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Novel Vesicular Drug Delivery: A Panoptic Perspective on the Preparation, Usage, and Clinical Application of Proniosomes

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Abstract

The emergence of nanotechnology has significantly transformed the scientific landscape, resulting in the creation of innovative drug delivery systems like niosomes. Using vesicular systems to deliver drugs is a new idea that could help encapsulated drugs be absorbed and used better while still allowing controlled and long-lasting therapeutic effects. These delivery systems have distinct advantages over conventional dosage forms. The notion of provesicular systems has undergone development to address the stability concerns associated with vesicular systems. Among several types of vesicular carriers, proniosomes have been found to exhibit greater performance. As a vehicle system, proniosomal technology is highly advantageous for transporting both hydrophobic and hydrophilic medications. It's a dense, dry, easily flowing powder that forms niosomes when hydrated. Encapsulated medications have the potential to enhance their bioavailability and deliver improved therapeutic activity under controlled conditions. Proniosome-derived niosomes exhibit enhanced drug delivery capability and superior physicochemical stability, rendering them a more favourable alternative to other vesicular systems. Dry proniosomal powder that is free-flowing is appropriate for unit dosage forms like tablets and capsules. This article provides an overview of the common preparation methods for proniosomes and primarily emphasizes the utilization of proniosomes in the field of medication administration and targeting. This paper evaluates proniosome research comprehensively. This comprehensive study also discusses how proniosomes can administer medications orally, intravenously, topically, or transdermally. Proniosomes should also be investigated for protein and peptide delivery in nutraceuticals and pilot plant scale-up investigations in industrial settings.

Keywords: Vesicular system; Proniosome; Non-ionic surfactant; Hydration; Targeted drug action

1. INTRODUCTION

Vesicular carriers exhibit distinct characteristics in terms of their composition, morphology, or mechanism of drug delivery [1]. It has been demonstrated to researchers that each of these vesicular carriers offers numerous benefits over conventional drug delivery methods. Such are the benefits associated with these vesicles like creating a drug delivery system that is durable, biodegradable, and compatible with the body, allowing it to remain in the bloodstream for an extended time without activating the reticuloendothelial system. This system should act as a carrier for both hydrophilic and lipophilic medications and be applicable through multiple administration routes like oral, transdermal, intravenous, and intramuscular methods.

Vesicular drug delivery systems that are novel have achieved significant advancements in the domain of nanotechnology. Given their capacity to transport a diverse array of pharmaceuticals, these systems have been extensively implemented for an array of objectives, including drug targeting, controlled release, and permeation enhancement [2]. Additionally, these systems are helpful because they get around many problems with traditional dosage forms, such as not dissolving well in water, not being bioavailable, non-permeating membranes well, plasma concentrations changing, side effects, patients not following the instructions properly, and ultimately poor patient outcomes [3–5].

TYPES OF VESICULAR DRUG DELIVERY SYSTEM [6–13]**:**

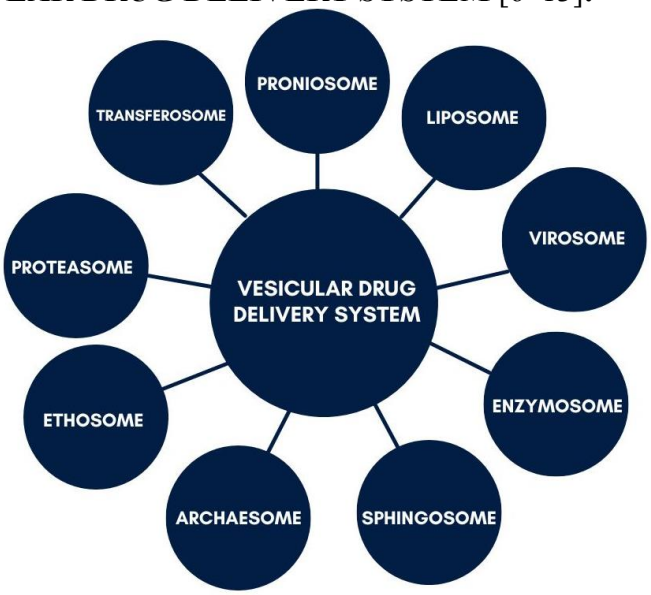

Fig.1 Types of vesicular drug delivery system

The vesicular drug carriers, such as niosomes, were given too much attention to prove that they were better than traditional dosage forms. Vesicles contain the drug in order to extend its effects and lower its side effects through drug targeting [14]. Both of these systems function as reservoirs for drugs, are capable of encapsulating and partitioning hydrophobic and hydrophilic drugs in hydrophobic domains, and are membrane-enclosed unilamellar or multilamellar spherical structures [15].

NIOSOME

Niosomes are vesicles composed of non-ionic surfactants, possessing the ability to encapsulate both hydrophilic and lipophilic drug candidates due to their unique composition containing both hydrophilic and hydrophobic components. Niosomes exhibit osmotic activity and possess stability, ensuring the preservation of the encapsulated medication [16–18].

