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Rajakarthikeyan U
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

Thamizhselvan S
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

M Sabareesh
Associate Professor, Department of Pharmaceutics, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

Saranraj L
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

R Yuvhraj
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

A Anthony Jerome
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

Marannambi S
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

Karthik Raja R
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

N Vijay Kumar
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

Sharan S
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

Correspondence
Rajakarthikeyan U
UG Student, Shri Venkateshwara College of Pharmacy, Ariyur, Puducherry, India

The systematic research on formulation and applications of proniosomal drug delivery system

Rajakarthikeyan U, Thamizhselvan S, M Sabareesh, Saranraj L, R Yuvhraj, A Anthony Jerome, Marannambi S, Karthik Raja R, N Vijay Kumar and Sharan S

Abstract
Nanotechnology has revolutionized the pharmaceutical sciences by facilitating the creation of nanovesicular drug delivery vehicles like ethosomes, proniosomes, niosomes, and liposomes. Proniosomes emerge as the best of them, overcoming the issues faced by other vesicular carriers. Proniosomes are dry, freely flowing, nanoscale vesicular structures of powder or gel that contain pharmaceuticals and, upon hydration, generate multilamellar niosomal dispersion. They can also be used to improve the solubility, permeability, and bioavailability of a variety of drugs. Proniosomes can effectively deliver drugs through the transdermal route, achieving controlled release action and increased therapeutic effectiveness for a variety of diseases. Additionally, when proniosomes are applied topically, the skin's natural water content converts them into niosomes in real time. This study intends to explore proniosomes for various pharmaceutical applications in drug delivery via different routes, such as topical, transdermal, oral, parenteral, ocular, vaginal, nebulizer, and intranasal routes. It also intends to discuss various aspects of proniosomes, including merits, mechanism, types, components, preparation, characterization, drug release, market scenario, and future trends. These proniosome-derived niosomes are superior to other vesicular and conventional dosage forms and may provide a great, affordable alternative delivery method.

Keywords: Nanotechnology, niosomes, proniosomes, proniosomal gel, transdermal delivery

Introduction
Medications have been administered to patients using a variety of pharmaceutical conventional dosage forms (Such as tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables as drug carriers) for many years in order to treat acute diseases (or) chronic illnesses. Even now, the majority of a prescription medication and drug store's space is occupied by conventional drug delivery systems. It is well recognized that this kind of medication delivery technology offers a rapid drug release. Therefore, it is frequently required to take this kind of drug delivery system multiple times a day in order to both achieve and maintain the drug concentration within the therapeutically effective range needed for therapy [1].

Disadvantages of Conventional Dosage Forms: [2]
1. Inadequate patient adherence raised the risk of forgetting to take a medicine whose short half-life necessitates frequent administration.
2. The obtained peak-valley plasma concentration-time profile is typical, making it challenging to achieve steady state conditions.
3. Steady State Concentration (Css) readings may decrease or climb above the therapeutic range due to inevitable variations in drug concentration, which could result in under- or overmedication.
4. When taking too much medication, the varying drug levels can hasten the onset of negative side effects, particularly when the drug has a low therapeutic index.
   The creation of drug delivery systems with the ability to regulate drug delivery rate, maintain therapeutic effect duration, and/or target drug delivery to a specific tissue is necessary to address the aforementioned drawbacks.

They are as follows, [3]
- Prolonged release

- Extended release
  Controlled Release (Rate controlled)
- Modified release
- Sustained Release
- Repeat action
- Delayed release

Delayed Release
The term "delayed release" refers to the release of the medication later on rather than right once after administration. For example, pulsatile release capsules and enteric coated pills.

Repeat action
Repeat action means that the first dose is released relatively quickly after administration, followed by the second or third doses at sporadic intervals.

Prolonged release
When a medicine is released in a prolonged release form, it is given for absorption over a longer duration than when it is given in a regular dosage form. On the other hand, a generally slower release rate from the dose form may be the reason for the delayed start.

Sustained Release
A sustained release is one in which the drug is gradually released over an extended period of time, with an initial release of enough to deliver a therapeutic dose shortly after administration.

Extended Release
Drugs are released gradually with sustained release dosage forms, allowing plasma concentrations to stay at a therapeutic level for an extended amount of time. (Usually takes eight to twelve hours.)

Controlled Release
Drugs in controlled release dosage forms are released at a consistent, predictable rate that may be repeated from one unit to another. It offers plasma concentrations that don't change throughout time.

Modified Release
In contrast, an extended release dosage form permits a two-fold reduction in dosing frequency or an increase in patient compliance or therapeutic performance. Modified release dosage forms are defined by the USP as those whose drug release characteristics of time course and for location are chosen to accomplish therapeutic or convenience objectives not offered by conventional forms. It is noteworthy that the USP views sustained release, prolonged release, and controlled release as synonymous with extended release.

Classification of Controlled Drug Delivery Systems (CDDS) [2, 14]
1. Rate-preprogrammed drug delivery systems
2. Activation-modulated drug delivery systems
3. Feedback-regulated drug delivery systems
4. Site-targeting drug delivery system

Targeted or Site-Specific Drug Delivery System [4]
Targeted drug delivery refers to the localization of the medication at therapeutic concentrations into the target or targets in a selective and efficient manner while limiting entry to the target location.

