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PRONIOSOMAL DRUG DELIVERY SYSTEM- A REVIEW

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Keywords:

Provesicular drug delivery system, Proniosomal gel, Proniosomes, Non-ionic surfactants, Transdermal drug delivery system

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ABSTRACT: Proniosomes are provesicular dried or anhydrous formulations that are composed using non-ionic surfactants and solvents. The non-ionic surfactant's hydrophilic portion orients outward to form a bilayer, while the hydrophobic portion moves inward. Medicines with hydrophilic properties are contained in vesicles, while hydrophobic drugs get embedded in proniosome bilayers. Proniosomes are physically stable while storage and handling when compared to liposomes and niosomes. They can be used to impart targeted drug action, enhance retention time, increase penetration of drug at target tissue, sustain/ control drug release and minimize side effects. These proniosomes can be rehydrated with hot aqueous solution and constant stirring and transformed to niosomes immediately when needed. Generally, proniosomes are either converted to niosomes or proniosomal gel for transdermal drug delivery to use of the benefits associated with proniosomes. This review article focuses on structure, mechanism of drug transport, composition, preparation, characterization methods of proniosomes and the research carried out in past in field of provesicular drug delivery system.

INTRODUCTION:

Vesicular Drug Delivery System: Vesicular drug delivery system is the system that consists of highly ordered and arranged assemblies of concentric lipid bilayer that are formed due to amphiphilic building blocks that assemble them in the presence of water [1]. Vesicular system is one of the approaches whereby the drug is encapsulated for several purposes. Vesicular drug delivery systems are novel and targeted drug delivery systems as they have the ability to reach at the targeted site of action in body which aids in reducing adverse effects at other sites in the body and effective therapeutic concentration in the body [2]. Vesicular drug delivery system has owned several advantages that include [3]:

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- Targeted and Localised site of action that reduce toxicity
- Prolongation of drug concentration in systemic circulation
- Elimination of metabolized drug is delayed
- Improved drug permeation through skin
- Sustained/ Controlled release of drug
- Improved bioavailability
- Reduced cost of drug therapy
- Both hydrophilic and lipophilic drugs can be incorporated [4, 5].

Classification of Vesicular Drug Delivery System: The vesicular drug delivery systems are categorised as Emulsions, Liposomes, Nanostructured lipid carriers, core-shell nanoparticles, Cubosomes, Transferosomes, Pharmacosomes, Ethosomes, Sphingosomes and Niosomes [6]. Although, vesicular drug delivery system has several advantages but this approach of

drug delivery is not opted in every formulation due to major stability issues which includes:

- Aggregation of drug and excipients
- Leakage of drug from the vesicular structure that results in sudden increase in drug concentration in systemic circulation
- Higher adverse effects
- Fusion and sedimentation of vesicles due to hydrophilic nature [7].

For this purpose, another system of drug delivery is approached which is known as Provesicular Drug Delivery System that includes Proniosomes and Proliposomes [8].

Proniosomes: Proniosomes are vesicular drug delivery systems or vesicles that are composed of non-ionic surfactants, cholesterol and other additives. Proniosomes are anhydrous or dry formulations prepared by non-ionic surfactant coated carrier [9].

The proniosomes are preferred over niosomes for its higher stability, appropriate release pattern and ease of packaging and transportation for its dry nature. The surfactants used in preparation of proniosomes act as important carrier/ ingredient in formulation as it enhances the drug permeation, biodegradable, non-toxic, amphiphilic and can encapsulate both hydrophilic and lipophilic drugs [10, 11].

Structure of Proniosomes: Proniosomes are semisolid gel structures that are said to be mixture of phases of liquid crystal such as lamellar, cubic and hexagonal. Proniosomes are lamellar structures of microscopic range. The proniosomes are prepared from non-ionic surfactants and cholesterol. The hydrophobic part of non-ionic surfactant directs itself inwards whereas the hydrophilic part orients outwards and form bilayer. During incorporation of drug, the hydrophilic drugs are enclosed in the vesicles whereas hydrophobic drugs are embedded within the bilayer of proniosomes [12].

Types of Proniosomes: Proniosomes are classified on the basis of type of carrier and method of preparation. Proniosomes are classified into:

Dry Granular Proniosomes: The dry granular proniosomes are classified into 2 types on the basis of method of preparation. These include:

Sorbitol Based Proniosomes: These are dry granular proniosomes prepared by addition of sorbitol (carrier) in non-ionic surfactants using simple agitation method.

Maltodextrins Based Proniosomes: These are dry granular proniosomes prepared by addition of maltodextrin (carrier) in non-ionic surfactant by the method of fast slurry technique [12, 13].