Understanding the fundamental structural components of niosomes is of paramount significance, as it plays a pivotal role in determining the potential chemicals capable of forming niosomes as well as the mechanism by which medications can be loaded for delivery purposes. Niosomes, similar to liposomes, are vesicles composed of non-ionic surfactants that possess a bilayer structure. The hydrophilic heads have an affinity for aqueous solutions, while the hydrophobic heads exhibit an affinity for organic solutions [19]. Niosomes often exhibit dimensions within the sub-micron range, characterized by their colloidal nature. The sizes of small unilamellar vesicles (SUV) ranged from approximately 10 to 100 nm, whereas large unilamellar vesicles (LUV) exhibited sizes between 100 and 3000 nm. Multi-lamellar vesicles (MLV) were found to have sizes exceeding 5 μm, and there have been reports of a limited number of "giant" vesicles with sizes more than 15 μm [20,21].

Researchers have become increasingly intrigued by niosomes due to their potential as drug-targeting agents and drug carriers, which offer numerous advantages while circumventing the drawbacks associated with conventional drug formulations [16,22]. Additionally, niosomes are better than liposomes as possible drug carriers because they are more chemically stable and better at encasing both hydrophobic and hydrophilic drugs [20,23]. Primarily, niosomes are produced through the incorporation of cholesterol as an excipient. Other excipients may be utilized as well. Niosomes possess a greater capacity for penetration than prior emulsion formulations. Although niosomes share a bilayer structure with liposomes, their superior stability can be attributed to the materials used in their preparation; thus, niosomes offer numerous advantages over liposomes [24]. As demonstrated with acyclovir and griseofulvin, niosomal formulations may enhance the bioavailability and solubility of certain poorly-soluble drugs. Additionally, they can regulate drug delivery while maintaining good chemical stability during storage; for instance, encapsulation can substantially increase the stability of peptide drugs [25].

PRONIOSOME

Even though niosomes have demonstrated benefits as drug carriers, including their chemical stability and low cost in comparison to liposomes, stability remains a primary concern in the creation of any formulation. Similarly, they are correlated with physical stability issues, including storage leakage, fusion, aggregation, and sedimentation [26–28]. To address the shortcomings associated with alternative vesicular drug delivery systems, it became imperative to develop a system that exhibited enhanced physical and chemical stability. Using provesicular carrier systems, which are also called ‘proniosomes’, is a modern and useful way to make stable niosomes.

The provesicular concept emerged as a solution to the stability challenges associated with traditional vesicular systems, such as liposomes and niosomes. The pro-vesicular systems use a porous, water-soluble powder to carry non-ionic surfactants (niosomes) and pharmaceuticals that are dissolved in organic solvents. The dry-flowing granular product that is made can be mixed with water before it is used, which gets around some problems that come up with water-based vesicular dispersions. The potential of pro-niosomes is to enhance the oral bioavailability and permeation of drugs across the stratum corneum is illustrated by this newly emergent concept. Evidently, according to the investigation, particular systems function as an alternative

drug carrier for a variety of drug administration routes. Numerous complications linked to aqueous vesicular dispersions can be circumvented [29].

These proniosome-derived niosomes are superior to conventional niosomes because they are readily reconstituted with an aqueous phase prior to administration or hydrated in body regions to form niosomal vesicles upon administration [30,31]. For transdermal and topical drug delivery, proniosomes represent an innovative vesicular system. Proniosomes elicit therapeutic responses, diminish or eradicate adverse effects, and augment the efficacy of pharmaceutical substances. The utilization of proniosomes serves the purpose of avoiding undesirable side effects associated with oral delivery, first-pass hepatic metabolism, and gastrointestinal tract (GIT) incompatibility. Moreover, proniosomes retain therapeutic concentrations of medications for an extended period, reduce administration frequency, and enhance patient adherence [32–36]. The utilization of proniosomal technology has the potential to mitigate the physical and chemical instabilities commonly observed in niosomes, as it circumvents the need for their preservation in an aqueous medium. Both cholesterol and non-ionic surfactants present in proniosomes have the potential to function as agents that promote penetration. It's possible that the relationship between the non-ionic surfactant and cholesterol ratios could change both how well the medications are released and how well they are trapped [37–39]. Proniosomes, alternatively referred to as 'dry niosomes', provide enhanced convenience in terms of transportation, distribution, storage, and dosage. This attribute renders them an effective delivery strategy that exhibits potential for utilization with a diverse array of active substances [26,31].

FORMATION OF NIOSOME FROM PRONIOSOME:

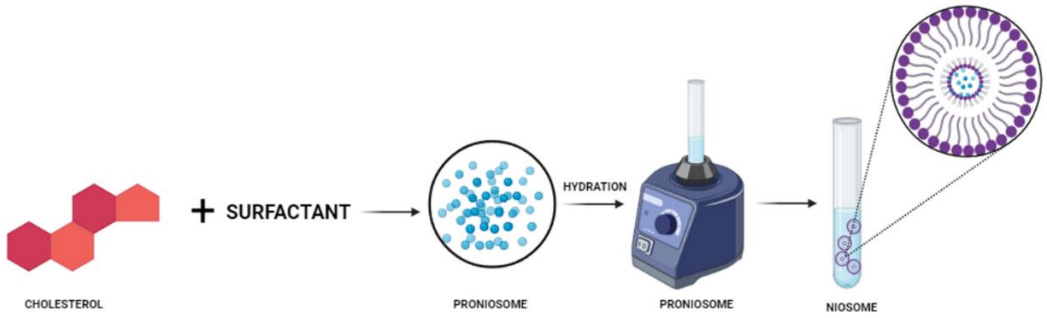

Fig.2 Formation of Niosome from Proniosome

Niosomes can be made from pro-niosomes by adding different water-based phases that contain the drug to the proniosomes and then stirring them for a short time.

