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Proniosomes: A review

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ABSTRACT

Proniosomes are novel and promising pro vesicular drug delivery systems used to deliver drugs. These are dry formulation of water soluble carrier coated with non ionic surfactant and can be converted into vesicular niosomes immediately before use by hydration. Proniosomes are physically stable during the storage and transport. The present review focuses on different aspects of proniosomes including overall methods of preparation, characterization, merits etc.

Keywords: Proniosomes, Carriers, Preparation, Characterization

INTRODUCTION

In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage forms are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery [1]. Approaches are being adapted to achieve this goal, by paying considerable attention either to control the of drug by incorporating it in a carrier system, or by altering the structure of the drug at the molecular level, or to control the input of the drug into the bio environment to ensure an appropriate profile of distribution.

Novel drug delivery system aims at providing some control, whether this is of temporal or spatial nature or both, of drug release in the body. Novel

drug delivery attempts to either sustain drug action at a predetermined rate or by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. It can also localize drug action by spatial placement of controlled release systems adjacent to, or in the diseased tissue or organ or target drug action by using carriers or chemical derivatization to deliver drug to particular target cell type [1, 2].

TRANSDERMAL DELIVERY

Optimization of drug delivery through human skin is important in modern therapy. Recently, the transdermal route vied with oral treatment as the most successful innovative research area in drug delivery [1]. Transdermal delivery is an important delivery route that delivers precise amount of drug through the skin for systemic action. Improved methods of drug delivery for biopharmaceuticals are important for two reasons; these drugs represent rapidly growing portion of new therapeutics, and are most often given by injection. Discovery of new medicinal agents and related innovation in drug

delivery system have not been only enabled the successful implementation of novel pharmaceutical, but also permitted the development of new medical treatment with existing drugs. Throughout the past two decades, the transdermal patches has become a proven technology holding the promise that new compound could be delivered in a safe and convenient way through the skin. Since the first transdermal patch was approved in 1981 to prevent nausea and vomiting associated with motion sickness, the FDA has approved through the past 22 years

more than 35 transdermal patch products spanning 13 molecules [2].

ROUTES OF PENETRATION

At the skin, molecules contact cellular debris, microorganisms, sebum and other materials, which negligibly affect permeation. The penetration has three potential pathways to the viable tissue - through hair follicles with associated sebaceous glands, via sweat ducts, or across continuous stratum corneum between these appendages (Figure –1).

