Review Article [Farooqui et al., 5(10): Oct., 2014:3939-3947]
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

A Review on Proniosomal Gel: Potential Carrier System in Transdermal Delivery for Non- Steroidal Anti-inflammatory Drugs (NSAID)

Nadeem Farooqui[1]*, Vikas Jaiswal[2] and Mousumi Kar[3]
1, Suresh Gyan Vihar University, Mahal Jagatpura, Jaipur, (RJ) - India
2, Indore Institute of Pharmacy (IIP), Pithampur Road, Opp. IIM, Rau, Indore, (MP) - India
3, College of Pharmacy, IPS Academy, Indore, (MP) - India

Abstract

Many novel approaches bring revolutionary changes to covering various routes of administration, to achieve either controlled or targeted delivery. Proniosomes are based on dry formulation of water soluble carriers that are coated with surfactant. It forms niosomal dispersion immediately during the rehydration to before use on agitation in hot aqueous media within minutes. Proniosomes are physically stable during the storage and transport. Drug encapsulated in the vesicular structure of proniosomes prolong the existence of drug in the systematic circulation and enhances the penetration into target tissue and reduce toxicity. Due to the limited amount of water present, these systems behave as viscous phases. The various phases of liquid crystalline structures can be utilized as such for topical/transdermal applications or can be used after further hydration to form niosomes. An introduction to the skin structure along with the conversion of proniosomal gel to niosomes is also explained. Proniosomes, hydrated by agitation in hot water for a short period of time, have been proposed for a number of potential therapeutic applications e.g. as carriers of anti-inflammatory drugs. The focus of this review is to bring out different aspects related to proniosomes merits, types, preparation, characterization, entrapment efficiency, in-vitro drug release, in-vitro permeation studies, stability studies and applications.

Key-Words: Niosomes, Proniosomes, Topical and Transdermal

Introduction

In the past few decades, considerable attention has been focused on the development of new drug delivery system. 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 drug carriers.

Topical/ Transdermal delivery systems, when compared with conventional formulations, generally show a better control of blood levels, a reduced incidence of systemic toxicity, no hepatic first-pass metabolism and a higher compliance[1&2]. A continuous interest toward the dermal and transdermal products can be seen, offering several advantages.

*** Corresponding Author**
E-mail: nadeem1712@rediffmail.com
Mob.: +91-81031728587

Niosomes are capable of entrapping hydrophilic and hydrophobic solutes [3]. Many disadvantages associated with Niosomes have overcome by the help of proniosomes.

Proniosomes, hydrated by agitation in hot water for a short period of time, have been proposed for a number of potential therapeutic applications, e.g. as carriers of anti-inflammatory drugs[4].

Meloxicam (MLX) is a nonselective, nonsteroidal, anti-inflammatory drug (NSAID) with preferential inhibition of cyclo-oxygenase-2 (COX-2) over COX-1. MLX does not have documented cardiovascular toxicity at doses of less or equal to 15 mg/day which are recommended for the treatment of rheumatoid arthritis and osteoarthritis. However, when orally administered, nonselective NSAIDs may adversely affect the gastrointestinal tract and can even reduce the life expectancy of patients with rheumatoid arthritis. Transdermal delivery of MLX would avoid major gastrointestinal side effects and provide steady plasma levels from a single dose. In addition, it has been demonstrated that NSAIDs promote local analgesia when administered locally through the skin. Therefore,

an alternative non-invasive mode of delivery of the drug is needed. Transdermal administration of MLX can overcome these side effects and higher local concentration can be maintained at the target site, which is desirable for anti-inflammatory agents, [5, 6, 7].

Advantages of Proniosomes

Liposomes and niosomes are well known drug/cosmetic delivery systems. But these delivery systems have been reported to have many disadvantages in terms of preparation, storage, sterilization, etc. The disadvantages of liposomes and niosomes are given below, which can be overcome by proniosomes[8].

- Liposomes and niosomes are dispersed aqueous systems and have a problem of degradation by hydrolysis or oxidation.
- Liposomes and niosomes require special storage and handling.
- Sedimentation, aggregation or fusion on storage is usually seen.
- In liposomes, purity of natural phospholipids is also variable.
- Difficulty in sterilization, transportation, distribution, storage uniformity of dose and scale up.
- Use of unacceptable solvents the preparation.
- Incomplete hydration of the lipid/surfactant film on the walls during hydration process.
- Problems associated with aqueous niosomes dispersions and problems of physical stability (aggregation, fusion, leaking) could be minimized.
- Good convenience in the transportation, distribution, storage, and dosing.
- Easy manufacturing[9].

