulated in the gel's niosomal vesicles, which makes it easier for them to pass through the epidermal barrier.
2. **Increased Drug Stability:** Proniosomal formulations provide enhanced stability by preventing medication breakdown. This is especially crucial for medications that are susceptible to oxidation, heat, or light.
3. **Sustained Release:** The medicine that is enclosed in proniosomal gels can be released gradually for a long time. Long-lasting therapeutic benefits, fewer applications, and increased patient compliance may result from this.
4. **Improved skin permeation:** Proniosomal gels' vesicles have the ability to increase skin permeability, which improves medication penetration. For medications that have low skin penetration on their own, this is advantageous.

5. **Reduced side effects:** Proniosomal gels may lessen systemic absorption and potential adverse effects linked to elevated medication concentrations in the bloodstream by enabling localized administration and controlled release.
6. **Ease of Application:** The gel formulation improves patient compliance by offering a practical and simple topical method. Additionally, it enables targeted therapy at the application location.
7. **Versatility:** Proniosomal gels are useful for a variety of therapeutic applications, such as dermatology, cosmetology, and pain treatment, because they are adaptable and may be made for different kinds of medications.
8. **Enhanced Bio-availability:** By preventing enzymatic breakdown and promoting absorption, the encapsulation of medications in proniosomal vesicles can increase their bioavailability.

MECHANISM OF PRONIOSOMES[12]

When skin moisture or aqueous media hydrate proniosomes, which are dry, dormant forms of niosomes, they become active vesicles. Depending on the characteristics of the vesicles, transdermal drug delivery systems use various penetration techniques. The skin can be penetrated by highly malleable vesicles without causing structural damage. By upsetting the densely packed epidermal lipid structure, ethosomes improve penetration. Surfactants are used by proniosomes and niosomes to enhance medication penetration through the epidermal barrier. Drugs used topically must first pass through the living epidermis and stratum corneum. Instead of skin appendages, the intercellular lipid route is the primary means of drug transport.

Proniosomes improve medication diffusion by increasing SC hydration and lipid fluidity. Drugs are released by niosomes by enzymatic membrane breakdown upon systemic penetration. Appropriate transdermal medications should have a log P value between 1 and 3 and a molecular weight of less than 600 Da.

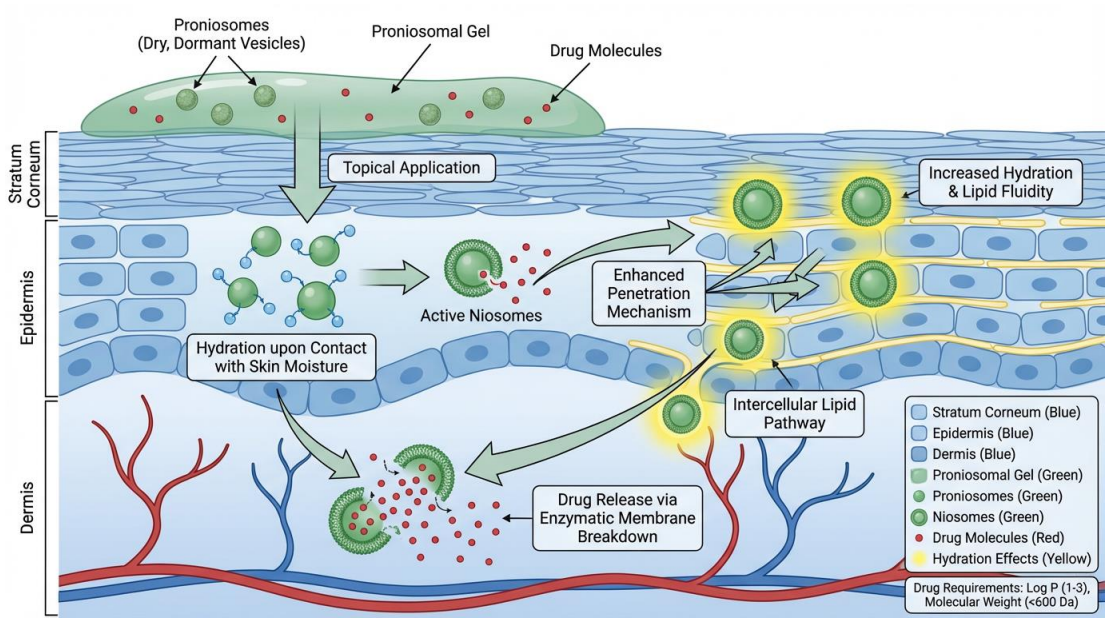

Figure 2: Mechanism of Proniosomes.
(SOURCE: lovart ai)

Factor affecting the formulation of proniosomes[13]