$$T > Tm$$

Where;

T – Temperature

Tm – mean phase transition temperature

Blazek-Walsh et al. has shown the development of niosomes using proniosomes derived from maltodextrin. This method enables the quick reformation of niosomes while minimizing the presence of remaining coating materials. Within the mixture of maltodextrin, a surfactant was subjected to a drying process, resulting in the formation of a powder with the ability to flow freely. This powder could be easily reconstituted by introducing warm water [40–42].

STRUCTURE

Proniosomes are formations with tiny lamellae. They hydrate cholesterol in aqueous media after combining it with a non-ionic surfactant. To create the bilayer, the molecules of the non-ionic surfactant self-adjust such that their hydrophilic ends face outward and their hydrophobic ends face inside. The bilayer structure is shared by both liposomes and proniosomes; however, phospholipids constitute the liposome bilayer and non-ionic surface-active molecules the proniosome bilayer.

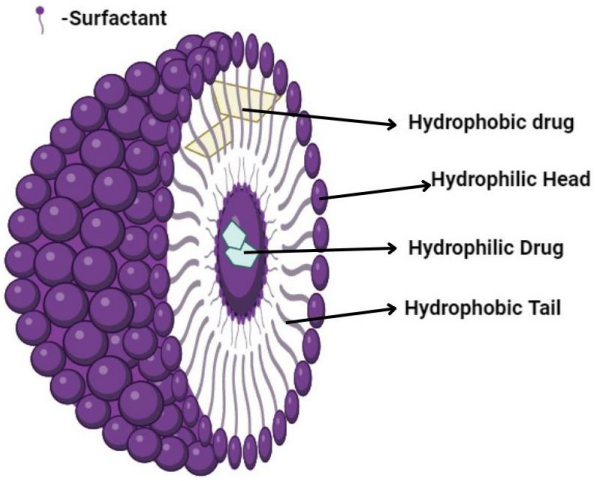

Fig.3 Structure of Proniosome

The preparation procedure also determines whether the proniosome forms a unilamellar or multilamellar structure. Inside the niosome, the hydrophobic chains face each other, and the hydrophilic ends of the surfactant bilayer are exposed on both the exterior and the inside of the vesicles. The proniosomes can contain both hydrophilic and hydrophobic medicines for this very reason. The hydrophobic medications are embedded in the bilayer, while the hydrophilic drugs are held inside the area enclosed in the vesicle [43,44].

The niosomal gel exhibits a semisolid, transparent, or translucent gel structure. The proniosomes that result from the restricted presence of solvent are a composite of various liquid crystal phases, including lamellar, hexagonal, and cubic. In this instance, the lamellar phase revealed bilayer sheets of surfactant, the hexagonal phase demonstrated a compact cylinder structure arrayed in a hexagonal fashion, and the cubic phase comprised a three-dimensional curved continuous lipid bilayer [45].

COMPONENTS OF PRONIOSOME

TABLE 1: Elements comprising proniosomes

COMPONENTS	MATERIALS	FUNCTION	REFERENCE
Non-ionic surfactant	Span 20	To maintain the hydrophilic-lipophilic balance (HLB)	[46,47]
	Span 40		[48]
	Span 60		[49]
	Span 80		[50]
	Span 85		[48]
	Tween 20		[48]
	Tween 60		[48]
	Tween 80		[48]
coating materials	Sorbitol	To hold the drug	[32]

	Spray dried lactose		[51]
	Lactose monohydrate		[51]
	Glucose monohydrate		[51]
	Sucrose stearate		[51]
	Maltodextrin		[49]
Membrane stabilizers	Cholesterol	Maintain the integrity, stability, and permeability of vesicles Penetration enhancer	[42]

MECHANISM OF ACTION OF PRONIOSOME

Proniosomes, which are inactive precursors to niosomes, necessitate hydration to undergo a transformation into their active forms. Utilizing moisture on the epidermis is one method of hydration; the other involves the use of solvents like water or buffer. Multiple mechanisms of skin penetration exist for transdermal drug delivery systems. Certain substances have the ability to get through the skin undamaged because of their deformable characteristics; these substances may utilize an external trans-gradient membrane, as in the case of transfers; others enter the skin undamaged by disrupting the dense structure of the epidermis, as in the case of ethosomes; or employ surfactants as penetration enhancers, as in the case of proniosomes and niosomes [52–55]. Prior to being administered topically, the molecule must traverse the stratum corneum and viable epidermis. This phenomenon can occur via one of three potential pathways: the intercellular pathway between cells and lipids; the intercellular pathway through the intricate network of lipids; or the path of appendages, which passes through hair follicles and perspiration glands [56–59].