A targeted drug delivery system is preferred in the following situations
1. **Pharmaceutical:** Drug instability, low solubility
2. **Pharmacokinetic:** short half-life, large volume of distribution, poor absorption
3. **Pharmacodynamic:** low solubility, low therapeutic index

By avoiding medication deterioration or inactivation during transportation to the target areas, targeted drug delivery may offer the highest level of therapeutic activity. In the interim, it can reduce the dosage of strong medications to lessen their toxicity and shield the body from negative consequences resulting from improper disposal. *In vitro* and *in vivo*, a targeted delivery system should be safe, biocompatible, biodegradable, and physicochemically stable. The distribution system setup needs to be generally straightforward, repeatable, and economical.

Site-targeted DDSs have also been characterized as, [5]
Passive targeting: refers to natural or passive disposition of a drug-carrier based on the physiochemical characteristics of the system in relation to the body.

Active targeting: refers to alteration of the natural disposition of the drug carrier, directing it to specific cells, tissues or organs; for e.g use of ligands or monoclonal antibodies which can target specific sites.
- Inverse targeting
- Ligand mediated targeting
- Physical targeting (Triggered release)
- Dual targeting
- Double targeting
- Combination targeting

Second-order targeting: refers to DDS that delivers the drug to a specific cell type such as the tumour cells and not to the normal cells.

Third-order targeting: refers to DDS that delivers the drug intracellularly. Drug targeting often requires carriers for selective delivery and can serve following purposes
1. Protect the drug from degradation after administration
2. Improve transport or delivery of drug to cells
3. Decrease clearance of drug
4. Combination of the above

Carriers for drug targeting are of two types
- **Carriers covalently bonded to drug:** where the drug release is required for pharmacological activity.
- **Carriers not covalently bonded to drug:** where simple uncoating of the drug is required for pharmacological activity. E.g: liposomes.
- Polymeric carriers
- Albumin
- Lipoproteins
- Liposomes
- Niosomes
- Microspheres
- Nanoparticles

- Antibodies
- Cellular carriers
- Macromolecules

Colloidal Drug Carriers [6]

Micro- and nanoparticles, liposomes, niosomes, and macromolecular complexes (Such as lipoproteins) are examples of colloidal drug delivery systems. Colloidal carriers are frequently used to develop extended-release systems with targeting features, to increase the therapeutic efficacy and decrease drug toxicity by altering the drug's distribution and disposition, and to improve the stability of the drug in biological fluids or in the formulation.

Novel Drug Delivery System (NDDS) [6, 9]

The creation of novel drug delivery systems (NDDS) has received a lot of attention during the last several decades. Ideally, the NDDS should meet two requirements.

- Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of the treatment.
- Secondly, it should channel the active entity to the site of action.

None of these can be met by conventional dose forms, even those with extended release. Although there isn't a drug delivery system that works perfectly right now, several innovative techniques to drug distribution have been tried with some success.

The goal of NDDS is to provide the body some control over drug release, whether that control is geographical, temporal, or both. Novel medication delivery aims to minimize unwanted side effects while maintaining a reasonably constant, effective drug level in the body or sustaining pharmacological action at a predetermined rate. Additionally, it can target drug action by employing carriers or chemical derivatization to deliver drug to specific cell type. Finally, it can localize drug action by spatially placing controlled release devices next to or within the diseased tissue or organ.

Various drug delivery systems (NDDS) have been developed with different modes of administration to accomplish targeted and controlled drug delivery.

One such approach is the encapsulation of a medication in a vesicular structure, which, if selective absorption is successful, is expected to extend the drug's half-life in systemic circulation and decrease its toxicity. Vesicular systems are highly organized assemblages of one or more concentric bilayers that arise from the reaction of specific amphiphilic building elements with water. Vesicles can be constituted by a wide variety of amphiphilic constituents. Bingham originally described the biological genesis of these vesicles in 1965, coining the term "Bingham bodies."

Vesicular Systems: [7-13]

The search is never done. The search for better and newer options has existed since the dawn of humankind, and in the case of drugs, it will continue until a medication is discovered that has both maximum efficacy and no negative side effects. Numerous medications, especially those used in chemotherapy, have a restricted therapeutic window, and the adverse effects of dose limitation restrict their clinical utility. Thus, by combining the best possible ingredients, the medications that are already on the market have more therapeutic efficacy.

Vesicles have emerged as the preferred method of medicine administration in recent years. It has been discovered that lipid vesicles are useful for diagnostic procedures, membrane biology, immunology, and, most recently, genetic engineering. Vesicles have a significant impact on the transport and targeting of active substances as well as the modeling of biological membranes.

The ubiquitous delimiting structures that encircle and divide all cells and organelles are made up of biological membranes. The sole organizational characteristic that all biological membranes may have in common is the bilayer configuration of lipids. From the publication of Schleiden and Sehwann's cell theory in 1839, a plethora of theoretical models pertaining to membrane structure have emerged.

The static structures and national dynamics of certain isolated biological membrane compartments can be understood with the use of experimental models. Lipid vesicles are but one kind of the numerous bio-membrane experimental models available. Despite being created for fundamental study, the applications of these models have led to several technical advancements. Lipid vesicles have effectively developed into carriers for the delivery of controlled drugs.