The development of Proniosomal formulations is influenced by various formulation and processing parameters, including surfactant chain length, cholesterol proportion, pH of the hydration medium, overall lipid concentration, and the electrical charge of lipids.

a) Surfactant chain length: Surfactants with longer alkyl chains generally exhibit higher drug entrapment capacity. Non-ionic surfactants such as Spans are commonly employed in Proniosome preparation. Among them, the entrapment efficiency follows the order: Span 60 (C18) > Span 40 (C16) > Span 20 (C12), indicating improved encapsulation with increasing chain length.

b) Cholesterol content: The effect of cholesterol on encapsulation efficiency depends on both the type and concentration of surfactant used in the formulation. While an appropriate amount of cholesterol can stabilize the bilayer structure, excessive cholesterol increases membrane rigidity, which in turn reduces drug release from the Proniosomal system.

c) pH of the hydration medium: Lowering the pH of the hydration medium enhances drug encapsulation, resulting in higher entrapment efficiency within the Proniosomes.

d) Total lipid concentration: An increase in total lipid content does not proportionally improve drug loading. At higher lipid concentrations, a smaller proportion of lipids actively participate in drug encapsulation, leading to reduced efficiency.

e) Charge of the lipids: The inclusion of charged lipids, whether positively charged (such as stearylamine or stearyl pyridinium chloride) or negatively charged (such as diacetyl phosphate or phosphatidic acid), tends to lower the encapsulation efficiency of Proniosomal formulations.

DIABETES MELLITUS

Chronic hyperglycemia, a pathogenic condition that may involve abnormalities in insulin secretion and/or action, is the result of diabetes mellitus (DM), a metabolic illness. One in three Americans are predicted to get diabetes at some point in their lives. About 90% of DM patients are type 2 diabetic mellitus (T2DM), the most prevalent kind of the disease. The main cause of type 2 diabetes is the body's tissues' inability to react to insulin or produce enough of it. According to a number of scientific studies, diabetes has a negative impact on people's quality of life since it increases the chance of serious consequences like stroke, amputation, renal failure, and blindness, which can result in severe morbidity and early death.

The International Diabetes Federation (IDF) predicted that there were about 463 million adults with diabetes in 2019, as shown in Figure 2. This number is expected to increase to 578 million individuals by 2030 and 700 million by 2045.

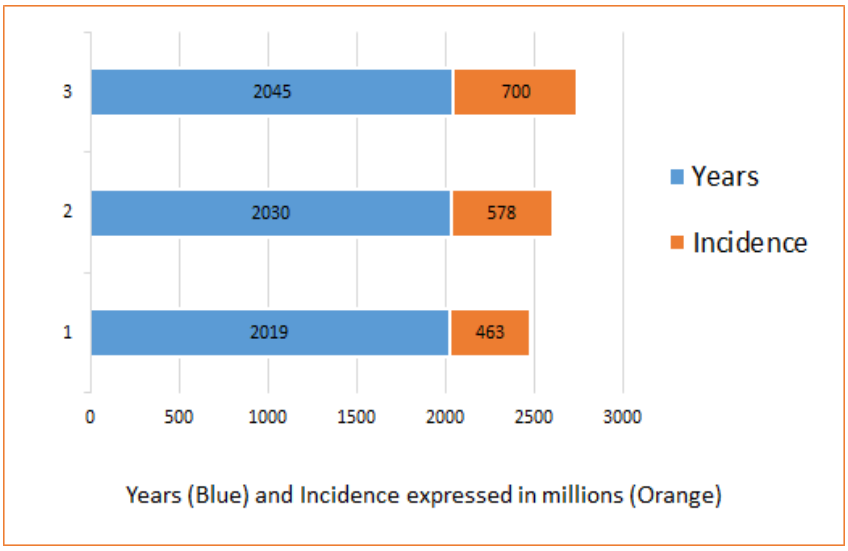

Figure 3: Forecast of a global rise in the number of people with diabetes.

Over the past few decades, DM treatment approaches have improved. However, hypoglycemia coma and liver and renal problems are among the dangerous side effects of anti-diabetic medications. For the treatment of diabetes mellitus, the World Health Organization (WHO) advises using medicinal herbs in food products. Medicinal plants are used by at least four billion individuals in underdeveloped nations to treat metabolic illnesses including diabetes mellitus. Consequently, anti-hypoglycemic vitamins, medicinal herbs, and vital elements continue to be crucial for the treatment of diabetes. Pre-clinical and clinical research have demonstrated the effectiveness of using medicinal herbs, vitamins, and critical elements to lower blood sugar levels. For instance, a study found that zinc consumption increases insulin activity and controls insulin receptors. Garlic protects adult albino rats from diabetic retinopathy, according to a study. Based on variations in chemical structure, several phytochemicals with anti-diabetic qualities found in medicinal plants have been identified and categorized into primary groups. Alkaloids, aromatic acids, carotenoids, coumarins, essential oils, flavonoids, glycosides, organic acid, phenols and phenolics, phytosterols, protease inhibitors, saponins, steroids, tannins, terpenes, and terpenoids are the main categories of phytochemicals. The anti-diabetic qualities of medicinal herbs and vitamins, such as their anti-hyperglycemic, anti-lipidemic, hypoglycemic, and insulin-mimicking effects, have been demonstrated by recent pharmacological research.[14]