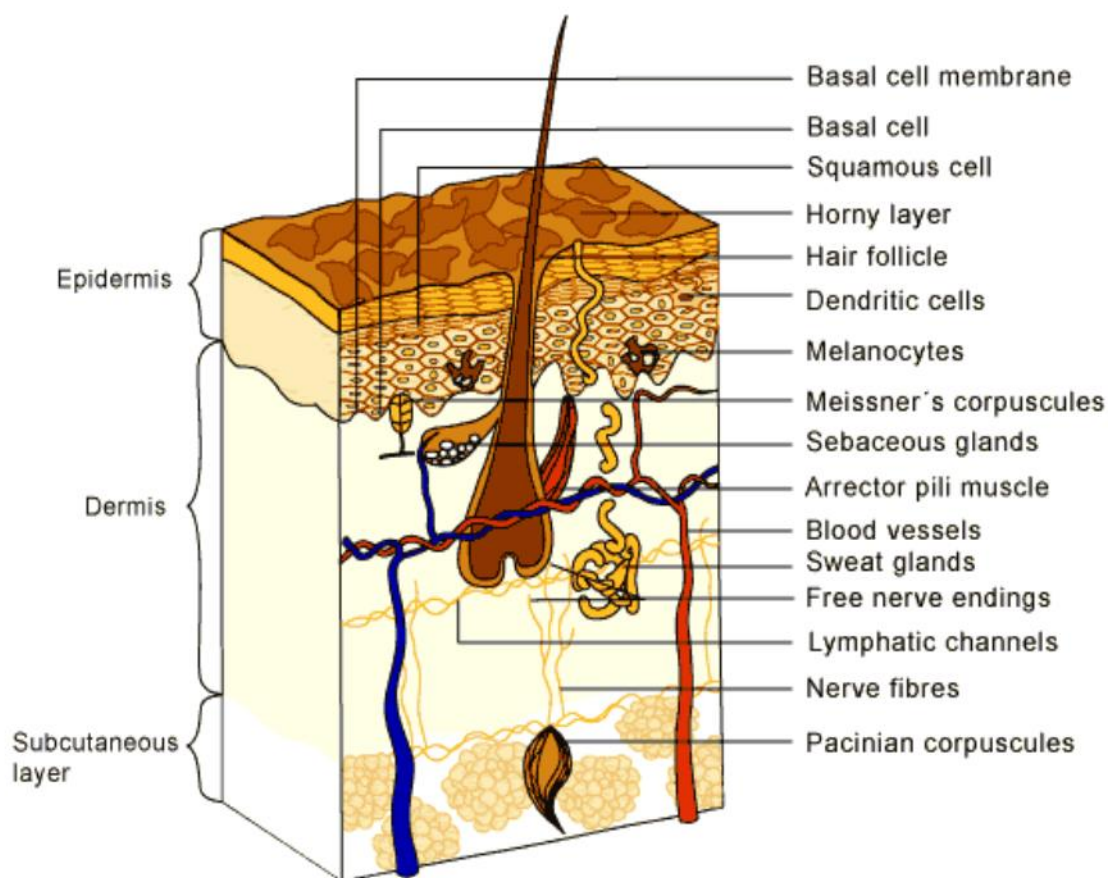


Figure 1: Structure of skin

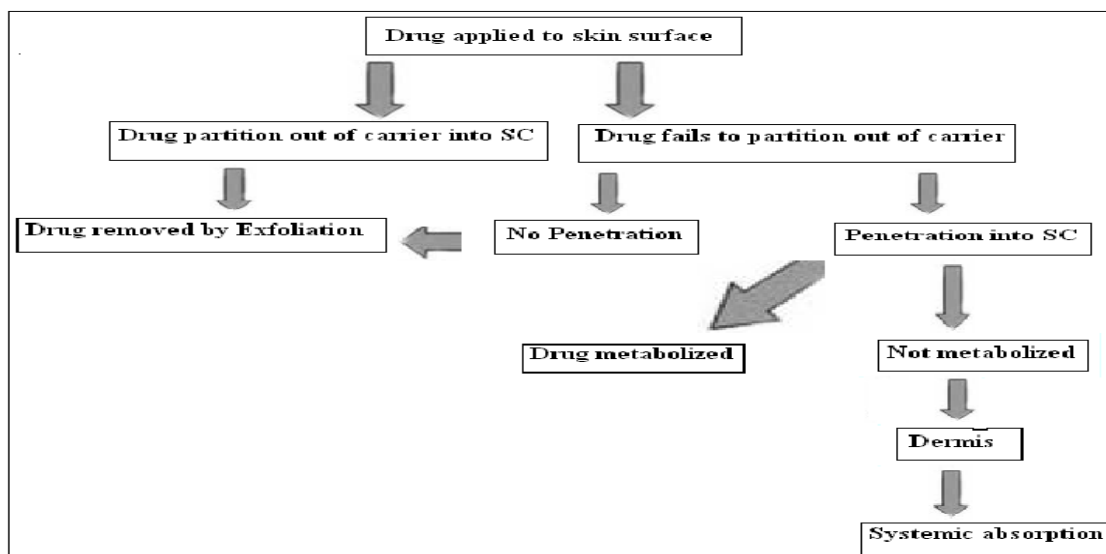


Figure 2: Proposed mechanism of drug absorption through skin

Fractional appendageal area available for transport is only about 0.1%; this route usually contributes negligibly to steady state drug flux. The pathway be important for ions and large polar molecules that struggle to cross intact stratum corneum. Appendages may be providing shunts, important at short times prior to steady state diffusion. Additionally, polymers and colloidal particles can target the follicle.

The intact stratum corneum thus provides the main barrier; its 'brick and mortar' structure is analogous to a wall (Figure-3). The corneocytes of hydrated keratin comprise of 'bricks', embedded in 'mortar', composed of multiple lipid bilayers of

ceramides, fatty acids, cholesterol and cholesterol esters. These bilayers form regions of semicrystalline, gel and liquid crystals domains. Most molecules penetrate through skin via this intercellular microroute and therefore many enhancing techniques aim to disrupt or bypass elegant molecular architecture.

Viable layers may metabolise a drug, or activate a prodrug. The dermal papillary layer is so rich in capillaries that most penetrants clear within minutes. Usually, deeper dermal regions do not significantly influence absorption, although they may bind e.g. testosterone, inhibiting its systemic removal [1].