Liquid Crystalline Proniosomes: Proniosomal gel are semisolid liquid crystal gel that are prepared by dissolving surfactant in minimal quantity of solvent and hydrating with small amount of water to form gel. These gels are semisolid transparent, translucent or white physically stable formulations that can be used topically/ transdermally. These proniosomes act as reservoir in transdermal drug delivery system. The Proniosomal gel is placed onto the backing membrane of the transdermal patch and release the drug accordingly. The liquid crystalline proniosomes have exceptional benefits that make it the suitable choice for the pharmaceutical researchers in the field of provesicular drug delivery system. These include: Higher stability, Higher entrapment efficiency, Good penetration enhancer and easy to manufacture and economical.

Advantages of Proniosomes [14, 15]:

Used for Hydrophobic and Hydrophilic Drugs: Proniosomes can be used for entrapment of both hydrophobic and hydrophilic active ingredients.

Ease of Packaging and Transportation: Proniosomes are dry formulations that can be easily sterilized, stored, transported, distributed and transported.

No Degradation Reaction: Proniosomes being dry formulations do no undergo hydrolysis or oxidation reaction and hence can be avoided from degradation.

No Special Conditions for Storage and Transportation: Proniosomes can be easily stored and transported and do not require any specific conditions.

Physical Stability: Proniosomes are physically stable formulations and hence fusion, sedimentation, leakage and aggregation are not seen.

Use of Solvents in Acceptable Range: Proniosomes are prepared by using solvents in minimum quantity and hence no skin irritation will be observed when used topically or transdermally.

Controlled and Sustained Release: Proniosomes show controlled, targeted and sustained drug release pattern.

Enhanced Bioavailability: Proniosomes offer targeted drug delivery and hence bioavailability is higher with no adverse effects.

Mechanism of Drug Transport through Skin [16, 17]: The mechanism of drug transport through skin depends on vesicle skin interaction. This interaction can be categorised into 2 types:

When vesicles/ proniosome come in contact with the skin layer stratum corneum, the proniosomes aggregate, adhere with surface of skin cells. This interaction leads to the penetration of hydrophobic (lipophilic) drugs through the skin layer (stratum corneum).

The second type of vesicle skin interaction involves the structural change in the intercellular and deep skin layer and leads to penetration of proniosomes across the skin.

Composition of Proniosomes:

TABLE 1: INGREDIENTS USED IN PREPARATION OF PRONIOSOMES

Ingredients	Example	Use
Surfactant (Non-ionic)	Span 20, 40, 60 Tween 20, 40, 60	Act as penetration enhancers
Stabilizers	Cholesterol, Lecithin	Strengthen the formulation and prevent leakage, and penetration enhancers
Solvents	Alcohol, Water, PBS 7.4, glycerol	Enhances solubilization of drug
Carrier	Maltodextrin or Sorbitol	Impart flexibility

Surfactants: The surfactants for proniosomes are selected on the basis of HLB value of the surfactants. The surfactants with HLB value in between 4 and 8 are considered as most compatible for the development of proniosomes. The hydrophilic surfactants with high aqueous solubility on hydration do not reach concentrated point that may lead to aggregation and coalescence. eg., Polysorbate 20 is used as surfactant with cholesterol to form proniosomes. The degree of drug entrapment is affected by the HLB value of surfactant. The transition temperature of surfactant also affects the drug entrapment. The surfactants with higher transition temperature show highest drug entrapment efficiency. Span 40 and Span 60 with higher transition temperature show highest drug entrapment efficiency. Higher HLB value of these surfactants results in less surface free energy and allows formation of vesicles (proniosomes) with larger size and hence large area is exposed to skin and higher penetration [18-20].

Stabilizers:

Cholesterol: Cholesterol is the most important ingredient after surfactants in the formation of proniosomes. The use of cholesterol in formation of vesicles not only increases the vesicle stability but also enhances permeability through skin. The entrapment efficiency of drug also increases with increase in concentration of cholesterol. But very high concentration of cholesterol leads to lowering of drug entrapment in the vesicles. This is due to the fact that cholesterol disrupts the bilayer structure leading to loss of drug entrapment [21, 22].

Lecithin: Phosphatidyl choline is major component of lecithin. Another stabilizer that can be used for preparation of proniosomes is lecithin. It has low solubility in water. The use of lecithin in proniosomes acts as permeation enhancers and leads to vesicles of smaller size due to hydrophobicity which results in reduction of vesicle size. Although the drug entrapment efficiency of lecithin is less when compared to cholesterol [23, 24].