Introduction to the skin

The skin is the largest human organ covering an area of about 2 sq. m. in an average human adult and consists of three functional layers: epidermis, dermis and subcutaneous *a*s described in fig.1. It is also composed of blood vessels, nerve endings, appendages, fat and connective tissue. The function of the skin is to protect the organism against the loss of endogenous substances and mechanical, chemical, microbial and physical influences. The outermost layer of the skin, the epidermis, provides the protective properties. Out of the five layers of the epidermis, it is mainly the uppermost stratum corneum (SC), which is responsible for the permeation barrier properties of the skin. The SC consists of the keratin-filled dead cells, the corneocyte, which are entirely surrounded by crystalline lamellar lipid region[10]. The cell boundary, the cornified envelope, is a very densely cross-linked protein structure, which reduces absorption of drugs into the cells. The dermis contains a variable amount of fat, collagen and elastin fibres which provide strength and flexibility. Subcutaneous fat is the innermost layer of the skin structure, varies its thickness in different regions of the body. For these reasons most of the active substances applied onto the skin diffuse along the lipid lamellae in the intercellular region. It is now widely reported that skin is not only a protective membrane but is increasingly becoming popular route for the administration of many drugs[11, 12, 13].

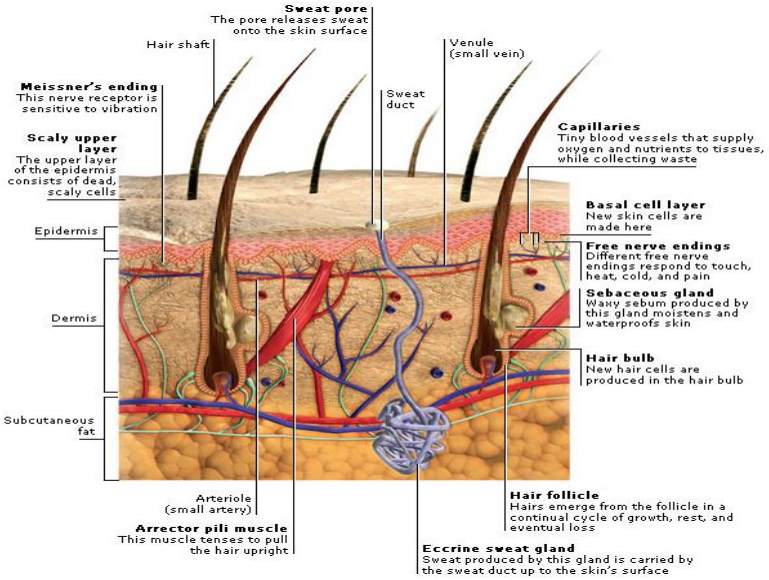

Fig. 1: Diagram of skin structure

Conversion of Proniosomes gel into niosomes

Proniosome gel is an intermediate state of formation of niosome. Minimum quantity of continuous phase, leads to the formation of liquid crystalline compact mass of proniosomes. Proniosome gel thus obtained has some advantages over conventional niosomes due to their compact gel nature, which helps in degradation, transportation and stability. The conversion of proniosome gel into niosomes can be achieved in two ways[14, 15].

Hydration by skin: The hydration is achieved by skin itself i.e. the water in the skin is used to hydrate the proniosome formulation and conversion to niosomes.

Hydration by solvents*:* Aqueous systems i.e. purified water, saline solution and buffers are used to convert proniosomes to niosomes with or without agitation and sonication.

The proniosome gel system is directly being formulated in the patch for used in dermal and

transdermal applications without the requirement of polymeric matrix for dispersion. The formulation takes water from the skin and converts into niosomes. The addition of aqueous phase from outside also leads to the formation of niosomes. After the addition of aqueous phase, agitation and sonication leads to formation of niosomes with small size vesicles. The addition of water into compact mass of proniosome leads to the swelling of bilayers as well as vesicles due to the interaction of water with polar groups of the surfactant. Due to the inclusion of water in the bilayers, the stacked structures tend to separate. Above a limiting concentration of solvent bilayers tends to form spherical structure which gives rise to unilamellar to multilamellar vesicular structures. Addition of shaking step in hydration process leads to complete hydration and formation of niosomes[16, 17, 18].

