Available online at www.abhipublications.org
Review Article
International Journal of Pharmacy and Engineering (IJPE)
ISSN 2320-849X

Structural and Functional significance of Niosome and Proniosome in Drug Delivery System

Arunima Debnath*, Anup Kumar

Department of Pharmaceutics, Calcutta Institute of Pharmaceutical Technology & AHS, Banitabla, Uluberia, Howrah-711316, West Bengal, India.

Abstract:

The present article describes the study and functional significance of noisome and proniosomes as specialized drug delivery system. Proniosomes are dry water soluble carrier particles optimizing the problems associated aggregation, fusion and leakage of drug. Niosomes are also studied as an alternative to liposomes. Niosomes are non-ionic surfactant based vesicles formed mostly of non-ionic surfactant and cholesterol incorporation as an excipient, which are biodegradable, relatively nontoxic, more stable and inexpensive, an alternative to liposome. Niosomes proved to be a promising drug carrier and has potential to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases. Niosomes have more penetrating capability than other preparation of emulsions. Though they have structural similarity with liposomes, the materials used to prepare niosomes make them more stable, hence niosomes offer more advantages than liposomes.

Received: 5th September, 2015, Revised: 1 3th September 2015, Accepted: 16th September 2015,

 Corresponding Author: * Arunima Debnath, [1]*Department of Pharmaceutics, Calcutta Institute of Pharmaceutical Technology & AHS, Banitabla, Uluberia, Howrah-711316, West Bengal, India. Email id: debaru.1993@gmail.com*

1. Introduction:

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.

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. The proniosomes are a versatile delivery system because of the ease of distribution, measuring, transfer, and storage.[1]

Colloidal vesicular carriers such as liposomes or niosomes can act as drug reservoirs and the rate of drug release can be modified by changing of their composition. These lipid carriers can encapsulate both hydrophilic drugs (by loading in inner space) and hydrophobic drugs (in lipid area). Because of their potential to carry a variety of drugs, these lipid vesicles have been widely used in various drug delivery systems like drug targeting, controlled release and permeation enhancement of drugs.[2]

Niosomes are microscopic lamellar structures composed of non-ionic surfactants and cholesterol. The niosomes have amphiphillic bilayer structure in a way that polar region is oriented outside and inside the vesicles where the hydrophilic drug will be entrapped and non-polar region is formed within the bilayer where hydrophobic drug can be entrapped. [3] The formation of vesicular system based on hydration of mixture of a single-alkyl chain nonionic surfactant and cholesterol was firstly reported in 1979. [4] Niosomes might be produced by various types of nonionic surfactants including polyglycerol alkyl ethers, crown ethers, ester-linked surfactants, glucosyldialkyl ethers, polyoxyethylene alkyl ethers, Brij, Tweens and Spans. Nonionic surfactants used to prepare niosomes carry no charge and are relatively nontoxic and mild to use. [5]

Niosome and Liposome:

Niosomes are made of non-ionic surfactants and cholesterol. Most surfactants have a single hydrophobic tail, eg: Sodium dodecyl sulfate. Liposome are made of phospholipids, they may or may not contain cholesterol. Phospholipids have two hydrophobic tails. Niosomes have unique advantages over liposomes. Niosomes are quite stable structures, even in the emulsified form. They require no special conditions such as low temperature or inert atmosphere for protection or storage, and are chemically stable. Relatively low cost of materials makes it suitable for industrial manufacture. A number of non-ionic surfactants have been used to prepare vesicles viz. polyglycerol alkyl ether, glucosyl dialkyl ethers, crown ethers, ester linked surfactants, polyoxyethylene alkyl ether, Brij, and a series of spans and tweens.Niosomes entrap solute in a manner analogous to liposomes. They are osmotically active, and are stable on their own, as well as increase the stability of the entrapped drugs. Handling and storage of surfactants require no special conditions. Niosomes possess an infrastructure consisting of hydrophilic and hydrophobic moieties together, and as a result, can accommodate drug molecules with a wide range of solubilities. They exhibit flexibility in structural characteristics (composition, fluidity, size,), and can be designed according to the desired situation. Niosomes improve the oral bioavailability of poorly absorbed drugsand enhance skin penetration of drugs.[7]