Advantages of Vesicular Systems [7]

- Effective technique for administering medication straight to the infection location
- Drug toxicity reduction without side effects
- Lowers therapeutic costs by increasing the medication's bioavailability
- Include medications that are both lipophilic and hydrophilic.
- Postpone the removal of medications that are quickly metabolized.
- Serve as mechanisms for sustained release
- Addresses the issues of fast degradation, instability, and insolubility of drugs

Types of Vesicular Systems [7-13]

Various types of vesicular systems are as follows,

- Liposomes
- Niosomes
- Proniosomes
- Transferosomes
- Pharmacosomes
- Enzymosomes
- Virosomes
- Ufasomes
- Cryptosomes
- Emulsomes
- Discosomes
- Aquasomes
- Ethosomes
- Genosomes
- Photosomes
- Erythrosomes
- Hemosomes
- Proteosomes
- Vesosomes
- Apsasomes
- Colloidosomes
- Cubasomes

Liposomes [2]

Liposomes, also known as lipid bodies, are spherical, tiny vesicles with a diameter ranging from 25 nm to 10,000 nm that are made up of one or more concentric lipid bilayers divided by water or aqueous buffer compartments. Liposomes are created when phospholipid molecules self-assemble in an aqueous medium.

Generally speaking, they consist of one or more amphiphilic phospholipid bilayer membranes, also known as phospholipid vesicles, which have the ability to ensnare both hydrophilic and hydrophobic medications. Hydrophilic medications are confined within the aqueous core of liposomes, whereas hydrophobic compounds might be retained within the phospholipid membrane of the liposome wall. Liposomes are made up of several different substances, the two primary ones being cholesterol and phospholipids. Phospholipids such as phosphatidylcholines (PC), phosphatidylethanolamines (PE), and phosphatidylserines (PS) are utilized in the production of liposomes. Moreover, liposomes can be made using sterols, glycolipids, phospholipids, and sphingolipids. Targeted therapy and modified drug pharmacokinetics are made possible by these vesicles.

Niosomes [9]

A non-phospholipid vesicular substitute for liposomes is called a niosome. Niosomes are unilamellar or multilamellar vesicular systems that are osmotically stable and are produced when synthetic non-ionic surfactants are hydrated. The discovery of niosomes was prompted by the success of liposomal systems and the hunt for additional vesicle-forming amphiphiles. Since many surfactants have been found to self-assemble into closed bilayer vesicles that are employed for drug delivery, non-ionic surfactants were among the first alternative materials explored.

Transferosomes [10]

Both liposomal and niosomal delivery techniques exhibit inadequate skin permeability, vesicle rupture, drug leakage, and vesicle aggregation and fusion, making them unsuitable for transdermal delivery. Transferosomes, a novel kind of carrier system that can deliver both high- and low-molecular-weight medications transdermally, have recently been developed as a solution to these issues. It was proposed that transferosomes might quickly and with little energy change their shape in response to external stress. These new carriers are administered without occlusion as a semi-dilute suspension. Transferosomes are excellent options for the non-invasive delivery of tiny, medium, and large sized medications because of their deformability.

Pharmacosomes

The pharmacosome technique has the potential to overcome the constraints of both liposomes and transferosomes. These are described as colloidal dispersions of pharmaceuticals that are covalently bonded to lipids. Depending on the chemical nature of the drug-lipid combination, these can exist as extremely fine vesicular, micellar, or hexagonal aggregates. The pharmacosomes strategy can circumvent many of the drawbacks of several traditional vesicular drug delivery systems, including issues with drug integration, leakage from the carrier, and inadequate shelf life.

The interaction between the drug and lipids in bulk and surface form the basis for the creation of the vesicular pharmacosome. Any medication with an active hydrogen atom (-OH, -COOH,-NH2, etc.) can be esterified with or without a spacer chain to the lipid. Such a molecule's synthesis may be directed in a way that substantially produces an amphiphilic compound, which will aid in the organism's ability to transfer membranes, tissues, or cell walls.

Enzymosomes

Liposomal constructs are designed to create a miniature bioenvironment whereby enzymes are either covalently immobilized or bonded to the liposome surface. used to convey specific messages to tumor cells.

Virosomes

Liposomes containing virus glycoprotein were integrated into liposomal bilayers made of lipids generated from retroviruses. used as adjuvants in immunology.

Ufasomes

Long chain fatty acids (oleic and linoleic acid) were used to create the vesicles encased in fatty acids by mechanically agitating evaporated films in the presence of buffer solutions. utilized to target drugs via ligands.

Cryptosomes

Lipid vesicles with a PC and appropriate polyoxyethylene derivative of phosphatidylethanolamine surface coat. utilized to target drugs via ligands.

Emulsomes

Water-insoluble medications are contained in the solution form in nanosize lipid particles (bioadhesive nano emulsion), which are made up of microscopic lipid assemblies with polar cores and don't require the use of surface active agents or co-solvents. These lipid particles with fat cores are distributed throughout an aqueous phase. Emulsomes are lipid-based drug delivery vehicles with a broad range of therapeutic uses, particularly in the parenteral administration of poorly water soluble medications

Discosomes

Non-ionic surfactant solution (Polyoxyethylene cetyl ether class, Solulan C24) was used to solubilize niosomes. Water-soluble solutes can be ensnared by enormous structures called discosomes, which range in size from 12 to 60 µm. utilized to target drugs via ligands.