Proniosomes Gel: An overview

Proniosomes are vesicular systems, in which the vesicles are made up of non-ionic based surfactants, cholesterol and other additives. Semisolid liquid crystal gel (proniosomes) prepared by dissolving the surfactant in a minimal amount of an acceptable solvent, namely ethanol and then hydration with least amount of water to form a gel. These structures are liquid crystalline compact niosomes hybrids that can be converted into niosomes immediately upon hydration or used as such in the topical/transdermal applications [19]. Use of proniosome gel in topical/dermal delivery does not require hydration prior to application, but they can be applied as such or loaded on a base material of emulsion, gel, ointment, etc. prior to application. The base material helps in the application of the formulation to the skin and dilution of the active material. Proniosomes are nowadays used to enhance drug delivery in addition to conventional niosomes. They are becoming popular due to their semisolid/ liquid crystalline compact nature when compared to niosome dispersion[20].

Proniosomal gels are generally present in transparent, translucent or white semisolid gel texture, which makes them physically stable during storage and transport. Dissolution of most surfactants in water, leads to the formation of lyotropic liquid crystals rather than micellar solution. Lamellar phase shows sheets of surfactants arranged in bilayer form, whereas in hexagonal phase cylindrical units are packed in hexagonal fashion. Cubic phase consists of curved bio-continuous lipid bilayer extending in three dimensions, separating two congruent networks of water channels. These liquid crystals present an attractive appearance because of their, transparency and high viscosity, although in the beginning of its formation, a short range of less viscous compositions (so called liquid/gel compositions) appear in some cases. Addition of water leads to interaction between water and polar groups of the surfactant results in swelling of bilayers.

When the concentration of solvent is increased above a limited value, the bilayers tend to form random spherical structures, i.e., multilamellar, multivesicular structures. When shaken with water i.e. the aqueous phase of water, complete hydration takes place leading to the formation of niosomes. The beauty of these proniosomes lies in their ability to rearrange as stable noisomal suspensions, on hydration with water[21].

Interaction Between skin and vesicles

There is a direct contact of proniosome formulation with skin after applies, so it is better to discuss the potential interactions between skin and vesicles formed in proniosome/niosome formulations. As we know that proniosomes or proniosomes derived niosomes are composed of non-ionic surfactants, and the vesicles are composed of these non-ionic surfactant only. So it is advisable to study the interactions between non-ionic surfactants and the skin. The non ionic surfactants are amphipathic molecules consisting of a hydrophobic (alkylated phenol derivatives, fatty acids, long chain linear alcohols, etc.) and a hydrophilic part (usually ethylene oxide chains of variable length). Nonionic surfactants are used widely in pharmaceuticals to increase their stability, solubility and permeation[22]. There is a strong indication that the degree of interaction between vesicles and skin mainly depends on physicochemical properties of the surfactant molecules of which the niosomes or proniosomes are composed. Skin consists of a range of bioactive material like membrane phospholipids, proteins, amino acids, peptides, etc.

Vesicles prepared from cholesterol and polyoxyethylene alkyl ether surfactants were studied with isolated human stratum corneum incubated for 48 hours and for vesicle skin interactions. Fusion of liquid as well as gel state vesicles on the superficial layer of stratum corneum takes place, but liquid state vesicles induced perturbations in liquid organization, so water pool formation within the stratum corneum was observed. Stacks of lamellae and irregular structures were formed on the skin with fusion and adsorption of vesicles onto the stratum corneum surface. These structures and interactions strongly depend on vesicle composition and physiological properties. After a 12-hour pretreatment, permeation across span 60-treated skin was significantly higher than that across non-treated skin. Surfactant treated formulations were found to be superior to phospholipid treated and non-treated formulations in facilitating the permeation as

well as drug deposition into the skin. On the basis of results, two types of interaction were observed between vesicles and skin surface. First, interaction was the skin–formulation interface involving adsorption and fusion of vesicles of niosome or proniosomes on the stratum corneum surface, resulting in new structure formation. Secondly, vesicle–skin interactions found in the deeper layers of the stratum corneum, involve alteration of the bilayer ultra-structure. A fluorescence depolarization study indicated that alkanoyl-N-methylglucamide surfactants decrease the fluidity of dipalmitoyl phosphatidylcholine membranes. Non-ionic surfactants decreased the phase transition temperature of negatively charged dilauroylphosphatidic acid membrane. The interaction between surfactant molecules incorporated in the lipid membrane was also observed [23].

Surfactants are known to increase the permeability of vesicles and phospholipid membranes, causing low molecular mass compounds to leak. The interaction between biological membranes and non-ionic surfactant tested for phospholipid composition and rate of biosynthesis of major phospholipid components indicate no significant change in the phospholipid composition, where as biosynthesis and turnover rates of phospholipids were increased two to four times. The available data suggests that the tested surfactant damaged the epidermis membranes. Surfactant cause modification in physicochemical characteristics of natural membranes and can disrupt artificial membranes but also. Nonionic surfactants have the ability to increase the permeability of sarcoplasmic reticulum. This phenomenon has been frequently exploited to extract and solubilize sparingly soluble proteins such as membrane proteins [24].