Niosome and Proniosome:

Proniosomes are dry formulation of water soluble carrier particles that are coated with surfactant. They are rehydrated to form niosomal dispersion immediately 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. From a technical point of view, niosomes are promising drug carriers as they possess greater chemical stability and lack of many disadvantages associated with liposomes, such as high- cost and variable purity problems of phospholipids. The present review emphasizes on overall methods of preparation characterization and applicability of proniosomes in targeted drug action.[1]

Structure of Proniosome:

Proniosomes are microscopic lamellar structures. They combine a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol followed by hydration in aqueous media. The surfactant molecule direct themselves such that the hydrophilic ends of the non-ionic surfactant orient outward, while the hydrophobic ends are in the opposite direction to form the bilayer. Like liposomes proniosomes are also made up of a bilayer. In proniosomes the bilayer is made of non-ionic surface active agents.

On the basis of method of preparation proniosomes are unilamellar or multi-lmellar. The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicles while the hydrophobic chains face each other within the bilayer. Hence the vesicle holds hydrophilic drugs within the space enclosed in the vesicle and the hydrophobic drugs are embedded within the bilayer.[1]

Formation of Niosomes from Proniosomes:

The niosomes can be prepared from the proniosomes by adding the aqueous phase with the drug to the proniosomes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant. T > Tm where, T = Temperature Tm = mean phase transition temperature. [6]

Types of Proniosomes:

According to the type of carrier and method of preparation of proniosomes they are of two types.

Dry granular proniosomes

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 the addition of hot water followed by agitation.

Maltodextrin based proniosomes are prepared by fast slurry method.

Liquid crystalline proniosomes

This type of proniosomes are reservoirs for transdermal delivery of the drug. The transdermal patch involves an aluminum foil as a baking material along with a plastic sheet. Proniosomal gel is spread evenly on the circular plastic sheet followed by covering with a nylon mesh.[1]

Preparation of proniosomes:

The proniosomes can be prepared by

1. Slurry method.

2.Slow spray coating method.

3.Coacervation phase separation method.

1. Slurry method

Proniosomes can be prepared from a stock solution of surfactants and cholesterol in suitable solvent. The required volume of surfactant and cholesterol stock solution per gram of carrier and drug should be dissolved in the solvent in 100 ml round bottom flask containing the carrier (maltodextrin or lecithin). Additional chloroform can be added to form the slurry in case of lower surfactant loading. The flask has to be attached to a rotary flash evaporator to evaporate solvent at 50- 60 rpm at a temperature of 45±20 C and a reduced pressure of 600mm Hg until the mass in the flask had become a dry, free flowing product. Finally, the formulation should be stored in tightly closed container under refrigeration in light47.

2. Slow spray coating method

A 100 ml round bottom flask containing desired amount of carrier can be attached to rotary flash evaporator. A mixture of surfactants and cholesterol should be prepared and introduced into round bottom flash on rotary evaporator by sequential spraying of aliquots onto carrier's surface. The evaporator has to be evacuated and rotating flask can be rotated in water bath under vacuum at 65-70oC for 15 – 20 min. This process has to be repeated until all of the surfactant solution had been applied. The evaporation should be continued until the powder becomes completely dry.

3. Coacervation phase separation method

Proniosomal gels can be prepared by this method which comprises of surfactant, lipid and drug in a wide mouthed glass vial along with small amount of alcohol in it. The mixture is warmed over water bath at 60-700C for 5min until the surfactant mixture is dissolved completely. Then the aqueous phase is added to the above vial and warmed still a clear solution is formed which is then converted into proniosomal gel on cooling. After hydration of proniosomes they are converted to uniformly sized niosomes.[6]