Transdermal drug delivery

With benefits including avoiding the hepatic first pass metabolism and a longer duration of action, shielding delicate medications from the gastrointestinal tract's harsh environment, and enabling continuous drug release to maintain a more consistent plasma concentration, transdermal drug delivery is a very favorable method of drug delivery when compared to other drug administration routes.[15,16,17] However, one of its primary constraints is the stratum corneum (SC), the skin's outermost layer. As a result, skin penetration enhancers are attracting the most attention in pharmaceutical

research.[18] By reducing the skin's impermeability, penetration enhancers aid in the intended drug's (penetrant's) passage through the skin. Permeation enhancers should have certain qualities, such as being pharmacologically inert, nonirritating, nontoxic, nonallergic, compatible with medications and excipients, odorless, tasteless, colorless, affordable, and having good solvent qualities.[19]

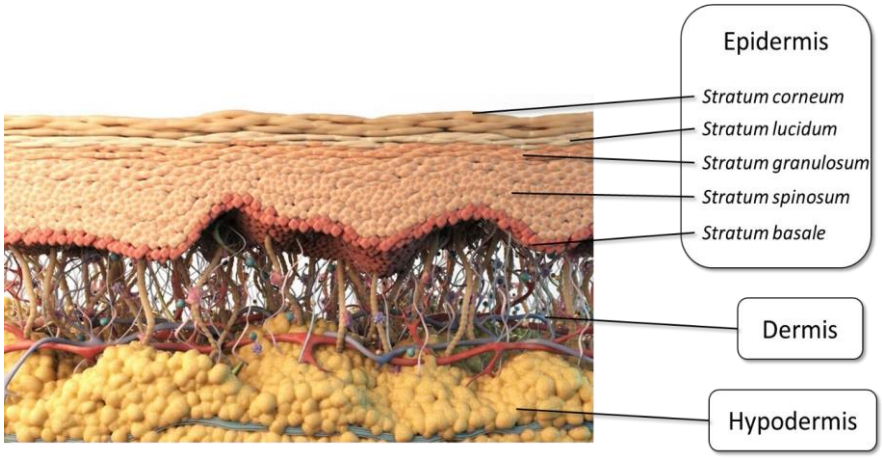

Figure 4: Schematic representation of the skin layers.

ANATOMY OF SKIN

The largest organ in the body is the skin. An average adult human's skin has a surface area of around 2 m^2, weighs 4.5-5 kg, or roughly 16% of their body weight, and gets one-third of the blood that circulates throughout their body. It has a thickness of only a few millimeters (2.97±0.28 mm), is robust, elastic, and self-regenerating under typical circumstances. Skin is divided into two basic structural components. The epidermis is the thinner, superficial layer that is composed of epithelial tissue, while the dermis, also known as the hypodermis, is the deeper, thicker layer that is composed of adipose and areolar tissues.

The skin is a multilayered organ with three tissue layers at the microscopic level

- The epidermis
- The dermis
- The subcutaneous fat tissue.[20]

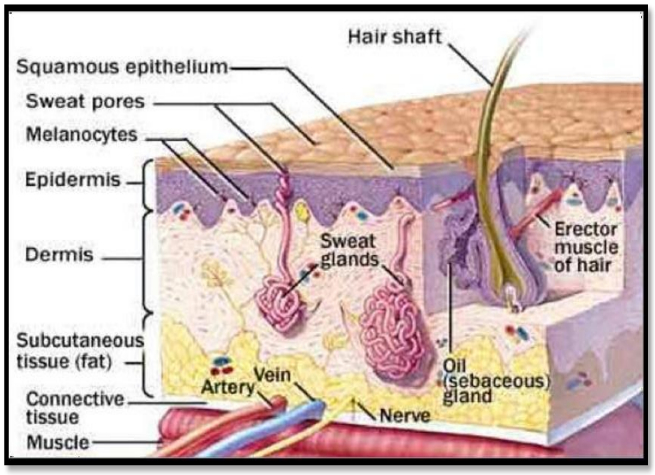

Figure 5: Anatomy of skin.