Carriers:

Maltodextrins: It is a polysaccharide with low solubility in organic solvents. During the preparation of proniosomes, the maltodextrin

particles are coated by adding surfactant in organic solvent.

Sorbitol: The use of sorbitol as carrier in preparation of proniosomes results in the formation of solid-cake like mass [25].

Solvents and Aqueous Phase:

Alcohol: The use of alcohol affects the vesicle size and drug entrapment efficiency. Ethanol is the most favourable solvent for the preparation of proniosomes. Ethanol has higher water solubility and forms vesicles of larger size when compared to other solvents such as Butanol and Isopropanol.

Aqueous Phase: Phosphate buffer with pH 7.4, hot water and glycerol is used as an aqueous phase for the formation of proniosomes [26].

Miscellaneous:

Dicetyl Phosphate: It is used as lipid phase in the preparation of proniosomes. The use of DCP enhances slightly greater amount of drug when compared to cholesterol and surfactant used alone.

Stearyl Amine: It is also a charged lipid but decreases the entrapment efficiency [27].

Drugs Suitable for Formulation of Proniosomes[21, 26]: Drugs with low aqueous solubility or lipophilic drugs:

- Drugs that are required in frequently for the treatment
- Drugs with lower half-life
- Drugs required for controlled or sustained release
- Drugs needed for targeted or localised action

Factors Affecting Formulation of Proniosomes [26]:

Chain Length of Surfactant: Spans are commonly used for the preparation of proniosomes. Variety of spans differs in the alkyl chain attached. Increasing the chain length of surfactant enhances the entrapment efficiency [28]. The entrapment efficient of Spans follows the order: Span 60 (C18) > Span 40 (C16) > Span 20 (C12).

Amount of Cholesterol: Increasing or decreasing the cholesterol content affects both permeability and entrapment efficiency. Increasing the cholesterol content increases the entrapment efficiency and makes a rigid layer or encapsulates the proniosomes that decreases the permeability through vesicles thereby preventing drug leakage [29].

pH of Hydration Medium: The pH of the hydration medium used for transforming proniosomes to niosomes also influence the encapsulation efficiency. It was studied that the decrease in pH from 8 to 5.5 increased the encapsulation efficiency of flurbiprofen almost 1.5 times.

Lipid Concentration and Charge of Lipids: The amount of lipid concentration positively influences the encapsulation efficiency. From the study conducted on flurbiprofen, it was concluded that increase in lipid concentration increases the encapsulation efficiency of flurbiprofen in proniosomes. The use of dicetyl phosphate or stearylamine in preparation of flurbiprofen vesicles induces negative and positive charge respectively that decreases the encapsulation efficiency of flurbiprofen [30].

Preparation of Proniosomes: The proniosomes can be prepared by following 3 methods:

1. Spraying method

2. Slurry method

3. Coacervation or Phase separation method

Spraying Method: This method involves the spraying of surfactant in an organic solvent onto sorbitol powder and then evaporation of organic solvent. The sorbitol is soluble in organic solvent, and the process of spraying is repeated until appropriate coating is achieved. The surfactant forms a very thin layer onto the carrier which results in formation of multi-lamellar vesicles [31].

Advantage:

- Stable proniosomes can be prepared
- Hydrophobic drugs can be easily incorporated

Slurry Method: In slurry method, the surfactant solution is added completely to carrier in round bottom flask and fitted to rotary evaporator and

vacuum is applied to dry the powder and make it free flowing. This method involves the use of maltodextrin as carrier for the preparation of proniosomes [32].

Advantages:

- Maltodextrin is easily soluble in water and can be easily coated by just adding surfactant organic solvent solution in dry maltodextrin.
- Higher surface area improves the rehydration process giving completely dried and free flowing powder.
- The carrier gives complete coverage/ coating on the active ingredient and the surfactant that gives protection against hydrolysis and oxidation reaction.

Phase Separation or Coacervation Method (CPS): In this method, accurately weighed or required quantity of surfactant, carrier, cholesterol, solvent and drug is taken. All the ingredients are heated and mixed at 60-70^{o}C for 5 minutes until the mixture dissolves completely. Then the mixture is allowed to cool till the dispersion gets converted into liquid crystalline mixture (Proniosomal gel) [33, 34].

Advantage:

- Simple and rapid method.
- Ease of manufacturing.
- Can be specifically used for gel preparations.
- Smaller formulations can be easily prepared on lab scale.

