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PREPARATION, CHARACTERIZATION AND EVALUATION OF NIOSOMES FOR FUTURE TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

Niosomes the formulation of surfactant vesicles, as a tool improve drug delivery. The scientists working in the area of drug delivery system has improved their interest. Niosomes are non-ionic vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or their lipids. As like liposomes, niosomes can be unilamellar or multilamellar are suitable as carrier of both hydrophilic and lipophilic drug and are able to deliver drug to the target site. Non-toxic, requiring less production cost, stable over a longer period of time in different condition, so over come drawbacks of liposomes present review describe history, all factor affecting niosomes formulation, characterization, stability, evaluation and also their comparison with liposomes this review also given relevant information regarding various application of niosomes in gene delivery, vaccine delivery, anti-cancer drug delivery, etc.

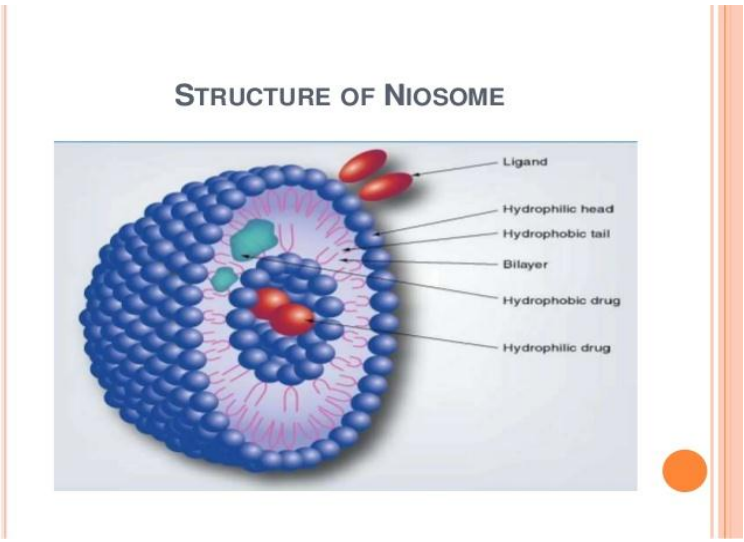
INTRODUCTION

Delivering drug with a controlled rate and targeted delivery received much attention in recent years. The application of nanotechnology to medicine has provided the development of multifunctional nanoparticles that, acting as drug carriers, can be loaded with different drugs. Nano carriers present a great approach in drug delivery with promising features such as protection of drug from degradation and cleavage, controlled release and in case of targeted delivery approaches the delivery of drug molecules to the target sites. Niosomes are one of the promising drug carriers that have a bilayer structure and are formed by self-association of nonionic surfactants and cholesterol in an aqueous phase. Niosomes are biodegradable, biocompatible and non-immunogenic. They have long shelf life, exhibit high stability and enable the delivery of drug at target site in a controlled and/or sustained manner. In recent

years, the potential of niosomes as a drug carrier has been extensively studied. Various types of nonionic surfactants have been reported to form niosomes and enable the entrapment of a large number of drugs with a wide range of solubility. The composition, size, number of lamellae and surface charge of niosomes can be varied and optimized to enhance the performance of niosomes for drug delivery. The aim of this review is to present the fundamentals of niosome preparation and characterization as well as a description of their use in drug delivery, with particular attention to more recent studies. This review will provide an overview on the increasing interest on niosomes in the field of drug delivery.[1]

1. Structure and Components of Niosomes

The main components of niosomes are nonionic surfactants, hydration medium and lipids such as cholesterol. The list of materials used in the preparation of niosomes has been shown in Table 1. The self-assembly of nonionic surfactants in aqueous media results in closed bilayer structures (Figure 1). A high interfacial tension between water and the hydrophobic tails of the amphiphile causes them to associate. The steric and hydrophilic repulsion between the head groups of nonionic surfactant ensure that hydrophilic termini point outwards and are in contact with water. The assembly into closed bilayers usually requires some input of energy such as mechanical or heat. Niosomes can be categorized in three groups according to their sizes and bilayers. Small unilamellar vesicles (SUV) (10–100 nm), large unilamellar vesicles (LUV) (100–3000 nm), and multilamellar vesicles (MLV) where more than one bilayer is present.



2. Formulation aspects

Formulation aspects are the most important independent parameter that can affect the characteristics of niosomes. Most commonly, niosomes are prepared by convenient accessible raw materials. Non-ionic surfactants are the basic components of niosomes.