PERMIATION ENHANCER

TDD is limited to a few medications with particular physicochemical characteristics, despite its many advantages. While hydrophilic and macromolecular drugs, like peptides, are often hindered by the stratum corneum (SC) barrier, a drug candidate for transdermal delivery should ideally have a molecular weight of less than 500 Da with a moderate lipophilicity (log P range 1–3) to pass freely through the skin.[21,22] The primary barrier is the SC, a 5–20 μm-thick layer of skin against the external surroundings. Because of the 10–15 layers of corneocytes, lipid matrix, corneo desmosomes, and tight connections that make up its structure, the SC is dense and impenetrable to drug molecules.[23,24] (Figure 6)[25,26] Therefore, getting past the SC barrier, delivering the medication to the skin, and letting it diffuse to the dermal blood vessels is the most difficult part of TDD. The problem is that TDD's use in clinical practice is restricted because very few medications can penetrate the skin. It is suggested that new and innovative TDD techniques for

improving skin penetration be developed in order to get over this restriction. Therefore, a number of potential approaches, including chemical and physical techniques, have been studied to get past the SC barrier.[25,27] The methods utilized to modify the barrier properties of the SC can be classified as chemical and physical methods, as summarized in Figure 7.[28]

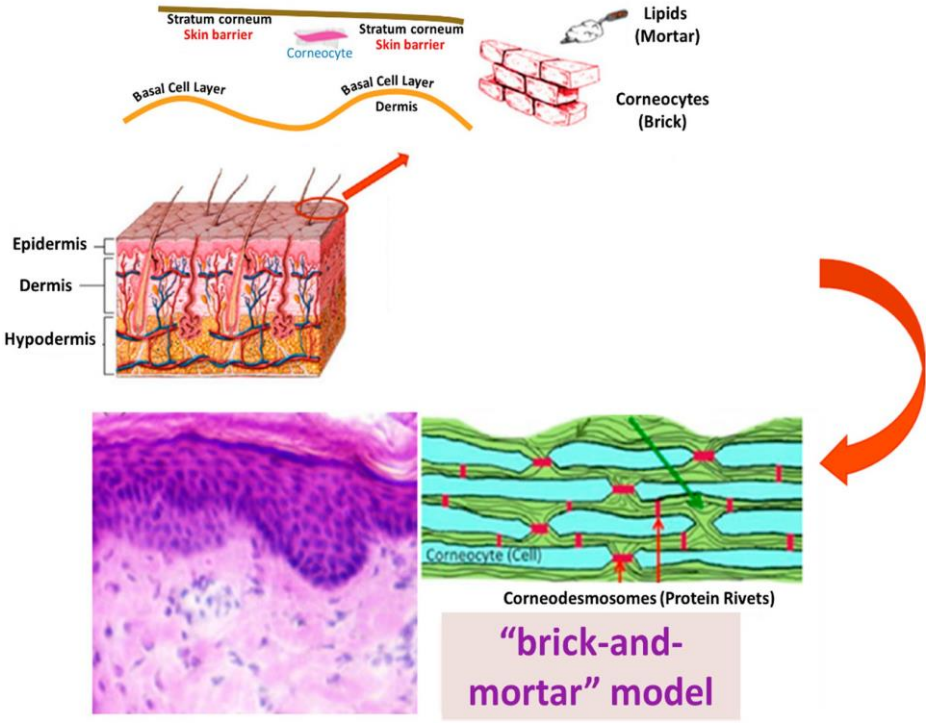

Figure 6: Structure of the SC.

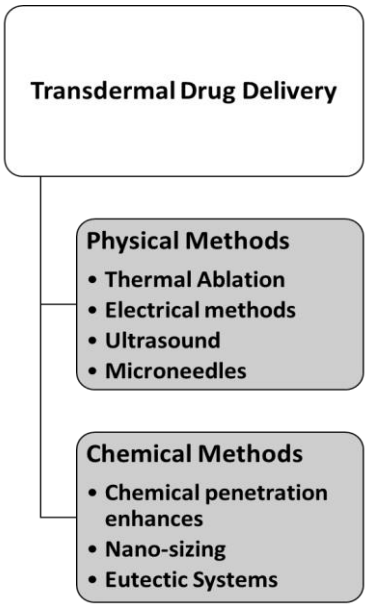

Figure 7: Approaches for enhancing drug transport across the skin.