Aquasomes

Three-layered self-assembly compositions covered in glassy cellobiose and featuring a ceramic carbon nanocrystalline particle core. Used for molecular shielding and targeted specificity.

Ethosomes

Ethosomes are phospholipid, ethanol, and water-based lipid "soft, malleable vesicles" that represent a permeation enhancer. utilized to send specific content to deep skin layers.

Genosomes

Catechol-based lipids are the most appropriate artificial macromolecular complexes for functional gene transfer because of their excellent bloodstream stability and biodegradability. utilized to deliver genes to targeted cells.

Photosomes
Photo-triggered changes in membrane permeability properties release the contents of photolyase encapsulated in liposomes. utilized in photodynamic treatment.

Erythrosomes
In regulated drug delivery systems, red blood cells present a variety of options for drug delivery. Both site-directed and sustained-release systems use erythrosomes, whose release rate, duration, and physical properties are easily adjusted to change the delivery method. Liposomal systems in which human erythrocytes are chemically crosslinked and cytoskeletons are coated with a lipid bilayer as a support. utilized to target macromolecular medications effectively. The "Nano erythrosome," a drug carrier based on erythrocytes, is created by extruding erythrocyte ghosts to create tiny vesicles with an average diameter of 100 nm. As oxygen carriers, artificial red blood cells made by encasing hemoglobin using interfacial polymerization have been employed.

Hemosomes
Liposomes containing hemoglobin that were created by immobilizing hemoglobin using phospholipids that can polymerize. utilized in systems that convey large amounts of oxygen.

Proteosomes
The assembly pattern of enzymes is specifically responsible for the catalytic activity of high molecular weight multi-subunit enzyme complexes. greater catalytic activity turnover than enzymes that are not associated when used.

Vesosomes
In vitro nested bilayer compartments created by adding ethanol to several types of saturated phospholipids, or the "interdigitated" bilayer phase. Application: The internal components of serum are better protected by the vesosome's many compartments.

Archaeosomes
Archaeal glycerolipid-based vesicles possessing strong adjuvant properties.

Apsasomes [11]
As a material for bilayer vesicles, ascorbyl palmitate vesicles (ASP) were investigated. Antioxidant-rich vesicles made from amphiphiles may find use in treating illnesses associated with reactive oxygen species.
One of the main antioxidants found in human plasma, as well as in and between cell membranes, is ascorbic acid, or vitamin C. Together with peroxides and reactive oxygen species like superoxide, it also lowers α-tocopherol

Colloidosomes [8]
A new kind of microcapsules known as colloidosomes is made up of fused or coagulated colloid particles at the interface of emulsion droplets. The spherical capsules known as "colloidosomes" are created when colloidal particles are carefully allowed to self-assemble onto emulsion droplets. In order to reduce the overall interfacial energy and function as a bridge between the particles, colloidal particles in aqueous solution adhere to the emulsion droplets in colloidosomes. This locks the particles together and stabilizes the structure, enabling the removal of the initial templating surfaces.

Cubasomes [12]
Cubosomes are made up of two internal aqueous channels, a sizable interfacial area, and honeycombed (cavernous) structures. Self-assembled cubosomes are active drug delivery vehicles that have distinct interior cubic compositions and structures as well as varied drug-loading mechanisms. Cubosomes are nanoparticles with a diameter ranging from 10 to 500 nm; they resemble square, slightly round dots.

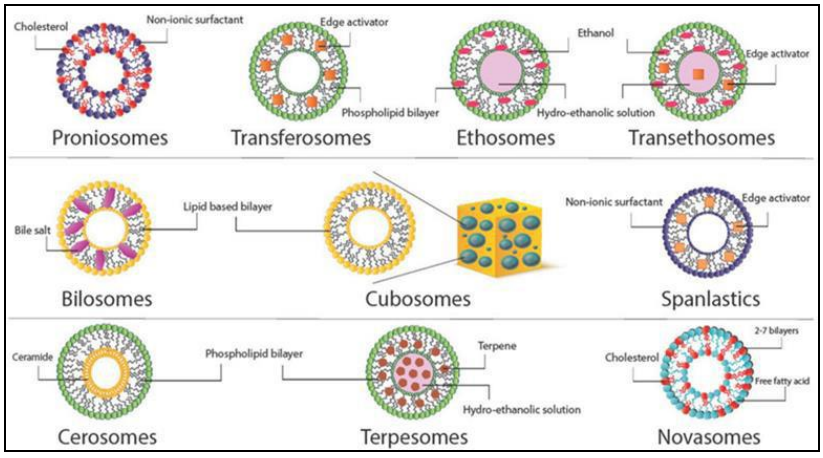

Fig 1: Schematic diagram represents the structure of different advanced vesicular systems

Proniosomes
Proniosomes are surfactant-coated, water-soluble carrier particles in a dry composition. Before being used on agitation in heated aqueous media, they are quickly rehydrated to produce niosomal dispersion in a matter of minutes. Proniosomes don't physically change when being transported or stored. The medication enclosed in the proniosome's vesicular structure increases the drug's penetration into the target tissue, decreases toxicity, and prolongs its presence in the systemic circulation.