Types of proniosomes

Dry Granular Proniosomes

According to the type of carrier and method of preparation of dry granular proniosomes are:

1. Sorbitol based proniosomes
2. Maltodextrin based proniosomes

Sorbitol based proniosomes is a dry formulation that involves sorbitol as a carrier, which is further coated with non ionic surfactant and is used as a noisome within minutes by addition of hot water followed by agitation. These are normally made by spraying surfactants mixture prepared in organic solvent on to the sorbitol powder and then evaporating the solvent. Since the sorbital carrier is soluble in organic solvent, the process is required to be repeated till the desired surfactant coating has been achieved. In Sorbitol based proniosomes size distribution is very uniform. It is useful in case where the active ingredient is susceptible to hydrolysis. The residual sorbitol decreases the entrapment efficiency to less than one half of that observed without sorbitol. These necessitate reduction in proportion of carrier in final niosomal suspension. The difficulty lies in testing of sorbitol particles because sorbitol is soluble in chloroform and organic solvents. It is prepared by slow spraying method.

Maltodextrin based Proniosomes prepared by fast slurry method. Time required to produce proniosomes by slurry method is independent of the ratio of surfactant solution to carry out. Proniosomes of high surface to carrier's ratio can be prepared. The method of obtaining niosomes from such a proniosomes for the drug deliver is very simple. An analogue process with the sorbitol results in a solid, surfactant/sorbitol cake. Since maltodextrine morphology is preserved, hollow blown maltodextrin particles can be used for significant gain in surface area. The higher surface area results in thinner surfactant coating, which makes the rehydration process efficient. This preparation has potential of application in delivering of hydrophobic and amphiphilic drugs[25, 26].

Liquid Crystalline Proniosomes

When the surfactant molecule are kept in contact with water, there are three ways trough which lipophilic chains of surfactants can be transformed into a disordered, liquid state called lyotropic liquid crystalline state (neat phase)[27]. These three ways are increasing temperature at Kraft point (Tc), addition of solvent which dissolve lipids; and use of both temperature and solvent. Neat phase or lamellar phase contains bilayers arranged in a sheet over one another within intervening aqueous layer. This type of structure gives typical X-ray diffraction and thread like birefringent structure under polarized microscope. For ternary lecithin, non-ionic surfactants as monoglyceride and alcohol system, lamellar liquid crystals are formed at Kraft temperature in presence of alcohol. The lamellar crystalline phase is converted into dispersion of niosomes at higher water concentration. The organization of lipid/ethanol/water mixture into lamellar structure can be conveniently utilized for transdermal of drugs. The liquid crystalline proniosomes and proniosomal gel act as reservoir for transdermal delivery of drug. The transdermal patch involves aluminum foil as a baking material along with the plastic sheet (of suitable thickness stuck to foil by means of adhesive). Proniosomal gel is spread evenly on the circular plastic sheet followed by covering of nylon mesh[28].

Vesicle formation in proniosomes

The ability of nonionic surfactant to form bilayer vesicles instead of micelles is not only depends on the

hydrophilic-lipophilic balance (HLB) values of the surfactant and the chemical structure of the components, but also on the critical packing parameter (CPP). In proniosomes the vesicle-forming tendency is similar to niosomes[29, 30]. The relationship between the structure of the surfactant including size of hydrophilic head group, and length of hydrophobic alkyl chain in the ability to form vesicles is described as:

CPP = $\upsilon / l_c a$

Where υ = hydrophobic group volume,

l_c = the critical hydrophobic group length and a = the area of the hydrophilic head group.

A CPP of between 0.5 and 1 indicates that the surfactant is likely to form vesicles. A CPP of below 0.5 (indicating a large contribution from the hydrophilic head group area) is said to give spherical micelles and a CPP of above 1 (indicating a large contribution from the hydrophobic group volume) should produce inverted micelles, the latter presumably only in an oil phase, or precipitation would occur.

Addition of cholesterol suppresses the tendency of the surfactants to form aggregates and also provides greater stability to the bilayer membranes by increasing the gel liquid transition temperature of the vesicle and also attributes to the higher HLB and smaller critical packaging parameters. Cholesterol addition also enables more hydrophobic surfactants to form vesicles. Apart form this addition of cholesterol also influences membrane permeability, encapsulation efficiency and bilayer rigidity.