TYPES OF PRONIOSOME

Proniosomes exhibit variations in their types due to the diverse coating materials utilized and the distinct preparation methods employed:

DRY GRANULAR PRONIOSOME:

(i) Sorbitol based proniosome:

Sorbitol-based proniosomes refer to a desiccated formulation that utilizes sorbitol as a bulking agent in lyophilization to retain the drug. It is subsequently coated with a non-ionic surfactant, and hot water is added, followed by agitation. Within a short period of time, the resulting mixture is employed as a niosome. The proniosomes are prepared by dissolving them in organic solvents, which are then evaporated from the sorbitol powder. Due to this particular factor, the sorbitol exhibits solubility in organic solvents, necessitating the repetition of the operation until the desired coating of surfactant is attained. One notable benefit of sorbitol-based proniosomes lies in their ability to exhibit a high degree of uniformity in terms of size distribution. This is particularly advantageous in situations where the active compound is prone to hydrolysis. The use of this proniosome formulation has some problems. The entrapment effectiveness is lower by more than 50% because there is still sorbitol present. The aforementioned circumstances require a decrease in the concentration inside the ultimate niosomal solution. The challenge arises in the examination of sorbitol particles due to their solubility in chloroform and other organic solvents. The substance is produced via a slow spraying technique [60,61].

(ii) Maltodextrin based proniosome:

The fast slurry approach is employed for the production of proniosomes that are based on maltodextrin. The utilization of the slurry technique does not have any impact on the quantity of surfactant solution required for the production of proniosomes. Maltodextrin is a polysaccharide that is soluble in water and is commonly used as a carrier ingredient in the formulation process. Hollow-blown maltodextrin particles have the potential to significantly enhance surface area. Surfactant coatings exhibit reduced thickness due to heightened surface area, hence enhancing the efficiency of the rehydration process. This formulation has the potential to facilitate the delivery of hydrophobic and amphiphilic medications [47].

PREPARATION METHODS OF PRONIOSOME

Proniosomes are composed of various components including non-ionic surfactants, with cholesterol or lecithin often serving as the primary ingredients. Several methods have been documented for the creation of proniosomes, some of which are outlined below:

(i) Coacervation phase separation method
(ii) Slurry method
(iii) Slow spray coating method

(i) Coacervation phase separation method:

The coacervation method encompasses the separation of liquids into distinct phases to generate polyelectrolytes from a uniform solution. This process results in the creation of a coacervate that envelops the active agent. Augmentation of the coacervate formation occurs through enzyme-based crosslinking, like transglutaminase, or the addition of suitable chemicals [63].
The method is extensively employed in the formulation of niosomal gel after hydrating the dry proniosome [64,65]. In this technique, a combination of cholesterol, surfactant, drug, and an appropriate alcohol are introduced into a wide-mouthed glass vial (the alcohol quantity is minimized to prevent micelle formation). Typically, the ratio of surfactant to alcohol in the aqueous phase is maintained at 5:5:4 w/w/w. Mixing ensues, and the vial is sealed to prevent solvent loss before being warmed in a water bath at 60–70 °C. This procedure is repeated for approximately 5 minutes until the surfactants dissolve completely. The resulted solution is allowed to solidify and filtered. Upon centrifugation the supernatant obtained is made as dry preparation by lyophilizing it. Further the dry formulation is hydrated to form niosomal preparation after which the gelling agent is added to form the niosomal gel. The resultant gel is stored in the same glass vial in darkness for characterization purposes [66–68].

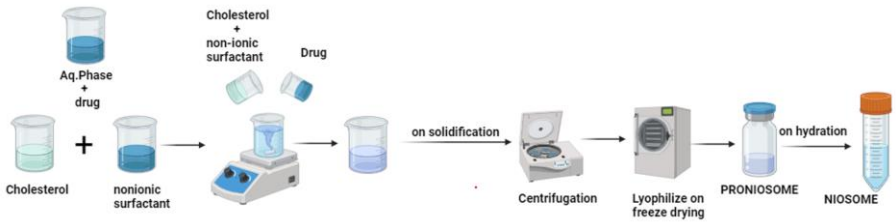

Fig.4 Coacervation phase separation method

Advantages:

1. The method is straightforward and efficient, requiring no specialized equipment, making it an essential process.
2. Tailored specifically for gel preparation, this method stands out.

3. It allows for the preparation of small-scale formulations or low-dose quantities in a laboratory setting.
4. No specialized instruments are necessary for this process.

(ii) Slurry method:

A stock solution of 250 µmol containing surfactant and a membrane stabilizer was prepared using a chloroform: methanol (2:1) solvent. A specific volume of this stock solution, along with a drug dissolved in chloroform: methanol (2:1) solution, was introduced into a 100 ml round bottom flask containing the carrier material. If a lower surfactant loading occurred, an additional organic solvent solution was added to create a slurry [69,70]. The flask was then connected to a rotary flash evaporator, which operated at 60–70 rpm, maintaining a temperature of 45 ± 2°C and a reduced pressure of 600 mmHg. The solvent was evaporated until the contents in the flask turned into a dry, free-flowing product. Following this, the materials were dried in a desiccator overnight at room temperature under a vacuum. The resulting dry preparation, known as "proniosomes," was utilized for subsequent preparations and for studying powder properties. These final proniosome products were stored in a tightly sealed container under refrigeration until further evaluation [71,72].