Methods of Preparation of Proniosomes[11]

1. Coaservation phase seperation
2. Hand shakeing methord
3. Slow spray coationg method
4. Slurry method

Coacervation phase separation

A clean, dry, wide-mouthed glass vial containing precisely weighed amounts of surfactant, lecithin, cholesterol, and medication was filled with three milliliters of alcohol. Following the warming process, all the materials were thoroughly mixed using a glass rod. The glass bottle's open end was sealed to prevent solvent loss, and it was heated over a water bath at 60°C to 70°C

for five to ten minutes, or until the surfactant combination had completely dissolved. After that, the Phosphate Buffer Solution (pH 7.4) was added, heated in a water bath until a clear solution formed, and then cooled to create proniosomal gel. The resulting gel was kept in the same glass bottle under dark circumstances.[30]

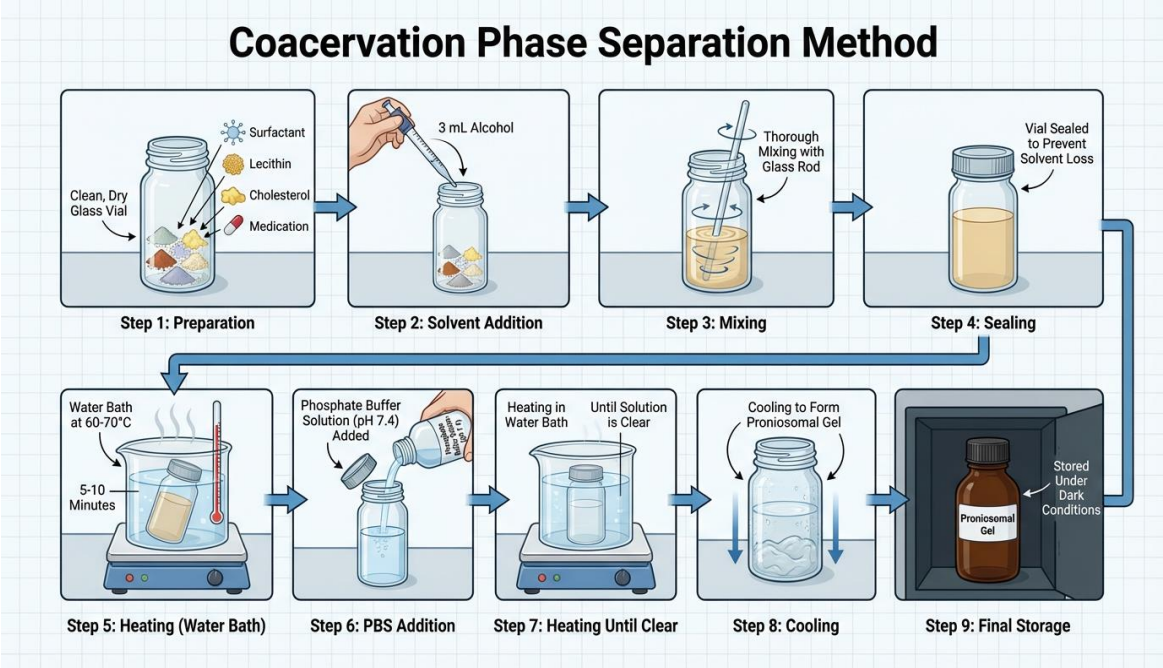

Figure 8: Coacervation phase separation method.

Hand shaking method: In a round-bottom flask, ether, methanol, or chloroform are used to dissolve the combination of vesicle-forming components, such as cholesterol and surfactants. A thin layer of solid mixture is left on the walls of the round-bottomed flask after the organic solvent in the rotary evaporator evaporates at room temperature (20°C). With minimal stirring, the dried surfactant film can be rehydrated with the aqueous phase at 0–60°C. Typical multi-lamellar niosomes are produced by this method.

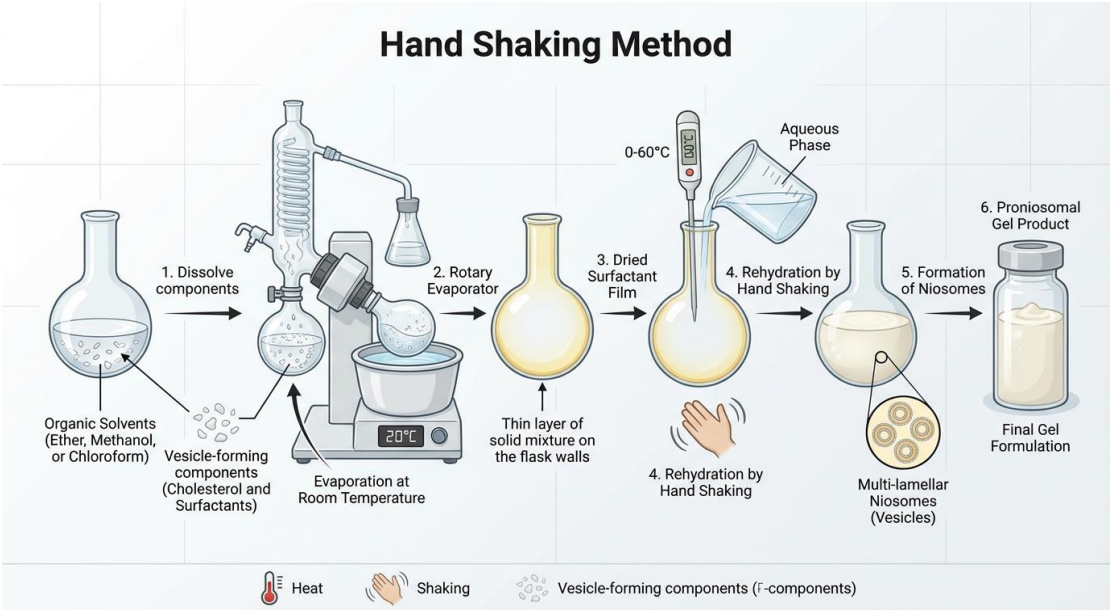

Figure 9: Hand shaking method.