Proniosomes are a niosomal formulation that requires hydration prior to use. They contain a carrier and surfactants. Proniosomes lessen the issues related to niosomal formation, such as fusion, leakage, and aggregation [15].

- Carrier + Surfactant = Proniosomes
- Proniosomes + water = Niosomes

Types of proniosomes [15-24]

Proniosomes are mainly 2 types

- Dry Granular Proniosomes
- Liquid Crystalline Proniosomes

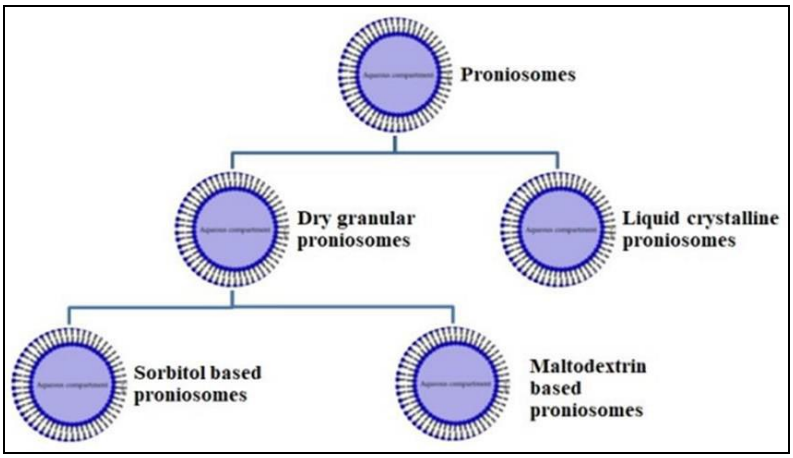

Fig 2: Schematic diagram represents the types of proniosomes

Dry granular proniosomes

The dry granular proniosomes are further divided into the following categories based on the preparation technique and carrier employed.

Sorbitol-based proniosomes,

This is a dry formulation that uses sorbitol as a carrier and non-ionic surfactants to coat it. When hydrated in hot water, the surfactants transformed into Niosomes.

Maltodextrin-based proniosomes

The process of making proniosomes based on maltodextrin is called the quick slurry method. A polymer with high water solubility, maltodextrin is utilized as a carrier during the manufacture of proniosomes. Particles of maltodextrin are added to improve surface area. The thinner surfactant coating produced by the increased surface area is appropriate for the rehydration process.

Preparation of Proniosomal Gel [16, 25, 26]

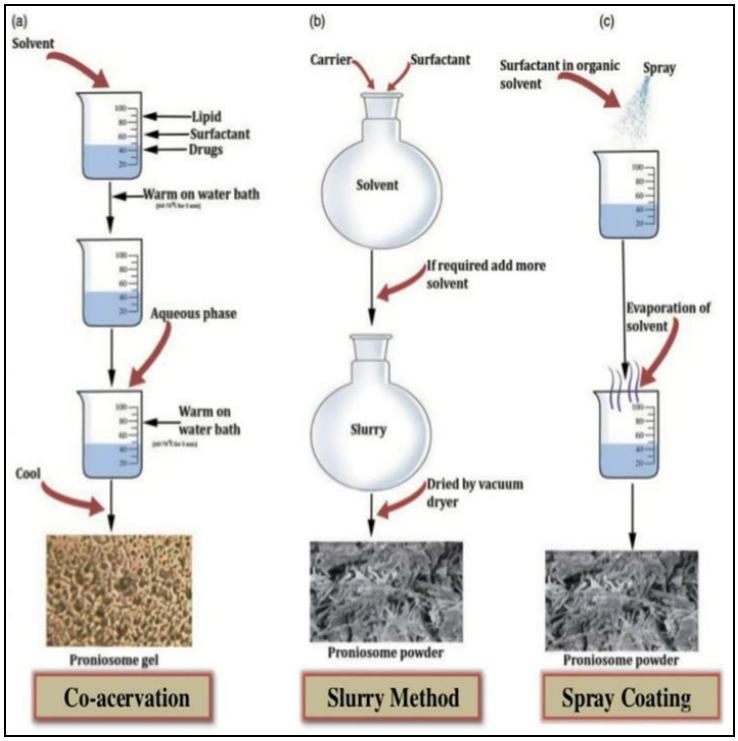

Fig 3: Schematic diagram represents the preparation of proniosomes

Different techniques and substances are employed in the production of proniosomes. The most widely used process for preparing proniosomal gels among these is called coacervation phase separation.

Slow Spray Coating Method

Weighed the carrier material precisely, then transferred it into a flask with a circular bottom and stored it in a rotating evaporator. Following that, spray the necessary amounts of surfactant and place the mixture of cholesterol onto the carrier and depart. The round-bottom flask should then be kept in a water bath between 65 and 70 °C for 20 minutes. To obtain a proniosome powder that is free to flow, repeat the process with the remaining amount of surfactants and keep up the evaporation process. Next, this powder was combined with 1-2% of the appropriate gelling agent.