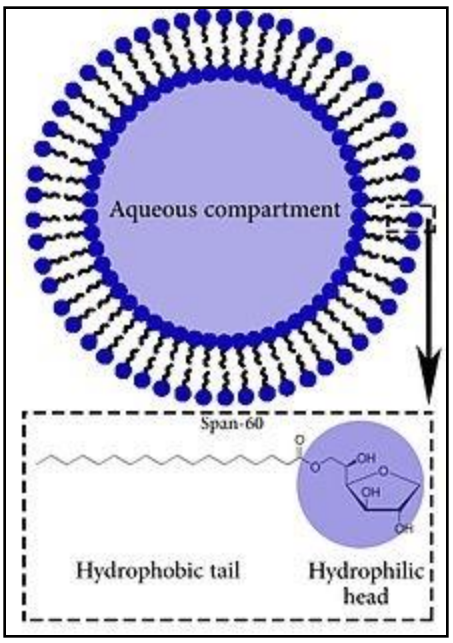

Figure 1: Niosome using Span-60 as surfactant

Factors Governing Niosome formation:

Non-ionic surfactant structure:

Theoretically niosome formation requires the presence of a particular class of amphiphile and aqueous solvent. In certain cases cholesterol is required in the formulation and vesicle aggregation for example may be prevented by the inclusion of molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic effects. An example of steric stabilisation is the inclusion of Solulan C24 (a cholesteryl poly-24-oxyethylene ether) in doxorubicin (DOX) sorbitan monostearate (Span 60) niosome formulation. An example of electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.

Surfactant and lipid level:

The level of surfactant/lipid used to make niosomal dispersions is generally 10-30 mM (1-2.5% w/w). Altering the surfactant: water ratio during the hydration step may affect the system's microstructure and hence the system's properties. However increasing the surfactant/lipid level also increases the total amount of drug encapsulated, although highly viscous systems result, if the level of surfactant/lipid is too high.

Nature of the encapsulated drug:

Another factor often overlooked is the influence of an amphiphilic drug on vesicle formation, when encapsulation of the amphipathic drug DOX was attempted. A steric stabilizer Solulan C24 (poly -24-oxyethylene cholesteryl ether) must be added to the formlation to ensure a homogenous formulation devoid of aggregates.DOX has been shown to alter the electrophoretic mobility of hexadecyl diglycerol ether (C16G2) niosomes in a pH dependent manner, an indication that the amphipathic drug is incorporated in the vesicle membrane.

Structure of surfactants:

The geometry of vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameters. On the basis of critical packing parameters of Surfactants can predicate geometry of vesicle to be formed.Critical packing parameters can be defined using following equation,

CPP=v/(lc*a0)

CPP≤0.5 micelles form

CPP=(0.5-1.0) spherical vesicles form

CPP≥1.0 inverted micelles form

Where v = hydrophobic group volume, lc = the critical hydrophobic group length, a0= the area of hydrophilic head group.

Temperature of hydration:

Hydration temperature influences the shape and size of the niosome. The hydrating temperatures used to make niosomes should usually be above the gel to liquid phase transition temperature of the system. [8]

Method of Preparation of Niosome:

The entire process of preparation of niosomes has been shown in the flow diagram

A. Hand shaking method (Thin film hydration technique)

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar noisomes.