2.1. Non-ionic surfactants

Surfactants form a unique class of chemical compounds. Surfactants are amphiphilic molecules with two distinct regions that have very different solubilities, a hydrophilic (water-soluble) end and a lipophilic (organic-soluble) end that is highly hydrophobic, for example, phospholipids (phosphatidyl choline) which are the foundation of biological cell membranes. The lipophilic region is chains made up of alkanes, fluorocarbons, aromatic or other non-polar groups. The head group involves highly solvated hydrophilic functionalities, such as sulfonates, carboxylates, phosphonates and ammonium derivatives. Surfactants can be classified to anionic, cationic, amphoteric and non-ionic; according to their hydrophilic functionality head group; being sulfonate, quaternary ammonium salts, zwitterionic butanes and fatty acids; respectively.[2]

Table 1. Surfactant classification (data has been collected from Refs.[3,4]

Surfactant class	Examples	Structures
Non-ionic	Polyoxyethylene alcohol	$C_nH_{2n+1}(OCH_2CH_2)_mOH$
	Polyoxyethylene glycol alkyl ethers (Brij)	$CH_3(CH_2)_{10–16}(O–C_2H_4)_{1–25}OH$
	Alkyl ethoxylate	$CH_3(CH_2)_{11}(OCH_2CH_2)_nOH$
	Alkyl phenol ethoxylate	$CH_3(CH_2)_8–C_6H_4–(OCH_2CH_2)_nOH$
	Fatty acid alkanolamides	$CH_3(CH_2)_{10}–OCN(CH_2CH_2OH)_2$
	Propylene oxide-modified polymethylsiloxane	$(CH_3)_3SiO((CH_3)_2SiO)_x(CH_3SiO)_ySi(CH_3)_3$
	(EO = ethyleneoxy, PO = propyleneoxy)	$C_3H_6O(EO)_m(PO)_nH$
Anionic	Stearate	$CH_3(CH_2)_{16}COO^-$
	Soap	$CH_3(CH_2)_{10}COO^-$
	Alkyl benzene sulfonate	$CH_3(CH_2)_9C(CH_3)C_6H_4SO_3^-$
	Alkyl sulfates	$CH_3(CH_2)_{11}OSO_3^-$
	Ether sulfates	$CH_3(CH_2)_{10}CH_2O(CH_2CH_2O)_4SO_3^-$
	Alkyl ether sulfate	$CH_3(CH_2)_{11}(C_2H_4O)OSO_3^-$
Cationic	Laurylamine	$CH_3(CH_2)_{11}NH_3^+$
	Trimethyl dodecylammonium	$C_{12}H_{25}N^+$

Surfactant class	Examples	Structures
	Cetyl trimethylammonium	$CH_3(CH_2)_{15}N^+$
	Alkyl diamine salt	$CH_3(CH_2)_{12}(NH_2)^+(NH_3)^+$
	Benzylalkyldimethylamonium salts	$CH_3(CH_2)_{11}N^+(CH_3)_2CH_2(C_6H_5)$
	Alkyl quaternary ammonium salts	$CH_3(CH_2)_{15}N^+(CH_3)_3$
Zwitterionic	Dodecyl betaine	$C_{12}H_{25}N^+(CH_3)_2CH_2COO^-$
	Lauramidopropyl betaine	$C_{11}H_{23}CONH(CH_2)_3N^+(CH_3)_2CH_2COO^-$
	Cocoamido-2-hydroxypropyl sulfobetaine	$C_nH_{2n+1}CONH(CH_2)_3N^+(CH_3)_2CH_2CH(OH)CH_2SO^-_3$
	Alkyl imidazoline	$CH_3(CH_2)_8CONH(CH_2)_2NH^+(C_3H_6OH)C_2H_4COO^-$
	Alkylbetaines	$CH_3(CH_2)_{11}N^+(CH_3)_2CH_2COO^-$
	Sulfur-containing amphoterics	$CH_3(CH_2)_{15}N^+(CH_3)_2CH_2CH_2CH_2SO_3^-$