Stabilization and permeability can also be enhanced by the addition of lecithin and by the addition of charged molecules like, diacetyl phosphate (DCP) and stearyl amine (SA) to the bilayer[31].

Mechanisms for permeation of vesicles through skin

Proniosome gel is a liquid crystalline compact mass, which upon hydration leads to unilamellar to multivesicular, multilamellar and spherical shaped niosomes. The drug is entrapped into the vesicles (derived niosomes self-assembly of non-ionic surfactant). Stratum corneum is considered to be a particularly impermeable barrier, so there is need to elucidate the mechanism through which the drug into vesicles is delivered to the deeper layers.

Proniosomes contain both non-ionic surfactant and phospholipids, both can act as penetration enhancer and useful in increasing permeation powers of many drugs. A single mechanism is not sufficient to describe the permeation of drug containing vesicles into the skin. Many hypotheses exist relating to the permeation of vesicles through skin for drug release in deeper layers. The ability of vesicles (present in many delivery systems) to modulate drug transfer across skin can be explained by several mechanisms[32].

- Adsorption and fusion of vesicles onto the surface of skin leading to a high thermodynamic activity gradient of drug at the interface, which is the driving force for permeation of lipophilic drugs.
- The penetration enhancers effect of vesicles to reduce stratum corneum barrier properties.
- The bilayers present in niosomes acts as rate-limiting membrane barrier for drugs.

Modification in the structure of stratum corneum is also one of the possible mechanisms for the permeation of the vesicle-encapsulated drug. Intracellular lipid barrier in the stratum corneum was found dramatically looser and more permeable after treating with liposomes and niosomes. Proniosome gel of Levonorgestrel formed from Span 80 showed highest flux due to their high permeability[33, 34].

Preparation of proniosome gel

Proniosome can be prepared by various methods. In one method proniosome are prepared by **slurry method using** maltodextrin as a carrier. In this method maltodextrin powder is added to round bottom flask and the entire volume of surfactant solution is added directly to the flask. The flask is attached to the rotary evaporator and vacuum is applied until the powder appears to be dry and free flowing. Then the flask is removed from the evaporator and is kept under vacuum overnight[34]. Then proniosome powder is stored in sealed container at 4°c.

In another **Spray coated method,** proniosome can be prepared by spraying the surfactant mixture containing span, cholesterol and dicetyl phosphate in to the round bottom flask on the rotary evaporator by sequential spraying of aliquot on to the surface of sorbitol powder. During the spraying period, the rate of application is controlled so that the powder bed of sorbitol does not become overly wet. The evaporator is than evacuated and rotating flask is lowered into a water bath at 65 to 70°c and flask is rotated under vacuum for 15 to 20 min or until sorbitol is appeared to be dries. This process is repeated until all of the surfactant solution has been applied. After addition of the final aliquot, evaporation is continued until the powder is completely dried (about 20-30 min). The material is further dried in desiccators under vacuum at room temperature overnight. Thus, a dry preparation is obtained; this dry preparation is referred to as **'proniosome'** and is used for preparation and for further study on powder properties. Proniosome-derived niosome dispersion is obtained by hydrating

proniosome preparation with 80ºc distilled water and vortex mixing for 2 min [35, 36, 37].

Coacervation phase separation method: Accurately weighed or required amount of surfactant, carrier (lecithin), cholesterol and drug can be taken in a clean and dry wide mouthed glass vial (5ml) and solvent should be added to it. All these ingredients have to be heated and after heating all the ingredients should be mixed with glass rod. To prevent the loss of solvent, the open end of the glass vial can be covered with a lid. It has to be warmed over water bath at 60-70^{0}C for 5 minutes until the surfactant dissolved completely. The mixture should be allowed to cool down at room temperature till the dispersion gets converted to a pronisomal gel [38, 39].

Characterization of Proniosomes

Surface characteristics

Surface characteristics include particle size; shape of proniosomal powder and niosomes derived from the proniosomes can be determined by means SEM, TEM, etc analysis.

Flow properties

Flow properties of the dry proniosomal powder can be determined by finding the densities, angle of repose and Carr's index of the proniosomal powder.

Angle of repose

Angle of repose can be determined by means of fixed funnel standing method

tan q = h / r

Where, q is angle of repose, h is the height of pile and r is the radius of the pile base.

Bulk and tapped densities

Bulk and tapped densities of proniosomal powder were measured by using 10 ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated.

Carr's index

Compressibility index (Ci) or Carr's index value of proniosomal powder is computed according to the following equation.