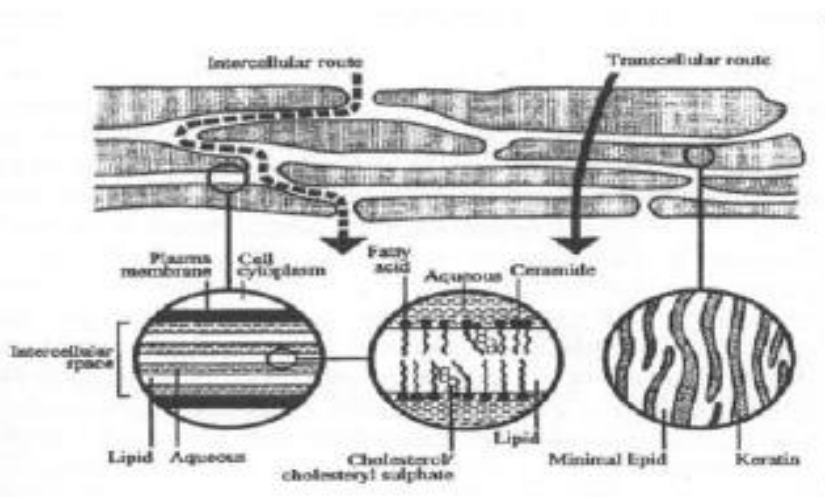


Fig no: 3 Simplified diagrams of stratum corneum and two micro routes of drug penetration

OPTIMISING TRANSDERMAL DRUG DELIVERY

Transdermal route offers several potential advantages over conventional routes like avoidance of first pass metabolism, predictable and extended duration of activity, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, and most importantly, it provides patient convince. But one of the major problems in transdermal drug delivery is the low penetration rate through the outer most layer of skin [3].

The non-invasive approaches for providing transdermal drug delivery of various therapeutics substances are [1]

Drug and vehicle interactions

- Selection of correct drug or prodrug
- Chemical potential adjustment
- Ion pairs and complex coacervates
- Eutectic systems

Stratum corneum modification

- Hydration
- Chemical penetration enhancers

Stratum corneum bypassed or removed

- Micro needle array
- Stratum corneum ablated
- Follicular delivery

Electrically assisted methods

- Ultrasound (Phonophoresis, Sonophoresis)
- Iontophoresis
- Electroporation
- Magnetophoresis
- Photomechanical waves

Vesicles and particles

- Liposomes and other vesicles
- High velocity particles

Vesicular systems are drug delivery system to deliver the drug dermally and transdermally. Liposomes have the potential of overcoming the skin barrier, as these are bilayered lipid vesicles, consisting primarily of phospholipids and cholesterol [4].

Liposomes were discovered in the early 1960's by Bangham and colleagues and subsequently became

the most extensively explored drug delivery system⁵. In early 1960's a great knowledge of vesicle derivatives have been tested for their abilities. Most experiments, however, have centered on liposomes, since derivations only add to their basic properties. Vesicles are closed, spherical membrane that separate a solvent from the surrounding solvent. Possible use of liposomes in topical drug delivery vehicles for both water and lipid soluble drug has been investigated. While it has been suggested that the external envelop of a liposomes would allow it to pass through lipophilic skin, most researches show that liposomal vesicles become trapped within the top layer of the stratum corneum cells². Generally liposomes are not expected to penetrate into viable skin, although occasional transport processes were reported [1]. This behavior is useful both for local treatment of skin disorders and for cosmetic formulations. Specific drug accumulation at the site of action and decreased systemic drug absorption can impart increased efficiency as well as decreased side effect to a compound applied topically [6].

In recent times, no single drug delivery system fulfills all the criteria, but attempts have been made through novel approaches. Many novel approaches emerged covering various routes of administration, to achieve either controlled or targeted delivery. The prime aim of novel drug delivery is maintenance of the constant and effective drug level in the body and minimizing the side-effects and it also localizes the drug action by targeting the drug delivery by using drugcarriers [3, 4].

Vesicular drug delivery is one of the approaches, which encapsulate the drug e.g.: Liposomes, niosomes, transferosomes, pharmacosomes, and provesicles such as proniosomes and proliposomes. Advantages of liposomes and niosomes over other conventional dosage forms are their particulate nature, which act as a drug reservoir. Few modifications can also be carried out in order to adjust the pattern and the drug release. It was also found out that modified vesicles had properties that successfully delivered drugs into deeper layers of the skin [1].