Non-ionic surfactants are absolutely one of the best polymeric nanocarriers with a wide role in controlled, sustained, targeted and continuous drug delivery. Commonly, surfactants are classified according to their polar head group. A non-ionic surfactant has no charge groups in its head. The head of an ionic surfactant has a net charge and is called an anionic surfactant. Examples of such surfactants include: fatty acid salts ("soaps"), sulfates, ether sulfates and phosphate esters. If the head charge is positive, it is called a cationic surfactant. If a surfactant contains a head with two oppositely charged groups, it is termed as a zwitter-ionic (amphoteric) surfactant. Cationic surfactants are also frequently irritant and sometimes even toxic; therefore their application in drug delivery is more limited than the three other classes of surfactants. Examples of each category have been listed in Table:1.[3,4]

Non-ionic surfactants are a category of surfactants which have no charge groups in their hydrophilic heads. Therefore in solutions, non-ionic surfactants can form structures in which hydrophilic heads are opposite to aqueous solutions and hydrophilic tails are opposite to organic solutions. Because of this property of the non-ionic surfactants, niosomes are formed by the self-assembly of non-ionic surfactants in aqueous dispersions. Non-ionic amphiphiles used in niosomes are classified in four categories: Alkyl esters, Alkyl amides, Alkyl ethers and esters of fatty acids.[5]

Advantages and disadvantages of niosomal carriers

Niosomes combine several advantages with respect to other nanocarriers:[6]

- Surfactants used to prepare niosomes are biodegradable, biocompatible and not immunogenic.
- The method used for routine and large-scale production of niosomes does not involve use of unacceptable solvents.
- Due to the chemical stability of their structural composition, the handling and storage of niosomes does not require any special conditions.
- The physicochemical properties of niosomes, such as their shape, fluidity and size, can be easily controlled by changing their structural composition and the method of production.
- Niosomes are able to encapsulate a large amount of material in a small vesicular volume.
- The structure of niosomes protect drug ingredients from heterogeneous factors present both inside and outside the body, so niosomes can be used for the delivery of labile and sensitive drugs.
- Niosomes improve the therapeutic performance of drug molecules by delaying clearance from the circulation and restricting effects to target cells.
- Niosomes can be administered via different routes, such as oral, parenteral and topical, and using different dosage forms such as powders, suspensions and semisolids, improving the oral bioavailability of poorly soluble drugs and also enhancing the permeability of drugs through the skin when applied topically.
- The aqueous vehicle-based suspension formulation results in better patient compliance when compared with oily dosage forms; in addition, niosomal dispersion, being aqueous, can be emulsified in a nonaqueous phase to regulate the drug release rate.
- Niosomes have been reported to achieve better patient adherence and satisfaction and also better effectiveness than conventional oily formulations.

At the same time, niosomes have some disadvantages, which may decrease their shelf life, and include physical and chemical instability, aggregation, fusion of vesicles and leaking or hydrolysis of the encapsulated drug. Moreover, the methods required for preparation of multilamellar vesicles, such as extrusion or sonication, are time-consuming and may require specialized equipment for processing.[7]

Niosomes versus liposomes

Niosomes and liposomes are functionally the same, with similar physicochemical properties depending on the composition of the bilayer and the preparation methods used (Table 2).

They act as amphiphilic vesicles, and both can be used for targeted and sustained drug delivery.

Table.2. Niosomes versus liposomes: a summary

	Niosomes	Liposomes
Components	Surfactants	Phospholipids
Component availability	High	Low
Component purity	Good	Variable
Preparation and storage	No special conditions required	Inert atmosphere and low temperature
Stability	Very good	Low
Cost	Low	High

Several authors have reported that the function of niosomes in vivo is similar to that of liposomes.[8] Niosomal and liposomal vesicular systems have similar applications in the pharmaceutical and cosmetic field, but differ chemically in their structure units; niosomes are made of surfactants whereas liposomes are based on phospholipids, meaning that niosomes have greater stability and lack many of the disadvantages associated with liposomes, ie, high cost, low availability and the variable purity problems associated with phospholipids. Niosomes do not require special conditions such as low temperature or an inert atmosphere during preparation and storage; these features make niosomes more attractive for industrial manufacturing.[9] On the other hand, niosomes offer several advantages over liposomes, such as intrinsic skin penetration-enhancing properties.[10]

Methods of Preparation

3.1. Thin-Film Hydration Method (TFH). Thin-film hydration method is a simple and well-known preparation method. In this method, the surfactants, cholesterol and some additives such as charged molecules are dissolved in an organic solvent in a round bottomed flask. Then the organic solvent is removed using a rotary vacuum evaporator to obtain thin film on the inside wall of the flask. An aqueous solution of drug is added and the dry film is hydrated above the transition temperature (Tc) of the surfactant for specified time with constant shaking.[11,12] Multilamellar niosomes are formed by this method.