Slurry Method [16]

Prepare the cholesterol and surfactant stock solution in a suitable solvent for this procedure. Pour this mixture into the drug-containing round-bottom flask. Add chloroform if the surfactant is not loaded adequately, and then evaporate the solvent at 600 mm Hg pressure and 50–60 °C. The free-flowing proniosome forms following the evaporation. To get proniosomal gel, add the appropriate gelling agent to this.

Coacervation Phase Separation Technique [25, 26]

It is the proniosomal gel preparation technique that is most frequently utilized. Using a wide mouth glass jug, the medication, surfactant, cholesterol, and lecithin are all precisely weighed in this approach. After that, add enough ethanol, the solvent, and warm the mixture to between 50 and 60 degrees Celsius in a water bath. To stop the solvent from evaporating, a lid is placed over the open end of the glass vial. Add aqueous phase phosphate buffer (pH 7.4) to this combination. The mixture should be heated to between 50 and 60 degrees Celsius over a water bath until the medication has fully dissolved in the surfactant combination. Either cool the liquid to room temperature or add an appropriate gelling agent, then cool the hot fluid over an ice bath to make the proniosomal gel.

Sturcture of Proniosomes [15-24]

Proniosomes are tiny structures that resemble lamellae. They mix cholesterol with a non-ionic surfactant belonging to the alkyl or di-alkyl polyglycerol ether family, and then hydrate in aqueous solutions. The non-ionic surfactant's hydrophilic ends point outward, while its hydrophobic ends point in the other way to create the bilayer. Proniosomes consist of a bilayer, just like liposomes. The bilayer of proniosomes is composed of non-ionic surface-active substances. Proniosomes are classified as unilamellar or multi-lamellar depending on the preparation technique.

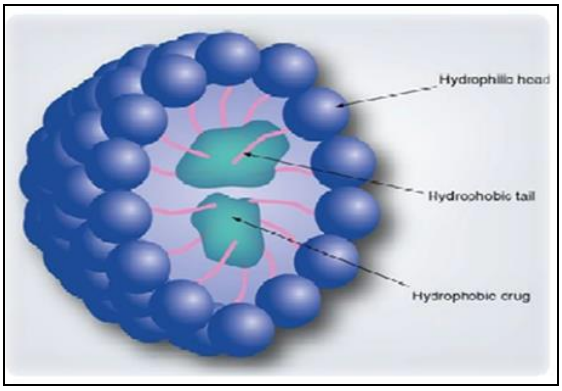

Fig 4: Structure of proniosomes

Action of proniosomes [15]

After being hydrated and changing into niosomes, pioniosomes begin to function. Niosomes Proniosomes (depending on moisture). The addition of aqueous solutions may cause the hydration to happen. Liposomal and hydrophilic substances can be ensnared by promethions.

Formulation of proniosomes [18-22]

Non-ionic surfactants [18]

There is a large variety of surfactants available, and the hydrophilic-lipophilic balance should be the basis for surfactant selection. It was discovered that vesicles formulations might work with an HLB of 4 to 8. Entrapment degree is influenced by HLB number.

The drug's entrapment in vesicles is also influenced by the transition temperature of surfactants. Span 40 and Span 60 yield larger vesicles with higher drug entrapment. Spans with the highest phase transition temperature also provide the highest entrapment for the drug. Low permeability and a high phase transition temperature prevent drugs from leaking out of the vesicles. Due to the bigger vesicles and less lipophilic nature of tween, its encapsulation effectiveness is lower than that of span. Additionally, span increases the drug's lipophilicity.

Lecithin [19]

The primary ingredient in lecithin is phosphotidyl choline. The nomenclature mostly refers to the place of origin, for example, egg lecithin from egg yolks and soy lecithin from soy beans. The solubility of phosphotidyl choline in water is poor. Because lecithin has a high phase transition temperature, it can promote penetration, stop drug leakage, and increase the percentage of drug entrapment in proniosomes. Because the intrinsic components of soy lecithin differ from those of egg lecithin, the vesicles made by soy lecithin are greater in size. Egg lecithin includes fatty acids, whereas soya lecithin contains unsaturated fatty acids, oleic and linoleic acid, making it a better contender in terms of penetration potential.

Cholesterol [22]

A vital component of vesicles is cholesterol. Cholesterol incorporation affects the permeability and stability of vesicles. The amount of cholesterol present is crucial for the drug's trapping in vesicles. By using span 60, which has a higher transition temperature, and by raising the cholesterol content, the entrapment efficiency and permeation rise.

Solvent [20]

The choice of solvent is a crucial factor that significantly impacts both the size of vesicles and the rate at which drugs penetrate them. The order of the distinct alcohol-formated vesicles is ethanol > propanol > butanol > isopropanol. They also vary in size. The reason why ethanol has larger vesicles is because it dissolves better in water, but isopropanol may have smaller vesicles because of its branching chain. Ethanol has the potential to promote skin penetration by decreasing lipid polar head interactions within the membrane

Aqueous phase [21]

Proniosomes primarily use phosphate buffer 7.4, 0.1% glycerol, and hot water as their aqueous phase. The hydration medium's pH has a significant impact on the effectiveness of entrapment. Proniosome tactiness may be influenced by the aqueous media, which could impact how well they entrap particles.