Slurry method: In a 2:1 chloroform:methanol solution, a 250µmol stock solution of surfactant and membrane stabilizer was made. A 100 ml round-bottom flask containing the carrier material was filled with a specific volume of stock solution and medication dissolved in a 2:1 chloroform :methanol solution. If there is less surfactant loading, a slurry is formed by adding more organic solvent solution. The flask was connected to a

rotary flash evaporator, which evaporates solvent at 60–70 rpm, 45 ± 2°C, and 600 mmHg of decreased pressure until the bulk in the flask turns into a dry, free-flowing product. These materials were vacuum-dried overnight at room temperature in a desiccator. This dry preparation, known as "proniosomes," was utilized for preparations and additional research on the characteristics of powder. These finished products, proniosomes, were kept at refrigerator temperature in a hermetically sealed container for further analysis.

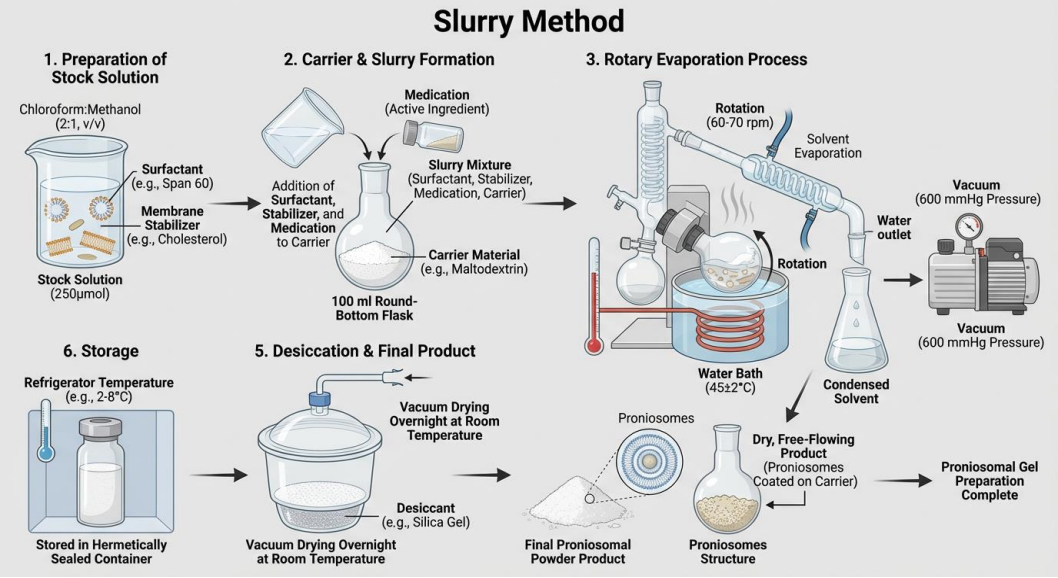

Figure 10: Slurry method.

Slow spray coating method: A rotary evaporator can be attached to a 100 ml round-bottom flask that contains the desired amount of carrier. The evaporator must be emptied, and the flask must be rotated in a water bath under vacuum at 65–70°C for 15–20 minutes. This process must be repeated until all of the surfactant solution has been applied, and the evaporation must continue until the powder is completely dry.[31]