Characterization Parameters for Proniosomes [35]:

Micromeritic Property (Angle of Repose): The angle of repose is measured by either funnel method or cylindrical method. In funnel method, the proniosomal powder was poured down from the funnel in order to form a cone and the height and diameter of the cone is measured and the angle of repose is calculated by the formula:

$\text{Tan } \theta = h / r$

$\theta = \tan -1 \times h / r$

Similarly in cylindrical method, the proniosomal powder is allowed to flow down from cylinder to form a cone and the height and diameter of the cone is measured and the angle of repose is calculated in similar way [36].

Surface Morphology (Scanning Electron Microscopy (SEM)): The surface morphology and particle size can be determined by Scanning Electron Microscopy.

Optical Microscopy: The proniosomes are mounted on the glass slide and viewed under optical microscope to determine the particle size [37].

Measurement of Vesicle size: The proniosomal dispersion is diluted 100 times with the solvent used in preparation of vesicles and stirred with the stirrer. The vesicle size is determined using particle size analyzer [38].

Drug Content: About 100mg of proniosomes are diluted with methanol by shaking for atleast 15 minutes. This solution is further diluted to 100 ml with methanol and again 10 ml of this solution is further diluted with phosphate buffer. The sample is withdrawn and analysed under UV spectrophotometer to determine the absorbance in order to calculate the drug content [39].

Entrapment Efficiency: The drug entrapped in the proniosomes is calculated by firstly separating the entrapped drug by dialysis and centrifugation method. The proniosomes suspension is carried in dialysis tube attached with cellulose membrane. The tube is suspended in 100ml of saline buffer and stirred with magnetic stirrer.

The entrapped drug is separated with centrifugation method and the amount of drug is measured with UV spectrophotometer [39]. The entrapment efficiency of proniosomes is calculated by the formula:

100 Entrapment efficiency = Amount of drug entrapped / Total amount of drug × 100

***In-vitro* Drug Release:** The *in-vitro* drug release study is performed using Franz Diffusion cell. The diffusion area of the cell is 1.75 cm^2 and the receptor compartment had a capacity of approximately 10.5 ml.

The membrane is cut to a diameter of 25 mm and saturated for 30 minutes in receptor medium (phosphate buffer pH 7.4) before starting the experiment. The cell is filled with degassed receptor medium and the membrane is placed in the top of the receptor compartment and checked for air bubbles. An aliquot of the sample is measured with the aid of a syringe and then placed in the cavity of a dosage wafer (donor compartment), on top of the membrane. The amount applied is around 50 mg with a spatula, the formulation is spread uniformly filling the donor compartment. A glass disk is carefully placed on the sample to occlude it, and an aligner cap is then used to centralize the assembly, which is held together by a clamp. The receptor medium is maintained at 37 ± 2°C under constant stirring. To characterize the drug release, 1ml samples were collected after 1, 2, 3, 4, 5, 6 and 7 hrs. After sampling, the volume collected is replaced with fresh receptor medium. The amount of drug is assayed by UV analysis [40-42].

Stability Studies: Samples (triplicate) are placed in flasks and air tightened completely. The samples are submitted to the thermo stable hot air oven at 45 ± 2^{o}C for 90 days. Control samples are kept at room temperature for the same period of time. The evaluation of the samples are performed initially at time zero and after 15, 30, 60, and 90 days and evaluated for drug content, entrapment efficiency and *in-vitro* drug release [43].

Research Carried out in Past: The pharmaceutical researchers have been working in the field of provesicular drug delivery system since long time. Some of the researches carried out in past in the field of proniosomes are mentioned below in **Table 2.**

TABLE 2: RESEARCH CARRIED OUT IN PRONIOSOMAL DRUG DELIVERY SYSTEM

Year	Drug loaded Proniosomes	Method of Preparation	Purpose	Reference
2001	Estradiol	CPS	To improve transdermal delivery of drug	44
2005	Ketorolac	CPS	To enhance therapeutic efficacy and entrapment efficiency	45
2005	Chlorpheniramine maleate	Slurry method	To optimize stability, loading efficiency, particle size and release kinetics suitable for transdermal delivery of drug	46
2007	Captopril	CPS	To prolong drug delivery and have good stability characteristics	47
2007	Piroxicam	Slurry method	To increase drug delivery from lipid vesicles	48
2008	Flurbiprofen	Slurry method	To control drug diffusion rates	49
2009	Haloperidol	CPS	To enhance entrapment efficiency	50
2009	Losartan potassium	CPS	To improve transdermal delivery of drug	51
2010	Celecoxib	Slurry method	To improve therapeutic efficacy at lower dose	52
2011	Valsartan	CPS	To enhance stablity and sustain transdermal delivery system for drug	53
2011	Vinpocetine	CPS	To improve absorption and penetration	54
2012	Irinotecan	Slurry method	To improve therapeutic efficacy, reduce toxicity and enhance therapeutic index	55
2012	Clotrimazole	CPS	To enhance transdermal drug delivery and improve the drug bioavailability for treatment of candidasis	56
2012	Carvedilol	CPS	To control drug release and improve stability	57
2012	Hydroxyzine hydrochloride	CPS	To enhance patient compliance, sustain drug release and target drug action for treatment of urticaria	58
2012	Diphenyl dimethyl bicarboxylate	CPS	To enhance dissolution and hepatocurative activity	59
2013	Isradipine	CPS	To improve oral bioavailability and gastrointestinal (GI) absorption	60
2013	Tretinoin	CPS	To improve therapeutic efficacy	61
2014	Nateglinide	Slurry method	To improve oral bioavailability	62
2014	Doxycycline hydrochloride and metronidazole	Slurry method	To improve combination therapy and patient compliance	63
2014	Mefenamic acid	CPS	To improve transdermal drug delivery and anti-inflammatory activity	64