Characterization of Proniosomes [24-30]

Proniosomes can be characterized using a variety of techniques, depending on the component of the system being studied. These features include vesicle size, lamellarity, surface potential, morphology, and microscopy, which are all connected to the general structure of proniosomes.

Vesicle shape

Transmission electron microscopy (TEM), scanning electron microscopy (SEM), and optical microscopy are readily used to detect promenoid structures.

Optical Microscope Observation

Using a glass rod, the Proniosomal dispersion was applied to the glass slide. By using an optical microscope with a 100X magnification power to examine the proniosomes, the formation of multilamellar vesicles was verified.

Vesicle size and zeta potentia

Photon correlation spectroscopy (PCS) and dynamic light scattering (DLS) can be used to measure the particle size of the prometheosomes. A Zeta meter can be used to measure the formulation's zeta potential.

Transition temperature

Differential scanning calorimetry can be used to find the vesicular lipid systems' transition temperature (DSC).

Drug entrapment

The ultra-centrifugation method can be used to determine the entrapment efficiency of pioniosomes.

Drug content

A UV spectrophotometer can be used to determine the drug content of the prometheosomes. A modified high performance liquid chromatographic method can also be used to quantify this.

Surface tension measurement

Using a Du Nouy ring tensiometer and the ring method, one can measure the drug's surface tension activity in an aqueous solution.

Applications of Proniosomes: [15, 18, 25-30]

Targeting of bioactive agents

The capacity of proniosomes to target specific areas with medications is one of its most advantageous features. Drugs can be targeted to the reticulo-endothelial system using pioniosomes. Proniosome vesicles are preferentially absorbed by the Reticulo endothelium system (RES). Opsonins are circulating blood factors that regulate proniosome uptake. Drugs that localize this way are used to treat cancers in animals that have a history of metastasizing to the spleen and liver. The medications' localization makes them useful in treating liver parasite infections as well. Drugs can also be targeted by promenoid endosomes to organs other than the RES. Proniosomes can be directed toward a particular organ by attaching a carrier system (such as antibodies) to them because immunoglobin binds to the lipid surface of the noisome with ease.

Anti-neoplatic treatment

The majority of antitumor medicines have serious adverse effects. Proniosomes have the ability to modify metabolism, extend the drug's half-life and circulation, and lessen its adverse effects. Doxorubicin and methotrexate entrapped in proteosomes exhibited advantageous properties compared to their unentrapped counterparts, including a slower rate of tumor growth and increased plasma levels with a delayed rate of clearance.

Treatment of leishmaniasis

A parasite belonging to the genus Leishmania infects the cells of the liver and spleen to cause leishmanasis. Antimonials, which are compounds of antimony that cause harm to the kidneys, liver, and heart in higher amounts, are frequently prescribed medications for treatment. The use of proniosomes demonstrated that bigger dosages of the medication could be given without causing side effects, which increased therapeutic efficacy.

Delivery of peptide drugs

For a long time, oral peptide medication administration has struggled to avoid enzymes that would break down the peptide. In order to properly shield the peptides from gastrointestinal peptide breakdown, proniosomes were used. Oral administration of a vasopressin derivative encapsulated in proniosomes demonstrated maximal drug entrapment and a noteworthy enhancement in the stability of the integrated peptide, according to a study.

Uses in studying immune response

Because of their higher stability, minimal toxicity, and immunological selectivity, promethiosomes are used in immunological response research. Research on the nature of the immune response triggered by antigens is being conducted using prionosomes.

Transdermal drug delivery systems

Proniosomes are very helpful since they significantly improve the absorption of medications through the skin. Cosmetics use proniosomal technology for transdermal medication delivery extensively; in fact, this was one of the original applications for niosomes. Antibiotics encapsulated in proniosomes are applied topically to treat acne. When compared to an unentrapped medication, the drug's skin penetration is significantly boosted. Proniosomal-based

transdermal vaccinations have also been the subject of recent research.

Sustained release drug delivery

medications with low therapeutic index and limited water solubility can benefit from the sustained release action of proniosomes since proniosomal encapsulation can keep those medications in the bloodstream.

Localized drug action

Because of their small size and limited capacity to pass through connective tissue and epithelium, proniosomes are one method of delivering drugs that have a localized effect at the site of administration. Drugs with localized action have higher efficacy and potency while having less systemic toxic effects. For example, mononuclear cells absorb antimonials encapsulated in proniosomes, which causes the drug to become more localized, more potent, and less toxic in terms of dose and toxicity. Although proniosomal drug delivery technology is still in its infancy, anti-leishmanial therapy and chemotherapy for cancer appear to benefit from this kind of drug delivery system.

Applications in cardiology

Captopril is delivered transdermally to treat hypertension using promethiosomes as carriers. According to the study, the proniosomal system contributes to the drug's prolonged release throughout the body. Lecithin, cholesterol, and sorbitan esters are used in the encapsulation process of the medication.

Application in diabetes

Furosamide proniosomes' skin penetration process involves the utilization of span, soy, lecithin, diacetyl phosphate, and cholesterol. Overall results point to proniosomes as a non-invasive furosamide delivery mechanism.