Carr's index =

[(tapped density – Bulk density)/ tapped density] × 100

Entrapment efficiency

To evaluate the entrapment efficiency, the dry proniosomal powder has to be hydrated with aqueous solution. The resulting niosomal suspension is centrifuged at 25000 rpm for 30 min at 20°C. The clear supernatant liquid is collected and assayed for un-entrapped drug using HPLC method.

The percentage of the entrapment efficiency is calculated by using the following formula.

% entrapment efficiency = [(Ct – Cf)/Ct] * 100

Where, Ct – concentration of the total drug;

Cf - concentration of the free drug

In vitro permeation study

The permeation of drug from noisomes can be evaluated using Franz diffusion cell. Here the Franz diffusion cell is mounted with semipermeable membranes like Wister rat skin etc. The noisomal suspension has to be placed on the donor compartment and phosphate buffer used as receptor medium. Receptor compartment maintained at temperature 37°C and stirred at 600rpm. At regular time intervals the aliquots has to be withdrawn and same quantities are replaced with receptor fluid. The samples were analyzed by HPLC method [40].

Stability studies on proniosomes: Stability studies carried out by storing the prepared proniosomes at various temperature conditions like refrigeration on (2°-8°C) room temperature (25°±0.5°C) and elevated temperature (45° C±-0.5°C) from a period of one month to three months. Drug content and variation in the average vesicle diameter were periodically monitored. ICH guidelines suggests stability studies for dry proniosomes powder meant for reconstitution should be studied foe accelerated stability at 75% relative humidity as per international climatic zones and climatic conditions.

Applications

Proniosome gel system is a step forward to niosomes, which can be utilized for various applications in delivery of actives at desired site. Proniosomes are easily hydrated using aqueous phase or by skin itself if used topically. Their incorporation into base gel/cream/ointment along with other ingredients leads to form a cosmetic preparation. These cosmetic formulations can be used for topical/transdermal applications for various functions. Proniosome gel formulation shows advantages in controlled drug delivery, improved bioavailability, reduced side effects and entrapment of both hydrophilic and hydrophobic drugs. Proniosome gel has an affinity towards biological membranes which helps in enhancing the permeation of actives through skin.

Drug targeting: One of the most useful aspects of proniosomes is their ability to target drugs. Proniosomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelium system (RES) preferentially takes up proniosomes vesicles. The uptake of proniosomes is controlled by circulating serum factors called opsonins. These opsonins mark the noisome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of the drugs can also be used for treating parasitic

infections of the liver. Proniosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to proniosomes (as immunoglobin bind readily to the lipid surface of the noisome) to target them to specific organs. Many cells also possess carbohydrates determinates, and this can be exploited by niosomes to direct carrier system to particular cells[41].

Transdermal drug delivery systems: One of the most useful aspects of proniosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing proniosomal technology is widely used in cosmetics; In fact, it was one of the first uses of the niosomes. Topical use of proniosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to un-entrapped drug. Recently, transdermal vaccines utilizing proniosomal technology is also being researched. The proniosome (along with liposomes and transferomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in proniosomes allows only a weak immune response, and thus more research to be done in this field[42].

Sustained release: The roles of liver as a depot for methotrexate after proniosomes are taken up by the liver cells. Sustained release action of proniosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via proniosomal encapsulation.

Localized drug action: Drug delivery through proniosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects e.g. Antimonials encapsulated within proniosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity[43].

Future trends

There is a strong need for exploring the proniosomal delivery systems for cosmetics, herbal actives and nutraceuticals. Use of proniosome in the cosmetic formulation will lead to prolong action, better absorption along with many advantages. To get the desired characteristics of a particular proniosome gel formulation, it is important to select the surfactant of suitable HLB in the formulation of proniosome gel. Studies on proniosome gel formulation indicate that it has become a useful dosage form for drug permeation into the skin, especially due to their simple, scaling-up production procedure and ability to modulate drug delivery across the skin. Hence, a more extensive study should be undertaken to find out the optimal proniosome formulation for drug/cosmetic permeation into the skin.

Conclusion

Pronisomal gel systems are widely accepted by the researchers and academicians in recent days because of its ability to deliver the drug to the desired organs and giving desired activity with less amount of drug with fewer side effects. Proniosomes are thought to be better module of drug delivery as compared to liposomes and niosomes due to various factors like cost, stability etc. These systems have been found to be more stable during sterilization and storage than niosomes. The use of proniosomal carrier results in delivery of high concentration of active agent(s), regulated by composition and their physical characteristics.

Proniosomes have been tested to encapsulate lipophilic as well as hydrophilic drug molecules. Various types of drug deliveries can be possible using proniosomes based niosomes like targeting, ophthalmic, topical, parenteral, peroral vaccine etc.