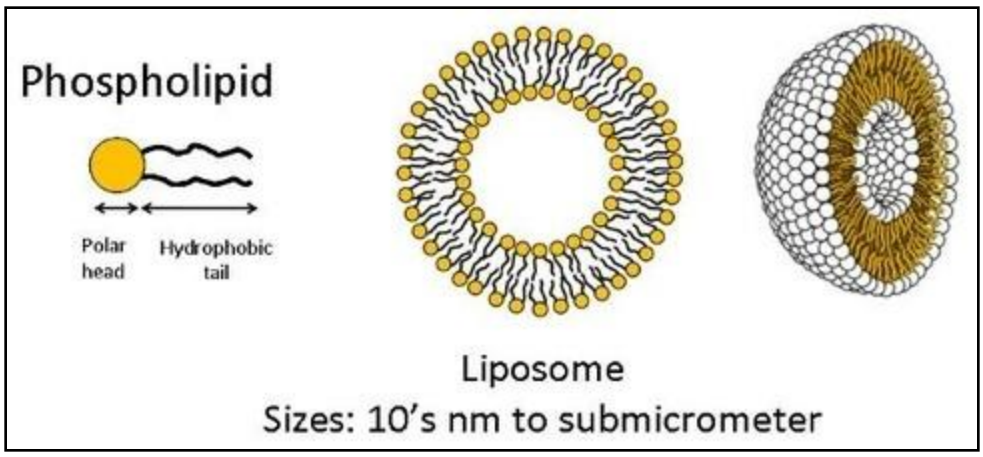

Figure 2: Structure of Liposome

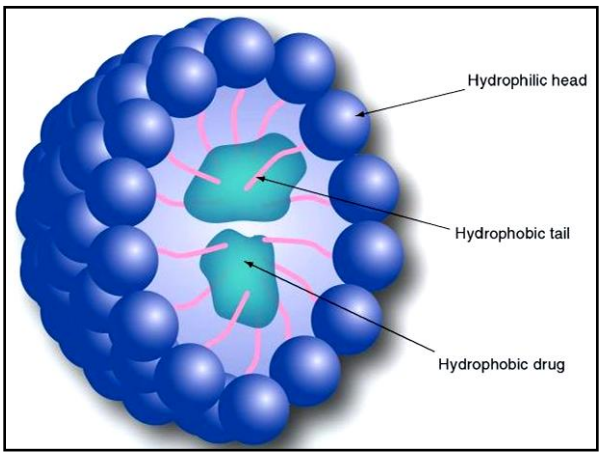

Fig 3: Niosome and its internal synthetic surfactant surrounding drug payload.

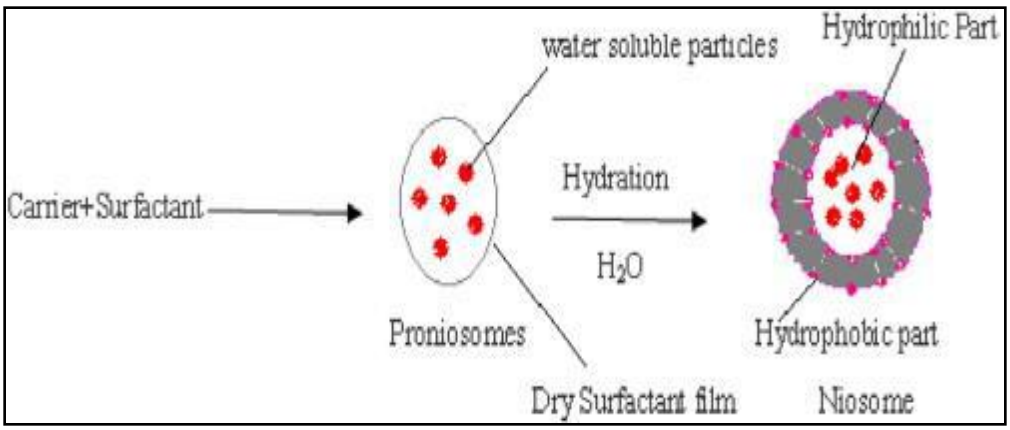

Fig 4: Formation of Niosomes from Proniosomes

B. Micro fluidization

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

C. Reverse Phase Evaporation Technique (REV)

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 45°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.Raja Naresh et al[8] have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method

D.Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm.

E.Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°Cfor 10 minutes to give niosomes.

F.The "Bubble" Method

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

G.Sonication

A typical method of production of the vesicles is by sonication of solution. In this method an aliquot of drug solution in buffer is added to the surfactant/choleste mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

H. Formation of niosomes from proniosomes

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation.

T=Temperature.

Tm = mean phase transition temperature.

The formulation of niosomes from maltodextrin based proniosomes have been reported.This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water. [10]

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.

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 (CnEOm), 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 C 16 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. Polyoxyethelene 4 lauryl ether (Brij30) has an HLB value of 9.7, phase transition temperature $<10^0$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. Polyoxyethylene cetyl ethers (Brij58) and Polyoxyethylene stearyl ethers (Brij72and76) are also used in preparation of Niosomes.

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. 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 sorbital and its mono and di-an-hydrides with oleic acid. These have been used to entrap wide range of drugs viz doxorubicin.

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 important 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 the movement of carbons of hydrocarbon. Cholesterol is also known to prevent leakage by abolishing gel to liquid phase transition.

