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NIOSOMES: AN OVERVIEW

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ABSTRACT

Niosomes are artificial vesicles with potential technological advantages. They are non-ionic surfactant vesicles. As efficient drug delivery systems with a wide range of uses, niosomes have the same potential benefits as phospholipid vesicles (liposomes), including the capacity to hold both water- and lipid-soluble pharmaceutical molecules. Niosomes can also be thought of as more cost-effective, chemically stable, and occasionally physically stable alternatives to liposomes. Simple preparation techniques and commonly used surfactants in pharmaceutical technology can be employed to create niosomes. Numerous studies have covered noisome physicochemical characteristics and their uses as drug delivery vehicles. In this report, a brief and simplified summary of different theories of self-assembly are discussed. Furthermore, manufacturing methods, physical characterization techniques, bilayer membrane additives, unconventional niosomes (discomes, proniosomes, elastic and polyhedral niosomes), their recent applications as drug delivery systems, limitations and directions for future research will be discussed.

Keywords: Niosomes, Zeta Potential, Proniosome, Bola surfactant, P-glycoprotein, Aspasomes

INDRODUCTION

"Paul Ehrlich, in 1909, initiated the development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with non-target tissue".[1]
Niosomes are non-ionic surfactant-based vesicles. "They were originally developed as an alternative controlled drug delivery system to liposomes, in order to overcome the problems associated with sterilization, large-scale production and stability".

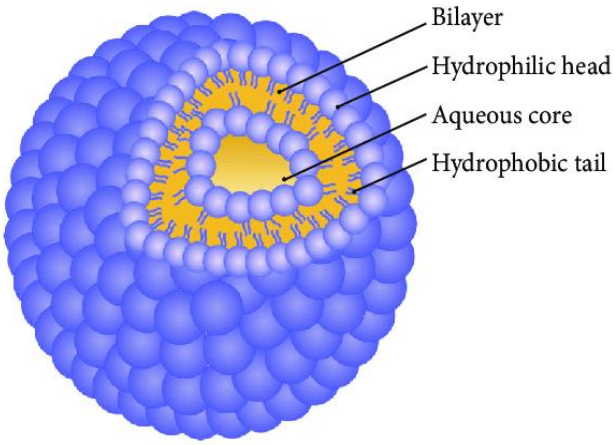
"The first niosome formulations were developed and patented by L'Oreal in 1975 (Sahin, 2007). Niosomes were first utilized in drug delivery for anticancer drugs. The developed niosome formulations were capable of altering the pharmacokinetic profile, organ distribution and metabolism of methotrexate in mice (Azmin et al., 1985, 1986). Niosomes are versatile in structure, morphology and size; they can entrap hydrophilic drugs in aqueous compartments or lipophilic drugs by partitioning of these molecules into bilayer domains". [2,3,4]

Defination

A non-ionic surfactant-based liposome is known as a niosome. Cholesterol is primarily used as an excipient in the formation of niosomes. Other excipients can also be used. Niosomes are more capable of penetrating than earlier emulsion formulations. "Although they share a bilayer with liposomes structurally, niosomes are more stable due to the materials employed in their preparation, and as a result, they have many more advantages over liposomes".[5,6]
Niosomes are tiny, lamellar structures that range in size from 10 to 1000 nm. The niosome is made up of surfactants that are non-immunogenic, biodegradable and biocompatible. "Niosomes are superior than liposomes because they are more cost-effective and have higher surfactant chemical stability than phospholipids, which are more easily dissolved by the ester bond".[7]

Structure of Niosome

'A typical niosome vesicle would consist of a vesicle forming amphiphile i.e. a nonionic surfactant such as Span860, which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle'.[8]



TYPES OF NIOSOMES

1. Bola surfactant containing niosomes
The surfactantuses inBola surfactantcontaining niosomes aremade ofomega hexadecylbis(1-aza-18 crown-6) (bola surfactant): span- 80/cholesterol in 2:3:1molar ratio.

2. Proniosomes
Proniosomes ismade from the carrierand surfactant mixture.After the hydration of proniosomes, Niosomes are produced.