From early 1980s, proniosomes have gained wide attention by researchers for their use as drug targeting agents and drug carriers to have a variety of merits while avoiding demerits associated with the conventional form of drugs. Niosomes are water soluble carrier particles, and these are dried to form a niosomal dispersion on brief agitation in hot aqueous

media. This dehydrated product is called proniosomes. The resulting niosomes are very correlative to conventional niosomes and of higher size uniformity. The proniosomal approach reduces the problems associated with dry, free-flowing product, which is more stable during the storage and sterilization [2].

Proniosomes were studied as alternatives to liposomes and other carrier systems for entrapping both polar and nonpolar or hydrophobic and hydrophilic drugs. The additional merits with proniosomes are low toxicity owing to non-ionic nature, no requirement of special precautions and conditions for formulation and preparations. In addition, it is the simple method for the routine and large scale production of proniosomes without the use of undesirable solvents. However, stability is a main concern in the advancement of any formulation and even proniosomes have advantages as drug carriers, such as cost productivity, chemically stability in comparison to liposomes. They also minimize problems of physical stability such as fusion, leakage, sedimentation, and aggregation on storage [6-10].

PRONIOSOMES

Proniosomes are dry formulation of water soluble carrier particles that are coated with surfactant and

can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. The resulting niosomes are very similar to conventional niosomes and more uniform in size [1]. The proniosome approach [13-15] minimizes problems associated with the liposome and niosomes by using dry, free-flowing product, which is more stable during sterilization and storage. Ease of transfer, distribution, measuring, and storage make proniosomes a versatile delivery system with potential for use with a wide range of active compounds. In general a limited number of studies are available which deal with the preparation and evaluation of proniosomes [16-24].

Preparation of proniosomes

There are number of components present in proniosomes with non ionic surfactants and cholesterol, lecithin being the main ingredient. Desirable characteristics of the selected carrier that could be used in the preparation of proniosomes includes safety and non-toxicity, free flowability, poor solubility in the loaded mixture solution and good water solubility for ease of hydration. Different carriers and non ionic surfactants and membrane stabilizers used for the proniosome preparation are shown in table 1. Three different methods were reported for the preparation of proniosomes.

Table 1: Non ionic surfactants, Coating materials, Membrane stabilizers used for the preparation of proniosomes

Non ionic surfactants used
Span 20, Span 40, Span 60, Span 80, Span 85. Tween 20, Tween 60, Tween 80
Carrier materials investigated
Sucrose state, Sorbitol, Dextrin, Maltodextrin (Maltrin M500, Maltrin M700), Glucose monohydrate, Lactose monohydrate, Spray dried lactose
Membrane stabilizers used
Cholesterol, Lecithin

METHODS FOR PREPARATION OF PRONIOSOMES

Slurry method

Carrier material 10 g is added to a 250-ml round-bottom flask and the entire volume of surfactant solution (14.5 ml) was added directly to the flask to form slurry. If the surfactant solution volume is less, then additional amount of organic solvent can be added to get slurry. The flask was attached to the

rotary evaporator and vacuum was applied until the powder appeared to be dry and free flowing. The flask was removed from the evaporator and kept under vacuum overnight. Proniosome powder was stored in sealed containers at 4°C. The time required to produce proniosomes is independent of the ratio of surfactant solution to carrier material and appears to be scalable [25].

Coacervation phase separation method

This method is widely adopted to prepare proniosomal gel. Precisely weighed amounts of surfactant, lipid and drug are taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol (0.5 ml) is added to it. After warming, all the ingredients are mixed well with a glass rod, the open end of the glass bottle is covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture is dissolved completely. Then the aqueous phase (0.1% glycerol solution) is added and warmed on a water bath till a clear solution was formed which is then converted into proniosomal gel on cooling.³⁴

Slow spray-coating method

This method involves preparation of proniosomes by spraying surfactant in organic solvent onto carrier material and then evaporating the solvent. Because the carrier is soluble in the organic solvent, it is necessary to repeat the process until the desired surfactant loading has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves [2]. The resulting niosomes are very similar to those produced by conventional methods and the size distribution is more uniform. It is suggested that this formulation could provide a suitable method for formulating hydrophobic drugs in a lipid suspension without concerns over instability of the suspension or susceptibility of the active ingredient to hydrolysis.

Structural components of niosomes

Surfactants

A wide range of surfactants and their combinations in different molar ratios have been used to entrap many drugs in niosomes of varying features such as size [21].