3.2. Ether Injection Method (EIM). In ether injection method, the surfactants with additives are dissolved in diethyl ether and injected slowly through a needle in an aqueous drug

solution maintained at a constant temperature, which is above the boiling point of the organic solvent. The organic solvent is evaporated using a rotary evaporator. During the vaporization the formation of single layered vesicles occurs.[13,14]

3.3. Heating Method. This is a patented method.[15,16] Surfactants and cholesterol are separately hydrated in buffer and the solution is heated to 120∘C with stirring to dissolve cholesterol. The temperature is reduced and surfactants and other additives are then added to the buffer in which cholesterol is dissolved while stirring continues. Niosomes form at this stage, are left at room temperature and then are kept at 4-5∘C under nitrogen atmosphere until use.[17]

3.4. The "Bubble" Method. In this method, surfactants, additives and the buffer are added into a glass flask with three necks. Niosome components are dispersed at 70∘C and the dispersion is mixed with homogenizer. After that, immediately the flask is placed in a water bath followed by the bubbling of nitrogen gas at 70∘C. Nitrogen gas is passed through a sample of homogenized surfactants resulting in formation of large unilamellar vesicles.[18]

3.5. Reverse Phase Evaporation Method (REV). In this method, niosomal ingredients are dissolved in a mixture of ether and chloroform and added to aqueous phase containing the drug. The resulting mixture is sonicated in order to form an emulsion and the organic phase is evaporated. Large unilamellar vesicles are formed during the evaporation of the organic solvent.[19,20]

3.6. Microfluidization Method. The microfluidization method is based on submerged jet principle. In this method, the drug and the surfactant fluidized streams interact at ultrahigh velocities, in precisely defined micro channels within the interaction chamber. The high speed impingement and the energy involved leads to formation of niosomes. This method offers greater uniformity, smaller size, unilamellar vesicles and high reproducibility in the formulation of niosomes.[21,22]

3.7. Supercritical Carbon Dioxide Fluid (scCO2). Manosroi et al. have described the supercritical reverse phase evaporation technique for niosome formation.[23,24] They added Tween 61, cholesterol, glucose, PBS and ethanol into the view cell and the CO2 gas was introduced into the view cell. After magnetic stirring until equilibrium, the pressure was

released and niosomal dispersions were obtained.[23] this method enables one step production and easy scale-up.

3.8. Proniosome. Proniosome technique includes the coating of a water-soluble carrier such as sorbitol and mannitol with surfactant. The coating process results in the formation of a dry formulation. This preparation is termed "Proniosomes" which requires to be hydrated before being used. The niosomes are formed by the addition of the aqueous phase. This method helps in reducing physical stability problems such as the aggregation, leaking and fusion problem and provides convenience in dosing, distribution, transportation and storage showing improved results compared to conventional niosomes.[25]

3.9. Transmembrane pH Gradient. In this method, surfactant and cholesterol are dissolved in chloroform and evaporated to form a thin lipid film on the wall of a round bottomed flask. The film is hydrated with a solution of citric acid (pH = 4) by vortex mixing and the resulting product is freeze-thawed for niosome formation. The aqueous solution of drug is added to this niosomal suspension, after that phosphate buffer is added to maintain pH between 7.0 and 7.2.[26] According to this method, the interior of niosome has a more acidic pH value than the outer medium. The added unionized drug passes through the niosome membrane and enters into the niosome. The drug ionizes in an acidic medium and cannot escape from the niosomal bilayer.[27]

Factors affecting niosomes formulation

1. Drug

Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size. In polyoxyethylene glycol (PEG) coated vesicles; some drug is entrapped in the long PEG chains, thus reducing the tendency to increase the size. The hydrophilic lipophilic balance of the drug affects degree of entrapment.

2. Amount and type of surfactant

The mean size of niosomes increases proportionally with increase in the HLB surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant. The bilayers of the vesicles are either in the so-called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are

present in a wellordered structure and in the liquid state, the structure of the bilayers is more disordered. The surfactants and lipids are characterized by the gel-liquid phase transition temperature (TC). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment.