Among all vesicular systems niosomes has special importance because of its rich quality in different factors like stability, cost, encapsulation capacity, etc. But its importance is limited by its physical instability. This problem can be effectively reduced by the proniosomes concept which was proved by many researchers. As a result of this proniosomes will become prominent drug delivery systems in this novel drug delivery system.

References

1. Parikh D. K. and Ghos T. K. (2005). Feasibility of transdermal delivery of fluoxetine. AAPS Pharm. Sci. Tech, 6: 144.
2. Csoka I, Csanyi E, Zapantis G, Nagy E, Feher-Kiss A and Horvath G. (2005).In-vitro and in- vivo percutaneous absorption of topical dosage forms: Case studies. Int. J. Pharm, 11:291.
3. Shahiwala A. and Misra A., (2002). Studies in topical application of niosomally entrapped nimesulide. J. Pharm. Sci. 5(3), 220-225.
4. Maibach H. I and Choi M. J. (2005). Liposomes and niosomes as topical drug delivery systems. Skin Pharmacol Physiol, 18:209–219.
5. Gamal M. (2010). Proniosomes as a drug carrier for transdermal delivery of Meloxicam. Bull. Pharm. Sci Assiut Uni, 33(2):131-140.

6. Ibrahim A, Bosela A. A, Ahmed S. M, and Mahrous G. M. (2005). Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm and Biopharm, 59: 485–490.
7. Jain N. K, Khopade A. J. and Vora B. (1998). Proniosomes based transdermal delivery of levonorgesterol for effective contraception. J Control Release, 54:149-165.
8. Mokhtar M, Sammour O. A, Hammad M. A. and Megrab N. A. (2008). Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared form proniosomes. Int J Pharm, 361:104-111.
9. Payne N. I, Browning I. and Hynes C.A. (1986). Characterization of proliposomes. J Pharm. Sci, 75:330–333.
10. Menon G. K. (2002). New insights into skin structure: scratching the surface. Adv Drug Del Rev, 54:S3-S17.
11. Structure: Skin and Hair. Available at: URL: http://www.aviva.co.uk/health-insurance/home-of-health/medical-centre/medical-encyclopedia/entry/structure-skin-and-hair/ [Accessed 14 July 2014].
12. Structure and function of normal skin. 2008 Available at: URL: http://www.talkacne.com/webdocs/info.php [Accessed 08 April 2014].
13. Bouwsta J. A. and Honeywell-Nguye P. L. (2002). Skin structure and mode of action of vesicles. Adv Drug Del Rev, 54: S41-S55.
14. Cserhati T. (1995). Alkyl ethoxylated and alkylphenol ethoxylated nonionic surfactants: Interaction with bioactive compounds and biological effects. Environ Health Perspect, 103(4):358- 364.
15. Hofland H. E.J, Van Der Geest R, Bodde H. E, Junginger H. E. and Bouwstra J. A. (1994). Estradiol permeation from nonionic surfactant vesicles through human stratum corneum in vitro. Pharm Res, 1994; 11: 659–664.
16. Gupta A, Prajapati S. K, Balamurugan M, Singh M. and Bhatia D. (2007). Design and development of a proniosomal transdermal drug delivery systems for captopril. Trop J Pharm Res, 6:687-693.
17. Fang J. Y, Hong C. T, Chiu W. T. and Wang Y. Y. (2001). Effect of liposomes and niosomes on skin permeation of enoxacin. Int J Pharm, 219: 61–72.
18. Inoue T, Muraoka Y, Fukushima K. and Shimozawa R. (1988). Interaction of surfactants with vesicle membrane of dipalmitoylphosphatidylcholine: A fluorescence depolarization study. Chem. Phys Lipids, 46:107-115.
19. Gupta A, Prajapati S. K, Balamurugan M, Singh M and Bhatia D. (2007). Design and development of a proniosomal transdermal drug delivery systems for captopril. Trop J Pharm Res, 6:687-693.
20. Mezei M. and Lee A. K. Y. (2006). Dermatitic defects of non-ionic surfactants IV: Phospholipid composition of normal and surfactant-treated rabbit skin. J Pharm Sci, 59(6): 858-861.
21. Murdan S, Gregoriadis G. and Florence A. T. (1999). Interaction of non-ionic surfactant based organogel with aqueous media. Int J Pharm, 180: 211-214.
22. Tsai Y. H, Fang J. Y, Yu S. Y, Wu P. C. and Huang Y. B. (2001). In vitro skin preparation of estradiol from various Proniosomal formulations. Int J Pharm, 215:91-99.
23. Schreier H. and Bouwstra J. (1994). Liposomes and niosomes as topical drug carriers: dermal and transdermal drug delivery. J. Control Release, 30:1-15.
24. Uchegbu I. F. and Florence A. T. (1995). Non-ionic surfactant vesicles (niosomes): physical and pharmaceutical chemistry. Adv Colloid Interface Sci, 58: 1-55.
25. Rhodes D. G. and Blazek-Welsh A. (2001). SEM Imaging predicts quality of niosomes from maltodextrins based proniosomes. Pharm Res, 18:656-661.
26. Alsarra I. A, Bosela A. A, Ahmed S. M. and Mahrous G. M. (2005). Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm Biopharm, 59:485-490.
27. Comelles F, Sanchez-leal J. and Gonzalez J. J. (2007). Influence of ionic surfactants on the formation of liquid crystals in oleic acid/glycol/water systems. Journal of Surfactants and Detergents, 10:137-144.
28. Perrett S, Golding M. and Williams W. P. (1991). A Simple Method for the Preparation of Liposomes for Pharmaceutical Applications: Characterization of the Liposomes. J. Pharm. Pharmacol, 43:154-161.
29. Lawrence M. J, Chauhan S, Lawrence S. M. and Barlow D. J. (1996). The formation. Characterization and stability of non-ionic surfactant vesicles. STP Pharm Sci, 1:49-60.