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 cetyl pyridinium chloride.[11]

Niosomally Entrapped Bioactive Agents:

A variety of drugs/active agents have been encapsulated in Niosomes. Various agents encapsulated in niosomes and the corresponding results.

Estradiol - Enhanced in vitro skin permeation of proniosome formulations.

Iopromide - Targeting of lopromide entrapped in MLV to the Kidney.

Flurbi profen - Enhanced bioavailability and anti-inflammatory activity of niosome encapsulated formulations as compared to conventional ointment base.

Timolol maleate - Sustained activity on ocular administration.

Cytarabine Hydrochloride - Niosomal encapsulation provides sustained release delivery.

Rifampicin - Prolonged drug release.

Cisplatin - Significant antimetastatic activity

Cytosine arabinoside - Effective release in acid environment

Tretinoin - Span 20 and Tween 80, Span 60 and Tween 80 combination gives good entrapment

Daunorubicin Hydrochloride - Improved therapeutic efficacy

Colchicine - Sustain release & reduced toxic side effects

Insulin - Sustained release after oral dosage form. Enhancing effect on vaginal delivery of insulin. Improved stability against proteolytic enzyme.

Finasteride - Enhance drug concentration by topical application

Hydroxycamphothecin - Enhanced stability and antitumor activity

Acetazolamide - Prolonged effect and decrease in intraocular pressure

Clotrimazole - Sustain and controlled release of clotrimazale for local vaginal therapy

Timolol maleate - Improved pharmacodynamics

Tetanous Toxoide - Mannosylated niosomes were found to be useful oral vaccine delivery carrier

Propylthiouracil - Control the release of propyl thiouracil [12]

Mechanisms of niosomal skin delivery:

Several mechanisms have been suggested to describe the ability of niosomes in transdermal and dermal drug delivery: i) niosomes diffuse from the stratum corneum layer of skin as a whole; ii) new smaller vesicles are formed in skin (re-formation of niosome vesicles). The water content of skin is crucial issue for interpreting and establishing this mechanism. Smaller diameter of lipid lamellar spaces of the stratum corneum than noisome vesicles makes this mechanism more meaningful

iii) Niosomes interact with stratum corneum with aggregation, fusion and adhesion to the cell surface which causes a high thermodynamic activity gradient of the drug at the vesicle-stratum corneum surface, which is the driving force for the penetration of lipophilic drugs across the stratum corneum.

Scanning electron microscopy confirmed the fusion of niosome vesicles of estradiol on the surface of skin; iv) niosomes may modify stratum corneum structure which makes the intercellular lipid barrier of stratum corneum looser and more permeable ; v) non-ionic surfactant itself, the composing ingredient of niosome, acts as a permeation enhancer and might partly contribute to the improvement of drug permeation from niosomes . The type of surfactant plays an important role in modification of permeation using niosome vehicles. Niosomes fabricated from polyoxyethylene stearyl ether and existing in the gel state did not enhance estradiol permeation, and those prepared from polyoxyethylene lauryl ether and polyoxyethylene oleyl ether, both existing as liquid crystalline vesicles, considerably improved transport. [13,14,16,17]

Toxicity of niosomes:

Surfactants are suspected to show toxicity but there are virtually not enough research about toxicity of niosomes . A study on the toxicity effect of surfactant type of niosomal formulations on human keratocytes showed that the ester type surfactants are less toxic than ether type due to