2015	Ketoconazole	CPS	To sustain drug release, deliver a desired concentration of drug at site of action and overcome the side effects of oral route	65
2015	Vinpocetine	CPS	To improve oral bioavailability and GI absorption	66
2015	Acemetacin	Slurry method	To enhance pharmacokinetic properties and anti-inflammatory effects	67
2015	Pioglitazone	CPS	To improve hypoglycemic effects by controlled release of drug	68
2016	Boswellic acid	CPS	To improve bioavailability, absorption and release kinetics	69
2016	Tolterodine tartrate	CPS	To reduce side effects and effective management of overactive bladder	70
2016	Lacidipine	CPS	To improve transdermal delivery, absorption and permeation	71
2016	Lornoxicam	CPS	To enhance stability and sustain transdermal delivery system for drug	72
2016	Candesartan cilexetil	Slurry method	To improve oral bioavailability	73
2016	Famotidine	CPS	To prolong drug delivery and enhance stability	74
2016	Ritonavir	CPS	To enhance stability and sustain transdermal delivery system for drug	75
2016	Bromocriptine	CPS	To deliver the drug transdermally	76
2017	Tacrolimus	Slurry method	To improve solubility and bioavailability of tacrolimus	77
2017	Risperidone	CPS	To improve the bioavailability of risperidone	78
2017	Felodipine	Slurry method	To Sustain the drug release	79
2017	Tolterodine tartrate	CPS	To reduce dosing frequency and avoid side effects	80
2018	Atenolol	CPS	To improve therapeutic efficacy and develop transdermal drug delivery system	34
2018	Fluconazole	CPS	To enhance patient compliance, sustain drug release and target drug action with good anti-fungal activity	81
2018	Atorvastatin	CPS	To improve hyperlipidaemia activity and enhance the bioavailability of drug	82
2018	Lovastatin	CPS	To improve hypercholesterolemia activity	83
2019	Ofloxacin	Slurry method	To Sustain drug release and improve entrapment efficiency	84
2019	Aceclofenac	Slurry method	To enhance stability and entrapment efficiency	36
2019	Doxorubicin HCl	Slurry method	To prolong drug release	85
2019	Fluconazole	CPS	To improve patient compliance, sustain drug release and target drug at particular site	9
2019	Ethinylestradiol and Levonorgestrel	CPS	To enhance anti-fertility activity	44
2019	Lornoxicam	CPS	To improve the clinical efficacy of drug	86
2020	Betaxolol	CPS	To Sustain drug release and improve entrapment efficiency	87
2020	Telavancin	CPS	To Sustain drug release and enhance therapeutic efficacy	88
2021	Lignocaine HCl	CPS	To enhance retention time at the site of application and provide prolong release for oro-dental conditions	37
2021	Miconazole nitrate	CPS	To sustain drug release for many hours and enhance anti-fungal activity	89
2021	Ciclopirox	CPS	To improve skin permeation, bioavailability and reside topical anti-fungal drug	90
2021	Etodolac	CPS	To treat pain and inflammation and reduce gastric disturbance	91
2022	Itraconazole	CPS	To overcome the gastrointestinal side effects and increase the drug bioavailability	92
2022	Amphotericin B	CPS	To improve patient compliance, sustain drug release and target drug at particular site	93

CONCLUSION: In a nutshell to conclude, the provesicular approach for any drug formulation has the potential of delivering the drug at targeted site with controlled/ sustained release of drug, imparting enhanced solubility and permeability in topical and transdermal drug delivery systems.

Proniosomes are flexible, dried formulations that make them stable for longer period of time, with non-toxicity. It is a promising approach for drug delivery systems and more research can be helpful in knowing the potential in this field and to filter out all the advantages associated.

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