Advantages:

1. Uniformly coating the carrier provides protection for the active ingredients and surfactants against factors like hydrolysis and oxidation.
2. The increased surface area leads to a thinner coating of surfactant, enhancing the efficiency of the rehydration process.

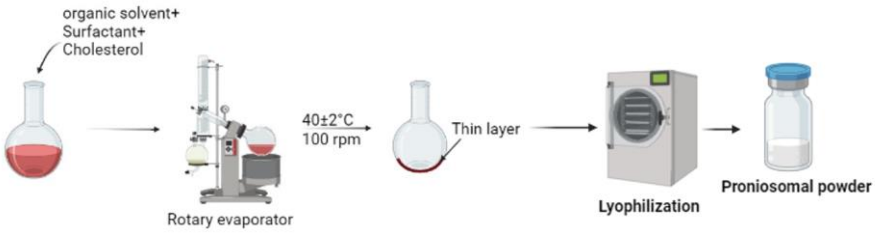

Fig.5 Proniosome preparation by Slurry method

(iii) Spray coating method:

The process involves spraying surfactant dissolved in an organic solvent onto a carrier, followed by evaporation to form proniosomes. The carrier is placed in a 100ml round-bottomed flask and subjected to this evaporation process. Surfactant mixtures, along with cholesterol and diacetyl phosphate, are sequentially manufactured and sprayed into the flask attached to a rotary evaporator. Throughout the spraying, it's crucial to regulate the application speed to prevent saturation of the carrier surface [73,74]. The flask, set in a water bath at 65-70°C, undergoes vacuum spinning for 15-20 minutes until evaporation, adjusting based on the final aliquots required. This process is repeated to ensure the complete dissolution of the carrier in the organic solvent. As the carrier dissolves, the hydrated surfactant coating facilitates the formation of multilamellar vesicles, resulting in a homogeneous size distribution of niosomes [75,76]. The material is further dried overnight in a desiccator under vacuum, forming the dry preparation known as "proniosomes," used in subsequent research and preparations.

To create the niosome dispersion, the proniosome preparation is hydrated with distilled water heated to 80°C for two minutes and mixed via vortexing. This method is simple for

hydrophobic drugs, ensuring stability without concerns about hydrolysis sensitivity. However, the time-consuming nature of the process is observed due to the carrier's solubility in the surfactant deposition solvent, affecting the encapsulation efficiency of the drug [74,77,78].

Fig.6 Spray coating method

Advantage:

This straightforward method is well-suited for hydrophobic drugs, eliminating worries about instability or vulnerability to hydrolysis of the active pharmaceutical ingredient.

Novel findings

After conducting a comprehensive analysis of the Proniosome concept, the determination is that Proniosomes represent dry formulations comprising water-soluble carrier particles enveloped in a surfactant coating. [79]. They are rehydrated to form niosomal dispersion immediately before use on agitation in hot aqueous media within minutes. Building upon this premise, it's been asserted that proniosomes primarily exist as a dry, free-flowing powder. However, certain authors, have erroneously claimed the existence of proniosomes in a liquid crystalline form, which deviates from the established understanding[44,80].

The definition of proniosomes emphasizes their composition involving non-ionic surfactants and cholesterol, distinguishing them from liposomes that typically contain lipids [32]. However, certain authors have incorrectly suggested the incorporation of lipids in proniosome formation, which contradicts the fundamental principles of niosomal and proniosomal construction. Introducing lipids into the formulation would lead to the creation of liposomes rather than proniosomes, rendering this information inaccurate and irrelevant to the process of proniosome formation[46,50].

CHARACTERIZATION OF PRONIOSOME

TABLE 2: Characterization

S.NO	PARAMETER	TECHNIQUE/INSTRUMENT EMPLOYED	REFERENCE
1	Measurement of vesicle size and size distribution	Malvern Master sizer Laser diffraction particle size analyser Optical microscopy Coulter submicron size analyser	[32,42,48,50,51]
2	Particle surface and shape morphological characteristics	Transmission electron microscopy Optical microscopy Scanning electron microscopy	[47,81]

3	Angle of repose	Funnel method Cylinder method	[73]
4	Spontaneity (Rate of hydration)	Using Neubur's chamber	[46]
5	Measurement of Particle Charge	Zeta potential analysis	[46]
6	Entrapment efficiency	Vesicle disruption using alcohol and propylene glycol	[82]
7	Aerodynamic behaviour	Twin –Stage impinge	[51]
8	Separation of unentrapped (free) drug	Dialysis method Gel filtration Centrifugation	[29,83]
9	*In vitro* drug release and skin permeation studies	Franz diffusion cell USP dissolution apparatus – 1 Cellophane dialyzing membrane In vitro skin permeation studies Keshary- Chien diffusion cell Spectrapor molecular porous membrane tubing	[47,81]
10	Drug content	Modified HPLC method	[46]
11	Stability of Proniosomes	Accelerated stability studies as per ICH guidelines	[65,84]

Factors Influencing the Formulation of Provesicles:

Surfactant chain length:

Spans are often used in provesicle preparation because they have identical head groups but differ in alkyl chain architectures. Longer alkyl chains have higher entrapment efficiency, with a trend of Span60 > Span40 > Span20 > Span80. Span 60 and Span 80 have comparable head groups; however, the unsaturation of Span 80's alkyl chain differs. The results from De Giere show that adding double bonds to the paraffin chains makes the liposomes much more permeable. This may explain why the Span80 formulation isn't as good at enclosing things [85].