enzymatic degradation of ester bounds. Hofland et al. studied the toxicity of CxEOy surfactants via ciliotoxicity model on nasal mucosa (which is important for intranasal administration) and on human kerationocytes (which is important for the transdermal application of vesicles). The results showed that increase in alkyl chain length of surfactant causes a reduction in toxicity, while, increase in the polyoxyethylne chain length enhances ciliotoxicity. The study supposed that ciliotoxicity related to liquid state formation with increasing in polyoxyethylene chain length, while increase in alkyl chain length of surfactant leads to formation of gel which is more safe than liquid state. In another study, vincristine, a potent anti-tumor agent, was loaded into niosomes and administered intravenously. Result showed a significant increase in vincristine anti-tumor activity in S-180 sarcoma and Erlich ascites mouse models followed by reduction of its side effect such as diarrhea, neurological toxicity and alopecia compared with free drug. Toxicity effect of niosomes should be considered according to the intended route of delivery. For example, hemocompatibility studies should be carried out when the niosomes are meant to be delivered by intravenous route to evaluate their toxic potential. The first in vivo experiment on drug delivery by means of synthetic non-ionic surfactant vesicles were carried out by Azmin et al. and reported that no unfavorable effects were observed in the performed experiment(Azmin et al., 1985). Rogerson et al. reported in vivo experiment over 70 male BALB/C mice and stated that no fatalities were related to niosomes. The drug associated toxicity were also reduced (Rogerson et al., 1987). Niosomes which have been prepared with Bola-surfactants showed a certain and encouraging safety and tolerability both in vitro on human keratinocyte cells up to an incubation time of 72 h for the different concentrations studied (0.01-10 μM) and in vivo on human volunteers that showed no skin erythema when topically treated with the drug free Bola-niosome formulation. [22,23,24]

Conclusion:

There has been lots of development in drug delivery technologies over the years. Niosomal drug delivery system is one such recently developed system. The technology utilized in niosomes is still greatly in its infancy, and already it is showing promise in various fields like cancer and infectious disease treatments. The system is already in use for various cosmetic products. Thus it can be concluded that Niosomes represent a promising drug delivery technology and much research has to be carried out to find all of its potential in this novel drug delivery system.

References:

1. G. V. Radha, T. Sudha Rani, and B. Sarvani. A review on proniosomal drug delivery system for targeted drug action. J Basic Clin Pharm. 2013; 4(2): 42–48

2. Akhilesh, D.; Hazel, G. & Kamath, J.V. Proniosomes – A propitious provesicular drug carrier. International Journal of Pharmacy and Pharmaceutical Science Research. 2011;Vol. 1, No. 3, pp. 98-103, ISSN: 2249-0337

3. Khan, A.; Sharma, P.K.; Visht, S. & Malviya,R. Niosomes as colloidal drug delivery system: A review. Journal of Chronotherapy and Drug Delivery. 2011; Vol. 2, No. 1, pp. 15-21

4. Handjani-Vila, R.M.; Ribier, A.; Rondot, B. & Vanlerberghe, G.. Dispersions of lamellar phases of non-ionic lipids in cosmetic products. Int J Cosmetic Sci. 1979; Vol. 1, pp. 303-314

5. Azeem, A.; Anwer, M.K. & Talegaonkar, S. Niosomes in sustained and targeted drug delivery: some recent advances. J Drug Target. 2009; Vol. 17, No. 9, pp. 671-689, ISSN: 1061-186X.

6. Dinesh Chandra, Ashish Kumar, Rakesh singh, Tirth Raj, Shrikant Verma, Niraj Sharma Proniosomes: A Recent Advancement In Nanotechnology As A Absorption Modulator for transdermal Drug Delivery System. Am. J. PharmTech Res. 2013; 3(6)

7. Thakur Varun, Arora Sonia, prashar bharat and Vishal Patil. Niosomes and liposomes-Vescicular approach towards Transdermal drug delivery. International journal of pharmaceutical and chemical sciences.2012;1(3).

8. Alemayehu Tarekegn, Nisha M Joseph,S Palani, Anish Zacharia, Zelalem Ayenew. Niosomes in targeted drug delivery: some recent advances. IJPSR,2010;Vol. 1 (9):1-8

9. Raja Naresh RA, Chandrashekhar G, Pillai GK and Udupa N. Antiinflammatory Activity of Niosome Encapsulated Diclofenac Sodium with Tween -85 in Arthitic rats. Ind JPharmacol.1994;26:46-48

10. Madhav NVS and Saini A. Niosomes: A novel drug delivery system. IJRPC 2011,1(3): 498-511

11. Anchal Sankhyan and Pravin Pawar. Recent Trends in Niosome as Vesicular Drug Delivery System. Journal of Applied Pharmaceutical Science 02 (06); 2012:20-32