3. Aspasomes
Aspasomes is produced using the mix of acorbylpalmitate,cholesterol andexceptionally charged lipid diacetyl phosphate prompts the arrangement of vesicles. Aspasomes are first hydratedwith water/fluid arrangement and afterward it is subjected to sonication to get the niosomes. Aspasomes can be utilized to build the transdermal saturation of medications. Aspasomes have likewise been utilized to diminish scatter caused by responsive oxygen species as it has innate cell reinforcement property.

4. Niosomes in Carbopol gel
Niosomes were prepared from drug, spans and cholesterol thenit is incorporated in carbopol-934 gel (1%w/w) base containing propylene glycol (10% w/w) and glycerol (30% w/w).

5. Vesicles in water and oil system (v/w/o)
In thisstrategy, theaqueous niosomesinto an oilstage frame vesicle in water in oil emulsion (v/w/o). This can be set up by expansion of niosomes suspension figured from blend of sorbitol monostearate, cholesterol and solulan C24 (Poly-24-Oxyethylene cholesteryl ether) to oil stage at 60 0C.Thisresult in the formation of vesicle in water in oil (v/w/o)emulsion which by cooling to room temperature forms vesicle in water in oil gel (v/w/o gel). The v/w/o gel thus obtained can entrap proteins/ proteinous drugs and also protect it from enzymatic degradation after oral administration and controlled release.

6. Niosomes of hydroxyl propyl methyl cellulose
In this type, a base containing 10% glycerin of hydroxyl propyl methyl cellulose was first prepared and then niosomes were incorporated in it.

7. Deformable niosomes
"The mixture of non-ionic surfactants, ethanol and water forms the deformable niosomes. These are smaller vesicles and easily pass through the pores of stratum corneum, which leads to increase penetration efficiency. It can be used in topical preparation".[9,10]

8. Proniosomes
Dehydrated forms of niosomes are called as proniosomes. Before their use, proniosomes should be hydrated. On hydration, they form a dispersion of aqueous niosome. Since Proniosomes are in the dryform, they offer advantages over niosomes, like aggregation, fusion, and thecaking problem is reduced, transportation and distribution become easy.

The niosomes are also classified according to the number and size
a) Small Niosomes (100 nm to 200 nm)

b) Large Niosomes (800 nm to 900 nm)
c) Big Niosomes (2µm to 4 µm)[11]

COMPONENTS OF NIOSOMES

1) Non-ionic surfactant (or) Amphiphilies.
2) Cholesterol.
3) Charged molecules
4) Drug.
5) Distilled water (or) Buffer

1) Non-ionic surfactants:

Non-ionic surfactants are amphiphilic (or amphipathic) molecules with two different regions in their chemical structure, one of which is water-liking or hydrophilic and the other of which is water-hating or hydrophobic. "These molecules' two parts can be connected by ether, amide, or ester linkages. Non-ionic surfactant vesicles can be prepared from different types of molecules, such as: amino acids, fatty acids, amides, alkyl esters and alkyl ether surfactants, the last one being mostly employed for such purposes". [12-16]

Based on how the hydrophilic head group is constructed, alkyl ether surfactants can be roughly divided into two classes: those whose hydrophilic head groups are made up of repeating glycerol subunits, related isomers, or larger sugar molecules, and those whose hydrophilic head groups are made up of repeating ethylene oxide subunits.
"The first niosomes were formulated using cholesterol and single chain surfactants such as alkyl (usually from C12 to C18) oxyethylenes".[17]Polyglycerol monoalkyl ethers and polyoxylate analogs are the most widely used single-chain surfactants. Ether surfactants, suitable for noisome formulations are composed, in their lipophilic moiety, of monoalkyl or dialkyl chains. The latest ones, being similar to phosphor-lipids, and possess higher encapsulation efficiency. Esther type amphiphilic surfactants are also used for niosome formulation. They are degraded by estherases to triglycerides and fatty acids.Although these types of surfactants are less stable than ether type ones, they are usually less toxic. Finally, also glucosides of myristil, cethyl and stearyl alcohols can be used to form niosomes.