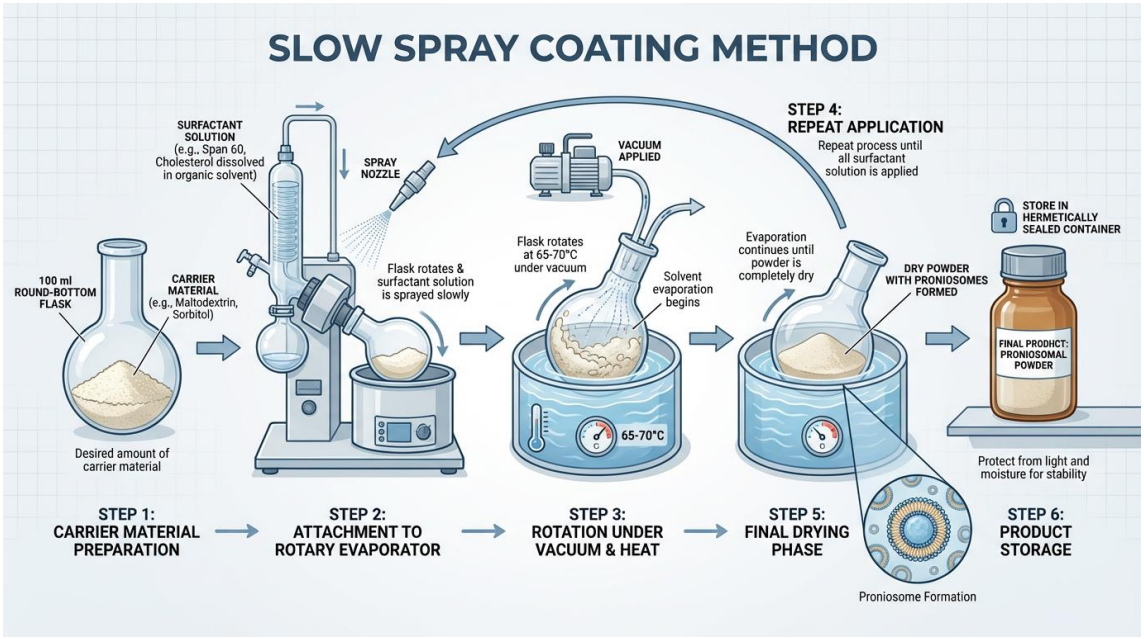

Figure 11: Slow spray coating method.

COMPOSITION OF PRONIOSOMES GEL

Proniosomal gels are primarily composed of non-ionic surfactants, cholesterol, organic solvents such as ethanol or isopropanol, and the incorporated drug. Upon hydration, non-ionic surfactants including Span 60, Span 80, and Tween 80 play a crucial role in the formation of bilayer vesicular structures. Cholesterol is commonly added to enhance membrane rigidity and stability, thereby minimizing drug leakage from the vesicles. Organic solvents facilitate the dissolution of surfactants and support gel formation, while water—either absorbed from the surrounding environment or applied

externally—induces the conversion of proniosomes into niosomes at the site of application. Owing to this distinctive formulation, proniosomal gels are capable of encapsulating a wide range of therapeutic agents, with lipophilic drugs being incorporated within the lipid bilayer and hydrophilic drugs residing in the aqueous core.[32]

APPLICATION OF PRONIOSOMES

Transdermal drug delivery systems

Proniosomes are particularly beneficial since they greatly increase the skin's ability to absorb drugs. Proniosomal technology is widely used in cosmetics for transdermal drug delivery; in fact, this was one of the first uses of niosomes. Proniosome-encapsulated antibiotics are administered topically to treat acne. The drug's skin penetration is greatly increased when compared to an unentrapped medicine. Recent studies have also focused on transdermal immunizations based on proniosomes.

Sustained release drug delivery

Proniosomes sustained release activity can help drugs with poor therapeutic index and restricted water solubility because proniosomal encapsulation keeps those drugs in the bloodstream.

Localized drug action

Because of their small size and restricted penetration into connective tissue and epithelium, proniosomes are employed to deliver medicines with localized effect. While lowering systemic toxicity, localized drug delivery boosts potency and efficacy. For instance, mononuclear cells preferentially absorb antimonials contained in proniosomes, improving drug localization and lowering dose-related toxicity. Proniosomal medication delivery has a lot of promise even if it is still in its infancy. This delivery technique is especially useful for applications like cancer treatment and anti-leishmanial therapy.

Applications in cardiology

Proniosomes are used as carriers to administer captopril transdermally to treat hypertension. The study indicates that the prolonged release of the medication throughout the body is facilitated by the proniosomal system. The drug is encapsulated using lecithin, cholesterol, and sorbitan esters.

Application in diabetes

Span, soy, lecithin, diacetyl phosphate, and cholesterol are used in the skin penetration process of furosamide proniosomes. The overall findings suggest proniosomes as a non-invasive method of delivering furosamide.[33]

Table No. 01: Recently Reported Proniosomal Gel Research Articles.