Ether linked surfactants

These are polyoxyethylene alkyl ethers which have hydrophilic and hydrophobic moieties are linked with ether. The general formula of this group is C_nEO_m , where n can be 12-18 and m can be 3-7. Surfactants with polyhydroxyl head and ethylene oxide units are also reported to be used in niosomes formation. Single alkyl chain surfactant C16 mono alkyl glycerol ether with an average of three glycerol units is one of the examples of this class of surfactants used for the preparation of niosomes.

Polyoxyethylene 4- lauryl ether (Brij30) has an HLB value of 9.7, phase transition temperature <100°C and cannot be used to formulate some drugs and iodides, mercury salts, phenolic substances, salicylates, sulfonamides and tannins as it cause oxidation leading to discoloration of product. Poxoxyethylenecetyl ethers (Brij58) and Poxoxyethylenestearyl ethers (Brij72and76) are also used in preparation of niosomes [18, 19].

Ester linked surfactants

These surfactants have ester linkage between hydrophilic and hydrophobic groups and have been studied for its use in the preparation and delivery of sodium stibogluconate to the experimental marine visceral leishmaniasis [14].

Sorbitan Esters

These are most widely used ester linked surfactants especially in food industry. The commercial sorbitan esters are mixtures of the partial esters of sorbitol and its mono and di-anhydrides with oleic acid. These have been used to entrap wide range of drugs viz doxorubicin [17].

Alkyl Amides

These are alkyl galactosides and glucosides which have incorporated amino acid spacers. The alkyl groups are fully or partially saturated C12 to C22 hydrocarbons and some novel amide compounds have fluorocarbon chains. Fatty Acids and Amino Acid Compounds: These are amino acids which are made amphiphilic by addition of hydrophobic alkyl side chains and long chain fatty acids which form "Ufasomes" vesicles formed from fatty acid bilayers.

Cholesterol

Steroids bring about changes in fluidity and permeability of the bilayer and are thus components. Cholesterol a waxy steroid metabolite is usually added to the non-ionic surfactants to provide rigidity and orientational order. It does not form the bilayer itself and can be incorporated in large molar ratios. Cholesterol is an amphiphilic molecule; it orients its -OH group towards aqueous phase and aliphatic chain towards surfactant's hydrocarbon chain. Rigidization is provided by alternative positioning of rigid steroidal skeleton with surfactant molecules in the bilayer by restricting movement of carbons of hydrocarbon. Cholesterol is also known to prevent leakage by abolishing gel to liquid phase transition [14].

Charge Inducers

Charge inducers increase the stability of the vesicles by induction of charge on the surface of the prepared vesicles.

It act by preventing the fusion of vesicles due to repulsive forces of the same charge and provide higher values of zeta potential. The commonly used negative charge inducers are dicetyl phosphate,

dihexadecyl phosphate and lipoamine acid and positive charge inducers are sterylamine and cetylpyridinium chloride [15, 16]

Characterization of proniosomes [32]

Proniosomes are characterized for vesicle size, size distribution, shape, surface morphology, aerodynamic behavior and spontaneity and are enlisted in table

Table: Methods for the characterization of proniosomes

Parameter	Instrument/Method
Vesicle size determination and size Distribution	Malvern Mastersizer
Shape and surface morphological characterization	Optical microscopy, Transmission electron microscopy
Aerodynamic behavior Angle of repose	Funnel method [26]
Spontaneity (Rate of hydration)	
Laser diffraction particle size	Twin-Stage Impinger

Separation free (untrapped) drug

The encapsulation efficiency of proniosomes is determined after separation of the untrapped drug from entrapped drug using techniques like centrifugation and by using cellophane dialysis tubing D- 9777 and dialyzing exhaustively against 400 ml saline at 4°C for 24 hours [28,33].

Determination of entrapment efficiency (measurement of partitioning)

The vesicles obtained after removal of drug by centrifugation, the pellet was collected and resuspended in 0.9% saline followed by addition of 1:1 ratio of absolute alcohol: propylene glycol mixture to lyses the vesicles. The vesicles obtained

after removal of untrapped drug by dialysis is then resuspended in 30% v/v of PEG-200 and 1ml of 0.1% v/v Triton X-100 solution was added to solubilize vesicles²⁹. The resulting clear solution is then filtered and analyzed for drug content.

In vitro drug release from proniosomal vesicles

In vitro drug release and skin permeation studies for proniosomes were determined by different techniques like Franz diffusion cell, Keshary-Chien diffusion cell, Cellophane dialyzing membrane, USP Dissolution apparatus Type I, Spectrapor molecular porous membrane tubing [29-31].

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