3. Cholesterol content and charge

Inclusion of cholesterol in niosomes increased its hydrodynamic diameter and entrapment efficiency. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid-ordered phase. An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore an increase of the rigidity of the bilayers obtained. Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

4. Resistance to osmotic stress

Addition of a hypertonic salt solution to a suspension of niosomes brings about reduction in diameter. In hypotonic salt solution, there is initial slow release with slight swelling of vesicles probably due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress.

5. Membranes Composition

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral noisome remains unaffected by adding low amount of solulan C24 (cholesterol poly-24- oxyethylene ether), which prevents aggregation due to development of stearic unhydrance. In contrast spherical niosomes are formed by C16G2: cholesterol: solution (49:49:2). The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2: solution C24 in ration (91:9) having bigger size (8.0 ± 0.03 mm) than spherical/tubular niosomes formed by C16G2: cholesterol: solution C24 in ratio (49:49:2) (6.6± 0.2 mm). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from noisome.

CHARACTERIZATION OF NIOSOMES[28,29]

a. **Measurement of Angle of repose**: The angle of repose of dry niosomes powder was measured by a funnel method. The niosomes powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

b. **Scanning electron microscopy**: Particle size of niosomes is very important characteristic. The surface morphology (roundness, smoothness and formation of aggregates) and the size distribution of niosomes were studied by Scanning Electron Microscopy (SEM). Niosomes were sprinkled on to the double- sided tape that was affixed on aluminium stubs. The aluminum stub was placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).

c. **Optical Microscopy**: The niosomes were mounted on glass slides and viewed under a microscope (Medilux-207RII, Kyowa-Getner, Ambala, India) with a magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.

d. **Measurement of vesicle size**: The vesicle dispersions were diluted about 100 times in the same medium used for their preparation. Vesicle size was measured on a particle size analyzer (Laser diffraction particle size analyzer, Sympatec, Germany). The apparatus consists of a He-Ne laser beam of 632.8 nm focused with a minimum power of 5 mW using a Fourier lens[30] to a point at the center of multielement detector and a small volume sample holding cell (Su cell). The sample was stirred using a stirrer before determining the vesicle size. Hu C. and Rhodes 7 in 1999 reported that the average particle size of niosomes derived niosomes is approximately 6µm while that of conventional niosomes is about 14µm.

e. **Entrapment efficiency:** Entrapment efficiency of the niosomal dispersion in can be done by separating the unentrapped drug by dialysis centrifugation or gel filtration as described above and the drug remained entrapped in noisomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzing the resultant solution by appropriate assay method for the drug. Where,

Percentage entrapment = (Total drug –Diffused drug)/ Total drug*100

f. **Osmotic shock**: The change in the vesicle size can be determined by osmotic studies. Niosomes formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours. Then the changes in the size of vesicles in the formulations are viewed under optical microscopy. g. Stability studies To determine the stability of niosomes, the optimized batch was stored in airtight sealed vials at different temperatures. Surface characteristics and percentage drug retained in niosomes and niosomes derived from proniosomes were selected as parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease. In the percentage drug retained. The niosomes were sample at regular intervals of time (0,1,2 and 3months), observed for color change, surface characteristics and tested for the percentage drug retained after being hydrated to form niosomes and analyzed by suitable analytical methods(UV spectroscopy, HPLC methods etc).

g. **Zeta potential analysis:** Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted niosomes derived from pronoisome dispersion was determined using zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method (Zeta plus™, Brookhaven Instrument Corporation, New York, USA). The temperature was set at 25°C. Charge on vesicles and their mean zeta potential values with standard deviation of measurements were obtained directly from the measurement.

Table.3. Method for evaluation of Niosomes

EVALUATION PARAMETER	METHOD
Morphology	SEM, TEM, freeze fracture technique
Size distribution, poly dispersity index	Dynamic light scattering particle size analyzer
Viscosity	Ostwald viscometer
Membrane thickness	X-ray scattering analysis
Thermal analysis	DSC
Turbidity	UV-Visible diode array
In-vitro release study	Dialysis membrane
Entrapment efficacy	Centrifugation, dialysis, gel chromatography
Permeation study	Franz diffusion cell

Applications of Niosomes

Niosomes were introduced for use in the cosmetic industry. The first report on surfactant vesicles came from the cosmetic applications devised by L'Oreal.[31] Phospholipids and nonionic surfactant have been reported to act as penetration enhancers that can overcome the barrier of transdermal drug delivery.[32] Since then, there has been increasing interest in the use of niosomes in the pharmaceutical, cosmetic and food industries, leading to the publication of more than 1,200 research articles, about 200 patents and six clinical trials from 1980 onwards. Most of these publications make reference to the importance of characterization of nanovectors.