While the number of hydrophobic permutations is at present quite limited, there has been a wide variety of hydrophilic head groups in vesicle forming surfactants, and the design of new molecules is in continuous evolution, according to the specific vesicle structure that are needed. "Some recent studies report the synthesis and the characterization of new surfactants with peculiar physical–chemical properties, showing promising applications in the field pharmaceutical colloid science. As an example, a new non-ionic surfactant molecule, in which the hydrophilic region consists of azacrown ether units, was synthesized by Muzzalupo and co-workers. This compound, known as bolasurfactant, is composed of two identical azacrown ether units, as polar heads, linked to a long alkyl chain".[18,19,20]

2) Cholesterol:

"It is well known that cholesterol (CHOL) influences the physical properties and structure of niosomes because of its interaction with non-ionic surfactants. Several surfactants form vesicles only after CHOL addition (up to 30–50 mol%). The amount of CHOL to be added depends on the HLB value of the surfactants. As the HLB value increases above 10, it is necessary to increase the CHOL concentration in order to compensate the effect of the larger head groups on the critical packing parameter (CPP), previously discussed".[21,22]

"The water soluble detergent Tw20 (HLB value = 16.7) forms stable non-ionic surfactant vesicles in the presence of equimolar CHOL concentration because in absence of CHOL it would be well hydrated and can be found as free monomers in solution (CMC = 60 mg/l, in water at 20 °C)".[23-26]

"It was suggested that an interaction occurs between the hydrophobic portion of the amphiphile (phospholipid/surfactant) next to head group and the 3-OH group of CHOL in vesicular systems at an equimolar ratio (CHOL:amphiphile),[27] and this interaction could explain the effect of CHOL on the formation and hydration behaviour of Tw20 niosomal membranes that were found to coexist with unsolubilized CHOL crystal".[28]

3) Charge- Molecule:

"Some charged molecules are added to niosomes for increasing the steadiness of niosomes through electrostatic repulsion which avoids aggregation and coalescence. e negatively charged molecules applied in niosomes arrangements are diacetyl phosphate (DCP) and phosphatidic acid. Stearylamine (STR) and stearyl pyridinium chloride are the famous positively charged molecules applied in niosomes construction. 2.5–5 molar % concentration of charged molecules is acceptable as high concentration can prevent the niosomes creation".[29]

FACTORS LEADING TO NIOSOME FORMATION

"The self-assembly of amphiphilic molecules into closed bilayers, both in the case of liposomes and niosomes, is not spontaneous but it involves some input of energy, for instance by means of physical shaking (hand-shaking, ultrasound, heat, etc.)"[30,31]"Moreover, thermodynamically stable vesicles are formed only in presence of appropriate mixtures of surfactants and charge inducing agents. Although previous studies showed that niosomes have a higher resistance to micellar solubilization than liposomes".[32,33]

Thermodynamic and physicochemical parameters like the hydrophilic-lipophilic balance (HLB) and the geometric characteristics of the amphiphilic molecules are the main factors that affect amphiphile self-assembling; however, a number of other factors are important for vesicle formation and properties and must be taken into account, particularly the aqueous interlayer, lipid chain-length, chain-packing, and membrane asymmetry. Three factors contribute to the energy needed to create vesicles containing amphiphilic molecules: surface energy, mechanical energy from overpressure, and chemical potential excess. It is the high interfacial tension between water and the hydrocarbon component (or any other hydrophobic group) of the amphiphile that drives the interaction of these groups, which leads to the associations of non-ionic surfactant monomers into vesicles during hydration.

"At the same time the steric, hydrophilic, and/or ionic repulsion among the head groups ensures that these groups are in contact with water. Of course also monomer concentration and temperature play an important role in vesicle formation. Thermodynamically this self-assembly must contend against a negative entropy component (ΔS) and the reduction in free energy (ΔG) and is only achieved by the favorable enthalpy (ΔH) contribution arising from the van der Waals attractions, the hydrophobic forces, the hydrogen bond formation and the screened electrostatic interactions. As above pointed out, vesicle formation may depend on the HLB value; thus the guidance offered by the HLB number is useful in the evaluation of new classes of compounds for their vesicles forming ability. With the sorbitan monostearate surfactants (Sp), an HLB number between 4 and 8 was found to be compatible with vesicle formation."[34]

"On the other hand, it was actually shown that, owing to their high aqueous solubility, hydrophilic surfactants cannot form free hydrated units (vesicles) but these free units rather aggregate and coalesce to form lamellar structures."[35,36]"Consequently, niosomes are not generally formed with surfactants with a HLB value between 14 and 17[37]and the addition of cholesterol plays a fundamental role in vesicle formation with surfactants with a HLB value around 10".[38]"To explain the behavior of non-ionic surfactants in water, a hydrophobic effect was proposed several years ago, as the essential strength leading to an enhancement of global system-free energy. Shapes of the spontaneously formed association colloids can be predicted with considerable certainty using nominal geometric parameters of the surfactant molecule. The critical packing parameter (CPP also named as Ps) was discussed by Israelachvili et al. in 1976"[39].