Cholesterol content:

The impact of cholesterol on the percentage vesicle formation varies, contingent upon both the surfactant type and its concentration within the formulations.

pH of the hydration medium:

The pH of the hydrating solution had a significant impact on the percentage of encapsulation efficiency in niosomes formed through the hydration of proniosomal gels containing Span 60/cholesterol (9:1). Specifically, the encapsulated fraction of flurbiprofen increased by approximately 1.5 times when the pH decreased from 8 to 5.5. It's because flurbiprofen has an ionizable carboxylic group in its chemical makeup that makes it more effective at being encapsulated when the pH goes down. Lowering the pH potentially enhances the proportion of the unionized form of flurbiprofen, which exhibits a higher affinity for partitioning into the lipid bilayer phase compared to its ionized counterpart [86].

Critical quality attributes:
The quality of the formulation mainly depends on the particle size which is evaluated by CPP and CMA. Thus, the impact of CMA and CPP makes them to attain the Quality Target Product Profile (QTPP).

Critical material attribute:
Surfactants and cholesterol concentration are to be the main ingredients which affects critical quality attributes (CQA) of the formulation. Surfactant with longer alkyl chain length are typically preferred for favourable skin compatibility and increased encapsulation efficacy [87]. The effectiveness of drug entrapment is contingent upon the hydrophilic head group and hydrophobic tail group characteristics exhibited by the non-ionic surfactant. The niosome size is significantly impacted by the HLB value of the surfactant; as the HLB value rises, so does the size of the niosomes. As a result of this characteristic, non-ionic surfactants exhibiting HLB values between 14 and 17 are suboptimal for the formation of niosomes [88]. An elevation in cholesterol levels resulted in a reduction in entrapment efficiency and an augmentation in particle size. This observed phenomenon could be attributed to two factors: (i) heightened cholesterol levels enhancing the hydrophobic nature of the bilayer, consequently reducing bilayer permeability and potentially facilitating efficient entrapment of hydrophobic drugs in the vesicle formed; (ii) increased cholesterol content causing greater rigidity in the niosome structure and enlarging the particle size, potentially competing with the drug for space within the bilayer [89–91].

Critical process parameter:
A decline in the particle size of the niosomes was noticed when the mixing speed gradient increased. The findings presented in this study are consistent with other research that has documented the influence of many factors, such as the manner of vesicle formation, the composition of the bilayer, and the concentration of biocomponents, on vesicle size. The observed correlation between an increase in mixing time and a decrease in particle size is evident. The observed trend can be attributed to the fact that a longer mixing period allows for sufficient hydration time, resulting in improved dispersibility. This, in turn, leads to the formation of smaller and more uniform niosomes. Previous studies have reported comparable results [92–94].
According to the published paper and expert opinions, it has been observed that elevating the mixing speeds from 450 to 650 rpm and extending the mixing times from 30 to 60 minutes have led to enhanced entrapment efficiency and reduced particle sizes [95].

Proniosomes in Drug Delivery and Targeting:
Proniosomes have garnered significant interest among researchers as an accomplished drug delivery system, serving as a versatile vesicular carrier and targeting agent since the 1980s. This section aims to illuminate the practical utility of proniosomes in drug delivery and targeting by reviewing several publications that showcase their applications in efficiently delivering a diverse range of therapeutic agents through various routes, including oral, parenteral, dermal, transdermal, ocular, pulmonary, vaginal, and mucosal administrations [84].

Oral delivery:
The oral route of drug administration is widely utilized and considered to be the preferred method. Many drugs are administered parenterally to enhance their bioavailability due to various issues associated with drugs administered orally [96–98]. These issues include low

stability in the gastrointestinal tract, degradation of drugs by acidic or enzymatic action before reaching the systemic circulation, and limited permeability through the intestinal epithelium. Hence, various nanocarriers are utilized in order to augment the absorption of drugs via the oral pathway. These nanocarriers include liposomes, niosomes, lipid nanoparticles, micelles, gold nanoparticles, and quantum dots. Extensive research has been conducted on proniosomes as a promising oral medication delivery method. Multiple studies have been documented that demonstrate the efficacy of oral proniosomal powders in enhancing the solubility and bioavailability of medicines with low solubility [99–101].

Parenteral delivery:

Parenteral administration is commonly used for medicinal components with low bioavailability and limited therapeutic potential. In emergencies, the parenteral route offers easy access, rapid onset of action, and is advantageous when the oral route is not feasible due to difficulties in swallowing, delayed gastric emptying, intestinal motility, vomiting, and unconsciousness. Although parenteral administration is most effective, it causes a decrease in systemic concentrations and requires frequent administration to maintain therapeutic concentrations, leading to poor patient compliance. Biodegradable polymeric nano-systems can overcome these restrictions by allowing regulated, gradual drug release for extended durations, reducing dose frequency and toxicity, and improving treatment quality [102]. Vesicular drug delivery systems have advanced features that ensure sustained drug release via parenteral administration and avoid the problems of conventional parenteral drug delivery systems, especially for drugs with narrow therapeutic index and poor bioavailability. Proniosomes can be kept, transported, disseminated, sterilized, and divided into unit dosages for parenteral medication delivery. Parenteral proniosome formulations can enhance patient compliance by avoiding frequent dosages and intravenous infusions, resulting in consistent plasma levels, efficacy, and reduced toxicity [103,104].