Niosomal carriers are suitable for the delivery of numerous pharmacological and diagnostic agents, including antioxidants, anticancer, anti-inflammatory, antiasthma, antimicrobial, anti-Alzheimer's and antibacterial molecules, oligonucleotides and others.[30] Depending on the type of drug, surfactant, disease and anatomical site involved, various routes of administration exist for niosomal drugs, ie, intravenous, intramuscular, oral, ocular, subcutaneous, pulmonary and transdermal. Several other routes have been used to administer niosomal drugs, including the intraperitoneal and vaginal routes. Niosomes have been used for successful targeting of drugs to various organs like the liver and brain or to pathological districts such as tumor, enhancing drugs pharmacological activities while reducing side effects.[33] In particular, targeted niosomal systems have been designed with different mechanisms of action, including active, passive and magnetic targeting, leading to more advanced and specific macromolecular drug carriers.[7]

Toxicity of Niosomes

The toxicity of niosomes is related to their components, ie, nonionic surfactants are more biocompatible and less toxic than their anionic, amphoteric and cationic counterparts. When the same surfactants are in the form of vesicular systems, these properties strongly decrease. There is little research published on the toxicity of niosomes and the types of surfactant included[34] evaluated the toxicity of the types of surfactant used in niosomal formulations to human keratinocytes and demonstrated that ester types of surfactant are less toxic than ether types due to enzymatic degradation of bonds in esters. Hemolytic tests are traditionally used to predict the toxicity of a surfactant and in vesicular systems derived from them.[35] Recently, it has been demonstrated that the ability of niosomes to disrupt erythrocytes depends on the length of the alkyl chain in the surfactant and on the size of the

colloidal aggregates in solution. Presumably, a shorter carbon chain intercalates better into the membranes of erythrocytes, destructing their molecular organization; niosomes have more difficulty to interact with biological membranes, resulting in substantial hemolysis.[30] Niosomes prepared with bolaform surfactants showed encouraging safety and tolerability data both in vitro in human keratinocytes and in vivo in human volunteers, who showed no skin erythema when topically treated with a drug-free bolaform niosome formulation.[36]

REFERENCE

1. Khan A, Sharma PK, Visht S, Malviya R. Niosomes as colloidal drug delivery system: a review. *Journal of Chronotherapy and Drug Delivery*. 2011; 2: 15–21.

A. Pardakhty, E. Moazeni Nano-niosomes in drug, vaccine and gene delivery: a rapid overview Nanomedicine J., 2013; 1: 1–12.

2. L.L. Schramm, E.N. Stasiuk, D.G. Marangoni Surfactants and their applications Annual Reports Section" C"(Physical Chemistry), 2003; 99: 3–48.
3. M. Malmsten Surfactants and Polymers in Drug Delivery, Marcel Dekker, Inc. (2002).
4. Gannu PK, Rajeshwarrao P. Nonionic surfactant vesicular systems for effective drug delivery an overview. *Acta Pharmacol Sin*. 2011; 1: 208–219.
5. Pawar SD, Pawar RG, Kodag PP, Waghmare AS. Niosome: an unique drug delivery system. *International Journal of Biology, Pharmacy and Allied Sciences*. 2012; 3: 406–416.
6. Vyas SP, Khar RK. Novel carrier systems. In: Jain NK, editor. *Targeted and Controlled Drug Delivery*. New Delhi, India: CBS Publishers and Distributors Pvt Ltd; 2010.
7. Florence AT, Baillie AJ. Nonionic surfactant vesicles – alternatives to liposomes. In: Prescott LF, Nimmo WS, editors. *Novel Drug Delivery and its Therapeutic Application*. New York, NY, USA: John Wiley and Sons Ltd; 1989.
8. Thakur V, Arora S, Prashar B, Vishal P. Niosomes and liposomes – vesicular approach towards transdermal drug delivery. *International Journal of Pharmaceutical and Chemical Sciences*. 2012; 1: 981–993.
9. Nasr M, Mansour S, Mortada ND, Elshamy AA. Vesicular aceclofenac systems: a comparative study between liposomes and niosomes. *J Microencapsul*. 2008; 25: 499–512.
10. S. Bhaskaran and P. K. Lakshmi, "Comparative evaluation of niosome formulations prepared by different techniques," *Acta Pharmaceutica Sciencia*, 2009; 51(1): 27–32.