METHODS OF PREPARATION

1) Hand Shaking Method.
2) Ether Injection Method.
3) Sonication Method.
4) Reverse Phase Evaporation Method.
5) Aqueous Dispersion Method.
6) Extrusion Method.
7) Microfludization Method.
8) Thin Film Hydration Method.
9) Transmembrane pH Gradient Method.

1) Hand Shaking Method

In this method surfactant and cholesterol are mixed in organic solvent and the organic layer is transferred to round bottom flask by vacuum. Then it is allowed to evaporate in round bottomed flask and upon hydration the surfactant swells to form vesicles.

2) Ether Injection Method

Here the vesicles are formed, when the surfactant: Cholesterol mixture in organic solvent is slowly injected by a 14 guaze needle at a rate of 0.25 ml/min in aqueous phase maintained at 600C.

3) Sonication Method

In this method surfactant: Cholesterol mixture was dispersed in a 2 ml of aqueous phase in a vial. Then the dispersion was probe sonicated for 3 minutes at 600C.

4) Reverse Phase Evaporation Method

Surface active agents are dissolved in chloroform and 0.25 volume of phosphate buffer saline is emulsified to get w/o emulsion. The mixture is then sonicated and subsequently chloroform is evaporated under reduced pressure. The lipid (or) surfactant forms a gel first and subsequently hydrates to form vesicles.

5) Aqueous Dispersion Method

This method essentially based on microdispersion of surfactants in aqueous media containing solutes for encapsulation (or) entrapment. Continuous agitation under controlled temperature condition leads to homogenous vesiculation.

6) Extrution Method

Niosomes were prepared by using C16 Cr2 a chemically defined non-ionic surfactant by extrution through a Polycarbonate membrane (0.1 mm nucleopore).

7) Microfludization Method

This method is based on submerged jet principle in which two fluidized streams interact at ultra-high velocities (upto 1700 ft/sec) in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheets along a common front is arranged such that the energy supplied to the system remains with in the area of niosome formulation.

8) Thin Film Hydration Method

The surfactant : Cholesterol mixture is dissolved in volatile organic solvent and the solvent is evaporated in round bottom flask at 600C until a thin film was formed. Then aqueous solvent is added and vortexed for 1 hour. The film peels off and later swells to form niosomes.

9) Transmembrane ph Gradient Method

Here the surfactant and cholesterol were dissolved in chloroform. The solvent was evaporated on the walls of round bottom flask. The film is hydrated with 300 mm citric acid by vortex mixing. Then the product was frozen. To this niosomal suspension, aqueous solution was added and vortexed. The pH of the solution was raised to 7.0 to 7.2 with 1ml of disodium hydrogen phosphate. The mixture was later heated at 600C for 10minutes.[40,41,42,43]

A. Thin Film Hydration Method

Surfactant, cholesterol and drug were weighed separately and taken in to two different beakers.
15 ml of Chloroform: Methanol (2:1) mixture was added to the surfactant : cholesterol mixture and stirred until it gets completely dissolved.

Then the above solution was added to drug and stirred until the drug gets completely dissolved.
Now the above organic layer was introduced into the round bottom flask of Rotary flash evaporator by vacuum.
The Round Bottom Flask was allowed to rotate at 180 rpm at 600C in a water bath until the organic layer was completely evaporated. After evaporation, the surfactant, cholesterol and drug formed a thin film on the inner sides of Round Bottom Flask.