SI.NO.	YEAR	DRUG	TITLE	REFERENCE (VANCOUVER)
1	2021	Rutin	Proniosomal gel for topical delivery of rutin	Pinzaru I, *et al.* Antioxidants.2021;10(1):85.
2	2022	Amphotericin B	Proniosomal gel for topical delivery of Amphotericin B	Baig RP, Wais M. Int J Pharm Pharm Sci. 2022;14(1):43237.
3	2022	Progesterone	Proniosomal gel of progesterone for transdermal delivery	Palle M, Shayeda S. Indo Am J Pharm Sci. 2022;9(12).
4	2023	Donepezil HCl	Proniosomal gel mediated transdermal delivery of Donepezil	Sreenidhi KS, Yegnoor AK. Int J Frontline Res Pharm Bio Sci. 2023;2(2):17–23.
5	2023	Ketorolac Tromethamine	Proniosomal gel for transdermal delivery of ketorolac	Farooqui N, *et al.* J Drug Deliv Ther. 2023;7(7):1580.
6	2023	Doxycycline	Formulation of doxycycline proniosomal gel	Fatma KS, *et al.* J Popul Ther Clin Pharmacol. 2023;30(4):753–764.
7	2023	Sildenafil/Tadalafil	Proniosomal gel loaded PDE inhibitors	Mohamed SA, *et al.* Gels. 2023;9(8):597.
8	2024	—	Proniosomal gel for enhanced topical delivery (Review)	Rana A, *et al.* World J Pharm Res. 2024;13(12):103–121.
9	2025	Econazole Nitrate	Proniosomal gel for enhanced topical delivery of econazole	Int J Pharm Sci Res. 2025.
10	2021	Curcumin	Curcumin proniosomal gel for skin permeability	Shehata TM, *et al.* Polymers. 2021;13(5):791.
11	2021	Naproxen	Proniosomal gel for transdermal naproxen delivery	Shah H, *et al.* J Drug Deliv Sci Technol. 2021;63:102479.
12	2024	Lidocaine HCl	Proniosomal gel of lidocaine HCl with penetration enhancers	Sakdiset P, *et al.* J Drug Deliv Sci Technol. 2024.

Evaluation Parameters

1. Determination of pH

The digital pH meter was used to determine the proniosomal gel formulation's pH. A beaker containing a certain amount of filtered water was filled with a little amount of formulation. The pH of the proniosomal gel was measured when the electrode was submerged in the mixture.

2. Homogeneity
The proniosomal gel formulation's homogeneity was assessed visually. Their appearance and the presence of any aggregates were examined.

3. Spreadability
Two slides (5 cm^2) were used to measure this proniosomal gel characteristic. For one minute, the formulation's 0.5g was placed in the center of two slides. We measured and compared the proniosomal gel's spread circle diameter.

5. Appearance
The clarity, color, and particle appearance of the proniosomal gel bases were examined visually.

6. Drug content
High-performance liquid chromatography and UV spectrophotometer scanning were used to determine the drug concentration of the formulation.

7. Determination of entrapment efficiency
Proniosome entrapment efficiency is measured using the ultracentrifugation technique. Ultracentrifugation is carried out at 4°C for 60 minutes at 1500 rpm. The amount of sediment was measured after the sediment and supernatant liquid were separated, and the drug entrapment efficiency was computed using the formula % Entrapment efficiency is equal to the amount of entrapped API multiplied by 100.

8. Infra-red spectroscopy
An FT-IR spectrophotometer was used to obtain the proniosomal gel's infrared spectrum in the 4000–400 cm1 region.

9. Viscosity
The proniosomal gel formulation's viscosity was measured using the Brookfield Rheometer with spindle number 64 at 10 rpm. The assembly was linked to a circulating water bath that was kept at 25°C by a thermostat. The beaker with a thermostatic jacket was filled with the measured viscosity. The data were recorded after the spindle was permitted to migrate into proniosomal gel.

10. In-vitro drug release study
The formulation's in-vitro drug release was investigated using the Franz diffusion cell device. The formulation was applied to a dialysis membrane that was placed in the center of the Franz diffusion cell's donor-receptor chamber. 30°C was the constant temperature. A magnetic field was used to continuously agitate this arrangement. The percentage of medication released from the proniosomal gel formulation was computed.

11. Stability study
Proniosomal gel was stabilized more quickly in accordance with ICH recommendations. To evaluate the stability of topical nanogel, a three-month stability research was conducted in an environmental stability chamber at 25 ±2°C and 60 ±5% relative humidity. The mixture was moved to glass vials with an amber hue, sealed, and stored in the stability room. Three months later, measurements were made of the consistency, drug content, and in vitro drug release.

CONCLUSION
Proniosomal gel represents a promising and advanced vesicular drug delivery system for transdermal application, offering improved drug stability, enhanced skin permeation, and sustained drug release. By overcoming the limitations of conventional dosage forms and the stratum corneum barrier, proniosomes enable effective delivery of both hydrophilic and lipophilic drugs. The coacervation phase separation method provides a simple and reproducible approach for preparing stable proniosomal gels. Evaluation parameters confirmed acceptable pH, homogeneity, spreadability, viscosity, and high entrapment efficiency. In-vitro release and stability studies demonstrated controlled drug release and good formulation stability during storage. Overall, proniosomal gels offer a patient-friendly, efficient, and versatile platform for transdermal drug delivery, particularly for chronic conditions such as diabetes mellitus.

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