30. Manosroi A, Wongtrakul P, Manosroi J, Sakai H, Sugawara F, Yuasa M. and Abe M. (2003). Characterization of vesicles prepared with various non-ionic surfactants mixed with cholesterol. Colloids Surf B Bio interfaces, 30:129-138.
31. Murdan S, Van Den Bergh B, Gregoriadis G. and Florence A. T. (1999). Water in sorbitan monostearate organogels (water in oil gels). J Pharm Sci, 88(6):615-619.
32. Inoue T, Iwanaga T, Fukushima K, Shomozawa R. and Suezaki Y. (1988). Interaction of surfactants with bilayer of negatively charged lipid: effect on gel-to-liquid crystalline phase transition of dilauroylphosphatidic acid vesicle membrane. Chem Phys Lipids, 48:189-196.
33. Sarpotdar P. P. and Zatz J. L. (1986). Percutaneous absorption enhancement by non-ionic surfactants. Drug Dev Ind Pharm, 12:1625-1647.
34. Barry B. W. (2001). Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci, 14(2):101-114.
35. Azeem A, Jain N, Iqbal Z, Ahmad F. J, Aqil M. and Talegaonkar S. (2008). Feasibility of proniosomes-based transdermal delivery of frusemide: formulation, optimization and pharmacotechnical evaluation. Pharm Dev Technol, 13:155-163.
36. Thakur R, Anwer M. K, Shams M. S, Ali A, Khar R. K, Shakeel F. and Taha E. I. (2009). Proniosomal transdermal therapeutic system of losartan potassium: development and pharmacokinetic evaluation. J Drug Target, 17:442-449.
37. Tiddy G. J. T. (1980). Surfactant-water liquid crystal phases. Phys Rep, 57: 1–46.
38. Varshosaz J, Pardakhty A, Mohsen S, Baharanchi H. (2005). Sorbitan monopalmitate-based proniosomes for transdermal delivery of chlorpheniramine maleate. Drug Del, 12:75-82.
39. Iwai H, Fukasava J. and Suzuki T. (1998). A liquid crystal application in skin care cosmetics. Int J Cosmet Sci, 20(2):87-102.
40. Ciotti S. N. and Weiner N. (2002). Follicular liposomal delivery systems. J Liposome Res, 12:143-148.
41. Ogiso T, Niinaka N. and Iwaki M. (1996), Mechanism for enhancement effect of lipid disperse system on percutaneous absorption. J Pharm Sci, 85: 57-64.
42. Mitsuno Y, Nomaguchi K. and Suzuki T. (1988). US4767625.
43. Sagar G. H, Arunagirinathan M. A. and Bellare J. R. (2007). Self-assembeled surfactant nanostructures important in drug delivery: A Review. Indian J Exp Biol, 45:133-159.

How to cite this article
Farooqui N., Jaiswal V. and Kar M. (2014). A Review on Proniosomal Gel: Potential Carrier System in Transdermal Delivery for Non- Steroidal Anti-inflammatory Drugs (NSAID). *Int. J. Pharm. Life Sci.*, 5(10):3939-3947.
Source of Support: Nil; Conflict of Interest: None declared

Received: 01.09.14; Revised: 12.09.14; Accepted:07.10.14