Then water was incorporated into round bottom flask by vacuum and allowed to vortexed for 1 hour. The thin film layer was peeled out and swelled in water to form Niosomes. The above white dispersion (Niosomes) was cooled in an ice bath and then sonicated using probe type ultrasonicator for 3 min at 150v.
he resulted vesicles of niosomes were stored at 40C in a refrigerator. Plain niosomes were also prepared without drug using the above procedure.[44,45]

B. Ether Injection Method

Here the surfactant, cholesterol and drug were weighed separately and dissolved by using 10ml of Diethyl ether: Methanol (1:1) mixture.
The above organic layer was taken in a 50 ml syringe having 14 guaze needle fitted in it.
Then in a separate beaker adequate amount of distilled water was taken and it was placed over a magnetic stirrer and kept in a temperature between 550C and 650C.
Aqueous layer was rotated by using a magnetic bead. The above organic layer was injected into swrilling aqueous phase at a rate of 0.25 ml / min.

Vapourization of ether and methanol resulted in the formation of niosomes.
Finally the niosomes were stored at 40C in a refrigerator. Plain niosomes were also prepared without drug using the above procedure.[46]

C. Hand Shaking Method

Here the surfactant, cholesterol and drug were weighed separately.
10ml of Chloroform: Methanol (1:1) mixture was added to surfactant, cholesterol mixture and stirred until it dissolved and the above solution was added to the drug and stirred until completely dissolved. Above organic layer was transferred to the round bottom flask by vacuum. The round bottom flask was vortexed at 600C until all the organic liquid was completely evaporated.

"After that adequate amount of the aqueous phase (Distilled water) was added and shaken by hands in a water bath at 600C until a white dispersion was formed (Niosomes). Plain niosomes were also prepared without drug using the above procedure".[47]

EVALUTION

1. Drug Content Analysis

"Drug content of the niosomal preparations were determined by lysis method. 50% n-propanol was used for lysing the niosomes. 1ml of the niosomal formulation was taken in 100ml standard flask. Then adequate amount of 50% n-propanol was added and shaken well until all the vesicles were completely lysed. The volume was made upto 100ml with distilled water. 10ml of the above solution was further diluted to 100ml with the same distilled water. Now the absorbance was measured at 242 nm by UV-spectrophotometer shimadzu using plain niosomes as blank".[48,49,50]

2. Estimation of Entrapment Efficiency

Entrapment efficiency was found out by dialysis method. The Cellophane membrane was used as a semipermeable membrane. Here the cellophane membrane was soaked in Glycerol: water (1:3) mixture for 15 min. It was tied in an open ended tube and 2ml of Niosomal solution was transferred into it. The was is placed into a 250ml beaker containing 100 ml Distilled water and it was stirred by magnetic stirrer. The samples were taken every 15 min for 6 hours. The absorbance was measured at 242 nm by UV-spectrophotometer shimadzu using distilled water as blank and the entrapment efficiency was calculated by the following formula.

"Entrapment efficiency = % Drug content - % of maximum drug release of unentrapped drug".[51,52]

3. Size, Shape and Morphology

"Vesicular structure of surfactant based vesicles has been visualized and established using freeze fracture electron microscopy while photon correlation spectroscopy could be successfully used to determine mean diameter of the vesicles. The vesicles can also be examined using light microscope, polarized light microscope, Olympus microscope, infrared spectroscopy and electron microscopy".[53,54,55]

4. Vesicle Stability

Vesicle stability is a complex issue and involves chemical stability, physical stability and biological stability, which are all inter-related. "The evaluation of these parameters is fundamental to determine the potential in vitro/in vivo applications in nanomedicine. Biological stability, however, depends on the presence of agents that interact with the vesicular structure after administration and it therefore depends also on the administration route. Generally, stability is determined by means of size and ζ-potential variations (DLS, Turbiscan Lab® Expert or microscopy techniques) or by evaluation of the release rate of different probes as a function of time and/or temperature, in absence or in presence of biological fluids".[56]

5. ζ-potential and surface properties

"ζ-potential value has critical importance on vesicle stability and in vivo fate. Several authors confirmed the importance of ζ-potential measurements to assess vesicle formation, to study drug/vesicle interaction and formulation stability"[57,58,59]

"ζ-potential is also a critical parameter to be taken carefully into account in the formation of aggregates, from charged niosomes and oppositely charged polyions, when these vesicles are proposed as drug carriers".[60,61]