Dermal and Transdermal delivery:

The human skin, covering a significant portion of the body, serves the vital function of maintaining body hydration and acts as a selective barrier, regulating the entry of specific molecules. Among its layers, the stratum corneum stands as the primary site for percutaneous absorption, forming a barrier that controls the rate of absorption and impedes penetration [105,106]. Drug carriers play a crucial role in targeting and delivering drugs to specific sites of action. Depending on the type of drug carrier employed, the skin may experience either deep penetration or accumulation in the stratum corneum and hair follicles. Dermal drug administration offers several advantages, including localized high drug concentrations, reduced systemic absorption, and minimized side effects. Additionally, the transdermal route presents benefits such as non-invasiveness, bypassing hepatic metabolism, enhanced drug bioavailability, avoidance of gastrointestinal degradation, steady plasma concentration, ease of self-administration, and improved patient adherence [107,108].

However, transdermal administration faces challenges, notably limited drug penetration through the stratum corneum, a significant hurdle to effective permeation. To overcome skin barriers without resorting to physical or chemical methods, vesicular drug administration has proven to be an effective approach [109,110].

Oral mucosal delivery:

Medication administration on the oral mucosa holds promise, yet researchers face hurdles in refining innovative approaches. Various mucosal surfaces, such as buccal, nasal, rectal,

ophthalmic, and vaginal, have been investigated as potential delivery routes. The oral mucosa, with its attributes of ready accessibility, higher permeability than skin, self-administration feasibility, abundant blood supply, resilience to irritants, and a conducive moist environment for drug solubility, enables rapid systemic drug distribution [74,111].

Proniosomes have been widely studied for oral mucosal medication administration and systemic drug delivery over the mucosal barrier. Additionally, saliva immediately washes over the application site, reducing retention. So, adding proniosomal gel to mucoadhesive Carbopol base gel makes the therapeutic concentration stay in contact with the mucosal surfaces for longer [112].

TABLE 3: An overview of proniosomes' drug delivery applications across diverse administration routes, their compositions, and the consequential in vitro and in vivo effects.

Route	Drug	Composition	*In-vivo/in-vitro* effects	References
Oral	Candesartan cilexetil	Span 60/maltodextrin/cholesterol	Enhance the bioavailability via oral administration.	[113]
	Pioglitazone	Span 60/maltodextrin/cholesterol	Enhance the hypoglycemic effects through controlled drug release.	[114]
	Nateglinide	Span 60/maltodextrin/cholesterol	Improve oral bioavailability	[115]
Parenteral	Flurbiprofen	Span 80: Span 20/Sorbitol/cholesterol	Prolonged anti-inflammatory efficacy and decreased dosing frequency.	[104]
Dermal	Boswellic acid	Span 40/cholesterol/soya lecithin	Enhance bioavailability, absorption, and kinetics of release.	[116]
Transdermal	Mefenamic acid	Span 80/cholesterol/soya lecithin	Improve transdermal delivery and antiinflammatory activity	[117]
	Lacidipine	Cremophor RH 40/cholesterol/soya lecithin	Enhance the delivery, absorption, and penetration in transdermal administration.	[118]
	Oxybutynin chloride	Span 20: Span 60/cholesterol/soya lecithin	Improve drug penetration and therapeutic efficacy.	[119]

Oral mucosal and dental	Lornoxicam	Span 60/cholesterol/lecithin	Improve patient compliance and reduce gastrointestinal (GI) side effects	[112]
Vaginal	Terconazole	Span 60: Brij76/Cholesterol/lecithin	Enhance mucoadhesive properties	[120]

TABLE 4: Various research studies conducted on proniosomes as carriers for drugs.

Drugs	Category	Results	References
Glipizide	Oral rapid and short acting anti-diabetic	Encapsulation of Glipizide within vesicle bilayers achieves high entrapment efficiency, offering a promising strategy for prolonging drug release and mitigating side effects associated with gastric irritation.	[80]
Piroxicam	NSAID	The investigation involved studying the permeation of piroxicam from a reservoir-type transdermal gel formulation based on proniosomes across excised rat abdominal skin using a Keshary-Chein diffusion cell. Significant enhancement in flux was observed compared to the control gel formulation.	[121]
Haloperidol	Antipsychotic	Formulations containing a singular surfactant enhanced drug permeation more effectively than those incorporating a blend of surfactants.	[122]
Amphotericin	Anti-bacterial	Enhancing the physical stability of formulations necessitates the use of vacuum during both preparation and storage to mitigate phospholipid oxidation.	[61]

Clinical application:

a) Cardiology

Captopril, a medication for hypertension, is administered transdermally by use of proniosomes. According to the research, the proniosomal system keeps the medicine in the body for a longer period of time. Using sorbitan esters, cholesterol, and lecithin, the medication is encapsulated [123].