Hormonal therapy

Research has been done on the transdermal delivery of levonorgestrel, an emergency contraceptive, using proniosomes. The niosome exhibited a liquid crystalline compact hybrid structure. Particle size, encapsulation efficiency, stability research, in-vivo, and *in vitro* testing were performed on the system. *In vitro* research. Progestational activity was also measured using bioassay. It involves blocking the formation of the corpora lutea and doing an endometrial assay.

Toxicity of Proniosomes

Proniosomes and niosomes made from comparable ingredients. Niosomes are created when proniosomes are moistened. Proniosome toxicity is non-specific since research study data are limited in scope. Proniosomes share two common components: cholesterol and a surfactant. The toxicity is a result of the surfactant's chemical makeup. It is clear that the ester-derived surfactant is more hazardous than the ether; this could be due to the ester bonds' enzymatic degradation. Notwithstanding the toxicity concerns mentioned above, the formulation—dry powders or gels—is unaffected by them. It was less obvious that the lomefloxacin proniosomes caused no redness, edema, or inflammation, but instead shown greater ocular toleration. The research study claims that non-ionic surfactants induce eye irritation, redness, and swelling as well as damage to the cornea and conjunctive epithelium. According to a different study, the most favored components for proniosomes are cholesterol and span 60. Due to its lack of ocular toxicity, cholesterol is the most preferred option. As a result, the model suggests that non-ionic surfactant encased proniosomes do not cause cytotoxicity when applied topically or ciliotoxicity when administered intranasally.

Future Trends

Proniosomes are a useful tool in medicinal studies. Compared to the vesicular system, the provesicular system is superior. Proniosomes are a dependable method for medication targeting. Furthermore, compared to the current drug delivery system, they offer the chance to administer more effective treatment. This has to be investigated in the fields of cosmetics, herbal goods, and nutraceuticals. Another significant development in vesicular drug delivery is the involvement of antibodies, peptides, vaccines, genes, and sera. Despite this, the majority of product categories fall within the realm of research. Thus, work needs to be done in a pilot plant at the study's scale while conducting research for therapeutic uses. Consequently, in order to introduce medication candidates into a vesicular system, industrial infrastructure for vesicular systems must be established.

Table 1: List of drugs under research as Proniosomal drug delivery [29]

S. No.	Drug	Category	Method of preparation	Purpose/reason
01	Tolnaftate	Antifungal	Coacervation phase separation method	To increase duration of action &improve systemic absorption
02	Celecoxib	Anti- inflammatory, analgesic, anti-pyretic.	Modified coacervation method	To reduce 1st pass metabolism
03	Risperidone	Anti-psychotic drug	Coacervation phase separation method	To increase bioavailability because it has low systemic absorption (orally)
04	Isoniazid	Anti-tubercular drug. Anti-bacterial	Coacervation phase separation method	To improve therapeutic efficacy and reduces side effects.
05	Ritonavir	Anti-viral, HIV treatment	Modified coacervation method	To improve stability of formulation and sustain release of drug
06	Olmesartan	Anti- hypertensive	Slurry method	To enhance the bioavailability due to their poor water solubility orally (26%)
07	Glimepiride	Hypo-glycemic activity	Coacervation phase separation method	To improve its therapeutic efficacy
08	Cefuroxime	Anti-biotic	Slurry method	To enhance bioavailability
09	Carvedilol	Anti-hypertensive (β-blocker	Coacervation phase separation method	To improve entrapment efficiency and bioavailability

10	Clotrimazole	Anti-fungal	Coacervation phase separation method	To enhance solubility

Patents filed

Table 2: Patents related to Proniosomes and Niosomes [29]

Patent No	Inventors	Title
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
US 6051250	Ribier, A. Simonnet, Jean-thierry	Process for the stabilization of vesicles of amphiphilic lipid (s) and composition for topical application containing the stabilized vesicle.
US 06576625B2	A. Singh, R. Jain	Targeted vesicular constructs for cytoprotection and treatment of *H. pylori* infections
US 06951655B2	Y. Cho, K. H. Lee	Pro-micelle pharmaceutical compositions

Products available in market [30]

Table 3: Available products in market

Brand	Product name
Orlane-lipcolor and lipstick	Lip gloss
Lancôme Flash retouch brush on concealer	Flash retouch brush on concealer

Conclusion

The purpose of this research was to prepare ramipril loaded proniosomes for controlled release of drug and a trial to improve the drug diffusion rate across the semipermeable egg membrane. It is concluded that the proniosomal gel, is a useful method for the successful incorporation of poorly water soluble drug ramipril into proniosomes with high entrapment efficiency. The prolonged release of the drug from the proniosomes suggests that the frequency of administration may be reduced. Further it may be presumed that if the nanometer range particles are obtained, the bioavailability may be increased. Based on all the characteristics, RPG2 was considered as best formulation for further studies. The entrapment efficiency of formulations was in the range of 84.38% and *In-vitro* drug release studies of formulation showed maximum drug release and the drug release was in the range of 81.90%. Hence, we can conclude that proniosomes provide controlled release of drug and these systems are used as drug carriers to enhance the permeation of poorly water soluble drugs. Further pharmacological and toxicological investigations in animals, human volunteers, may help to exploit the proniosomes as prosperous drug carriers for targeting drugs more efficiently.

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