6. Bilayer characterization

"Niosomes, as liposomes, can be morphologically classified according to the number of membrane bilayers (lamellae) in uni- and multilamellar vesicles. Uni-lamellar vesicles are characterized by the presence of one surfactant bilayer while multi-lamellar vesicles by several concentric surfactant bilayers in an onion-like skin arrangement. The number of lamellae can be determined by AFM, NMR and small angle X-ray scattering (SAXS). The latter method, together with the in situ energy-dispersive X-ray diffraction (EDXD), has been also used to characterize the bilayer thickness"[62,63,64,65]

7. pH-sensitivity assessment

Stimuli-sensitive NSVs, which release their cargo in response to external stimuli, represent interesting alternatives for therapies directed towards solid tumors and other spatially well-defined targets. "The gradual decrease in pH, experienced by niosomes that are internalized via endocytosis, is actually a very useful intrinsic stimulus and several pH-sensitive niosome formulations, based on this strategy, have been developed and biologically evaluated"[66,67,68]

8. Zeta Potential

Physical stability of niosomes is an important factor which depends on the surface charge of the niosomes zeta potential is helpful to determine the charge. Particle image systems and information can be used to determine the surface factor, and the degree of the zeta potential represents the extent of electrostatic aversion among the two neighboring particles. Niosomes having a zeta potential of greater than+30 mV or less than -30 mV are thought to be stable.

APPLICATIONS OF NIOSOMES

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against diseases. By niosomal formation we can potentially deliver both hydrophobic (or) amphiphilic drugs.

Targeting of bioactive agents to reticulo endothelial system and to organs other than reticulo endothelial system
Used in Neoplasia.
Used in Leishmaniasis.
Used to delivery peptide drugs.
Used in immunological applications.
Used as a carrier of haemoglobin.
Used in Transdermal drug delivery of drugs.
Used in Diagnostic imaging.
Used in oral drug delivery.
Useful in sustained release and localized drug action.

Delivery of Proteins and Peptides

"It was always difficult to deliver protein and peptide drugs via oral route because of their destruction by the acidic media and enzymes of GIT. But niosomes provide protection to these drugs from the proteolytic enzymes",[69,70]"Moghassemi et al"[71.] prepared niosomes of Bovine serum albumin (BSA). "The formulation was optimized for loading and release as a function of cholesterol to span 60 M ratios and used methyl orange to detect the position of protein in the vesicle with the help of an inverted light microscope. Niosomes of trimethyl chitosan-coated insulin are also prepared for oral delivery to enhance the permeation of insulin".[72]

Delivery of Anticancer Drugs

"Targeted delivery of anticancer drugs can be achieved using niosomes. This targeting could be passive,[73] (deposition of niosomes within the tumor because of the special properties of the tumor cells not existing in the normal cells)[74], physical (delivery based on specific environment conditions like pH or magnetic fields)[75]. "The active targeting can be achieved either by modifying the structure features of the surface or by attaching the ligand to the niosomes. For ligand attachment either cholesterol-PEG-ligand conjugate be incorporated to the niosomes or it can be attached to cholesterol or to the end of the polyethylene glycol chain".[76,77,78,79]

Carrier For Hemoglobin

"Niosomes can also be used as a carrier of hemoglobin in the blood1 because they have good oxygen absorptive properties".[80]

Delivery of Vaccine and Antigen

"Wilkhu et al.[81]prepared bilosomes for the oral delivery of vaccines. Bilosomes are prepared by the incorporation of bile salt in the bilayer of vesicles. These bilosomes protects the antigens from degradation by enzymes present in the GIT".

Treatment of HIV-AIDS

For the sustained delivery of drugs in AIDS treatment niosomes can be utilized. The problem in the delivery of these drugs is low potency and toxicity, which could be overcome by forming niosomal system. "Zidovudine is an anti-HIV drug with limitations in therapeutic effectiveness due to dose-dependent hematological toxicity, extensive firstpass metabolism, short biological half-life and poor bioavailability".[82,83]Lopinavir is a specific reversible HIV protease inhibitor. Its systemic bioavailability through oral route is limited due to very low aqueous solubility, very high log P value, sensitivity for cytochrome P450 3A4 and susceptibility towards P-glycoprotein efflux

transporters. To overcome these issues transdermal niosomes were prepared and compared with the ethosomal gel. "The results from ex-vivo skin permeation studies indicated that the deposition of a drug into the skin was more with the ethosomal gel as compared to niosomal gel but niosomes penetrated deeper through the skin and has shown a better drug release profile".

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