b) Diabetes

Researchers looked into how furosemide proniosomes get into the skin using a mixture of span, soya, lecithin, diacetyl phosphate, and cholesterol. The overall findings indicate that proniosomes function as a non-invasive method for delivering furosemide [124].

c) Hormonal therapy

The efficacy of transdermal delivery of levonorgestrel has been demonstrated through the utilization of the levonorgestrel proniosome. The biological assays incorporated endometrial assays that involved the development of corpora lutea [125].

d) Delivery of peptide drugs

The presence of an enzyme that breaks down the peptide has hampered the delivery of oral peptide therapy. Proniosomes have the potential to mitigate the degradation of peptides within the gastrointestinal system. Giving a vasopressin derivative enclosed in a proniosome by mouth has been found to be a very effective and dependable way to deliver drugs [126].

e) Anti-neoplastic treatment

Antineoplastic drugs have many serious side effects. Niosomes can modify metabolism, improve medication circulation, and lengthen half-life to lessen side effects. Two trials found that entrapping doxycycline and methotrexate in niosomes improved tumor proliferation and plasma levels while slowing drug clearance [127].

f) Haemoglobin carrier

In their work, Moser et al. (1989) investigated the potential of utilizing noisome as a carrier for haemoglobin in the bloodstream. They proposed that proniosome vesicles could serve as effective carriers for haemoglobin in individuals with anaemia, as proniosomes exhibit permeability to oxygen [128].

g) Antiparasitic treatment

The main therapeutic option for Leishmania parasite infections of the liver and spleen is antimonials. However, excessive quantities of antimonials can be detrimental to vital organs such as the heart, liver, and kidneys. According to the findings of Hunter et al. (1988), the inclusion of sodium stibogluconate in proniosomes resulted in enhanced treatment efficacy and reduced the occurrence of adverse effects [129].

Future aspects:

Proniosome-derived niosomes have been introduced in pharmaceutical research in recent decades and are widely used to target certain organs or tissues for better therapeutic effects. Modern proniosomes enable pharmacological research. New biocompatible carrier materials can be tested for proniosome synthesis. Proniosomes are promising drug delivery carriers in vesicular systems, although nutraceuticals, herbal compounds, and cosmetics need further study. They can also transport peptides because enzymes and acidic conditions degrade them orally. Peptides can be stabilized via proniosomal technology. They are also convenient for vaccine and antigen delivery and may present antigens to antigen identification cells better.

Furthermore, proniosomal carriers can carry medications with significant side effects to improve therapeutic efficacy and reduce side effects. Since proniosomes are oxygen-permeable, they can transfer haemoglobin to the circulation to treat anaemia.

Proniosomes in cosmetics extend, improve absorption, and have other benefits. Selecting the right HLB surfactant for a proniosome gel formulation is crucial to its desired properties. Studies show that proniosome gel formulation is a viable dosage form for skin medication permeation due to its simple, scaling-up production process and capacity to modify drug delivery. Thus, more research is needed to determine the best proniosome formulation for skin drug/cosmetic penetration.

TABLE 5: Patents related to Proniosomes

Patent publication number	Inventors	Title	References
US 4830857A	R. Handjani, A. Ribier, G. Vanlerberghe, A. Zabotto, J. Griat	Cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide, and a process for preparing these compositions	[130]
US 6051250	Ribier, A. Simonnet, Jean-thierry	Process for the stabilization of vesicles of amphiphilic lipid (s) and composition for topical application containing the said stabilized vesicle	[131]
WO/2010/ 12346	Madhavan, Eva-Kathrin	Madanagopal. Vesicular Systems and Uses	[132]

2. CONCLUSION

Recent advancements in drug delivery systems have propelled proniosomes into the spotlight within the drug delivery domain. Offering numerous advantages over traditional drug carriers like liposomes and niosomes, proniosomes stand out as a versatile drug delivery system. These dry formulations swiftly transform into niosomes upon hydration. The resulting niosomes from proniosomal technology exhibit enhanced stability compared to conventional counterparts and boast simpler hydration processes, circumventing the extensive shaking procedures involved in standard film hydration methods.

Proniosomes present solutions for addressing solubility and permeability challenges associated with class II and IV drugs, catering to both hydrophilic and hydrophobic drugs. Their adaptable nature enables the development of unit dosage forms, including tablets, beads, and capsules, facilitating transportation, distribution, storage, and dosing. Extensive research has highlighted proniosomes' effectiveness in drug delivery and targeting across various routes such as oral, parenteral, dermal, transdermal, ocular, vaginal, mucosal, pulmonary, and nasal administration. Proniosomes are particularly utilized in oral and transdermal delivery to enhance drug bioavailability and absorption in the gastrointestinal tract. Their penetration-enhancing properties, coupled with their non-toxicity and capacity for modulating drug release, make them promising candidates for transdermal delivery. In mucosal drug delivery, proniosomes have garnered significant attention, offering new perspectives in pharmaceutical research.

Moreover, proniosomes have found broad applications in drug delivery and targeting, presenting opportunities for research in diverse areas including anticancer drugs, vaccines, and genetic materials.

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