12. Rajesh Mujoriya, Ramesh Babu Bodla, Kishor Dhamande, Devendra singh and Lokesh Patle. Niosomal drug delivery system: The magic bullet. Journal of Applied Pharmaceutic al Science 01 (09); 2011:20-23
13. Sahin, N.O. Niosomes as nanocarrier systems. Nanomaterials and nanosystems for biomedical applications2007. p. 67-81
14. Ogiso, T.; Niinaka, N. & Iwaki, M., (1996). Mechanism for enhancement effect of lipid disperse system on percutaneous absorption.J Pharm Sci, Vol. 85, pp. 57-64, ISSN: 1520-6017
15. Schreier, H. & Bouwstra, J., (1994). Liposomes and niosomes as topical drug carriers: dermal and transdermal drug delivery. J Control Release, Vol. 30, No. 1, pp. 1-15, ISSN: 0168-3659.
16. Fang, J.Y.; Hong, C.T.; Chiu, W.T. & Wang, Y.Y., (2001). Effect of liposomes and niosomes on skin permeation of enoxacin.Int J Pharm, Vol. 219, No. 1-2, pp. 61-72, ISSN: 0378- 5173.
17. Javadzadeh, Y.; Shokri, J.; Hallaj-Nezhadi, S.; Hamishehkar, H. & Nokhodchi, A., (2010). Enhancement of percutaneous absorption of Finasteride by cosolvents, cosurfactant and surfactants. Pharm Dev Technol, Vol. 15, No. 6, pp. 619-625, ISSN: 1083-7450.
18. Hofland, H.; Bowuwstra, J.A.; Ponec, M. Boddé, H.E.; Spies,F.; Coos Verhoef, J.; Junginger H.E., (1991). Interactions of non-ionic surfactant vesicles with cultured keratinocytes and human skin in vitro: a survey of toxicological aspects and ultrastructural changes in stratum corneum. J Control Release, Vol. 16, No. 1, pp. 155-167, ISSN: 0168-3659.
19. Yadav, J.D.; Kulkarni, P.R.; Vaidya, K.A. & Shelke, G.T., (2011). Niosomes: a review. J Pharm Res, Vol. 4, pp. 632-636, ISSN: 0974-6943
20. Hofland, H.E.J.; Bouwstra, J.A.; Spies, F. & Bodde, H.E., (1992). Safety aspect of nonionic surfactant vesicles- a toxicity study related to the physicochemical characteristics of nonionic surfactants. J Pharm Pharmacol, Vol. 44, pp. 287-292, ISSN: 0022-3573

21. Parthasarathi, G.; Udupa, N.; Umadevi, P. & Pillai, G.K., (1994). Niosome encapsulated of vincristine sulfate: Improved anticancer activity with reduced toxicity in mice. J Drug Target, Vol. 2, No. 2, pp. 173-182, ISSN: 1061-186X.
22. Uchegbu, I.F. & Duncan, R., (1997). Niosomes containing N-(2-hydroxypropyl) methacrylamide copolymer-doxorubicin (PK1): effect of method of preparation and choice of surfactant on niosome characteristics and a preliminary study of body distribution. Int J Pharm, Vol. 155, No. 1, pp. 7-17, ISSN: 0378-5173.
23. Azmin, M.N.; Florence, A.T. & Handjani-Vila, R.M., (1985). The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. J Pharm Pharmacol, Vol. 37, No. 4, pp. 237-242, ISSN: 0022-3573
24. Rogerson, A.; Cummings, J. & Florence, A.T., (1987). Adriamycin-loaded niosomes: drug entrapment, stability and release.J Microencapsul, Vol. 4, No. 4, pp. 321-328, ISSN: 0265-2048
25. Paolino, D.; Muzzalupo, R.; Ricciardi, A.; Celia,C.; Picci, N. & Fresta, M., (2007). In vitro and in vivo evaluation of Bola-surfactant containing niosomes for transdermal delivery. Biomed Microdevices, Vol. 9, No. 4, pp. 421-433, ISSN: 1387-2176.

Received: 5th September, 2015, Revised: 1 3th September 2015, Accepted: 16th September 2015,

 Corresponding Author: * Arunima Debnath, *[1]Department of Pharmaceutics, Calcutta Institute of Pharmaceutical Technology & AHS, Banitabla, Uluberia, Howrah-711316, West Bengal, India. Email id: debaru.1993@gmail.com*