A. J. Baillie, A. T. Florence, L. R. Hume, G. T. Muirhead, and A. Rogerson, "The preparation and properties of niosomes non-ionic surfactant vesicles," *The Journal of Pharmacy and Pharmacology*, 1985; 37(12): 863–868.

11. S. Srinivas, Y. A. Kumar, A.Hemanth and M. Anitha, "Preparation and evaluation of niosomes containing aceclofenac," *Digest Journal of Nanomaterials and Biostructures*, 2010; 5(1): 249-254.

A. Marwa, S. Omaima, E. L. G. Hanaa, and A.-S. Mohammed, "Preparation and in-vitro evaluation of diclofenac sodium niosomal formulations," *International Journal of Pharmaceutical Sciences and Research*, 2013; 4(5): 1757–1765.

12. M. R. Mozafari, C. J. Reed and C. Rostron, "Cytotoxicity evaluation of anionic nanoliposomes and nanolipoplexes prepared by the heating method without employing volatile solvents and detergents," *Die Pharmazie*, 2007; 62(3): 205–209.

13. H. Talsma, M. J. Van Steenbergen, J. C. H. Borchert and D. J. A. Crommelin, "A novel technique for the one-step preparation of liposomes and nonionic surfactant vesicles without the use of organic solvents. Liposome formation in a continuous gas stream: the 'bubble' method," *Journal of Pharmaceutical Sciences*, 1994; 83(3): 276–280.

14. S. Moghassemi and A. Hadjizadeh, "Nano-niosomes as nanoscale drug delivery systems: an illustrated review," *Journal of Controlled Release*, 2014; 185(1): 22–36.

15. L. Tavano, R. Aiello, G. Ioele, N. Picci and R.Muzzalupo, "Niosomes from glucuronic acid-based surfactant as new carriers for cancer therapy: preparation, characterization and biological properties," *Colloids and Surfaces B: Biointerfaces*, 2014; 118: 7–13.

16. S.Moghassemi, E. Parnian, A. Hakamivala et al., "Uptake and transport of insulin across intestinal membrane model using trimethyl chitosan coated insulin niosomes," *Materials Science and Engineering C*, 2015; 46: 333–340.

17. H. Kiwada, H. Niimura, Y. Fujisaki, S. Yamada and Y. Kato, "Application of synthetic alkyl glycoside vesicles as drug carriers. I. Preparation and physical properties," *Chemical and Pharmaceutical Bulletin*, 1985; 33(2): 753–759.

A. S. Zidan, Z. Rahman and M. A. Khan, "Product and process understanding of a novel pediatric anti-HIV tenofovir niosomes with a high-pressure homogenizer," *European Journal of Pharmaceutical Sciences*, 2011; 44: 1-2, pp. 93–102.

18. S. Verma, S. K. Singh, N. Syan, P. Mathur and V. Valecha, "Nanoparticle vesicular systems: a versatile tool for drug delivery," *Journal of Chemical and Pharmaceutical Research*, 2010; 2(2): 496–509.

19. A.Manosroi, W. Ruksiriwanich, M.Abe, H. Sakai,W.Manosroi and J. Manosroi, "Biological activities of the rice bran extract and physical characteristics of its entrapment in niosomes by supercritical carbon dioxide fluid," *The Journal of Supercritical Fluids*, 2010; 54(2): 137–144.
20. L.D.Mayer, M. B. Bally, and P. R. Cullis, "Uptake of adriamycin into large unilamellar vesicles in response to a pH gradient," *Biochimica et Biophysica Acta (BBA)—Biomembranes*, 1986; 857(1): 123–126.
21. V. R. Yasam, S. L. Jakki, J. Natarajan and G. Kuppusamy, "A review on novel vesicular drug delivery: proniosomes," *Drug Delivery*, 2014; 21(4): 243–249.

A. K. Verma and J. C. Bindal, "A vital role of niosomes on controlled and novel drug delivery," *Indian Journal of Novel Drug Delivery*, 2011; 3: 238–246.

22. M. R. Mozafari, "A new technique for the preparation of nontoxic liposomes and nanoliposomes: the heating method," in *Nanoliposomes: From Fundamentals to Recent Developments*, pp. 91–98, Trafford Publishing, Oxford, UK, 2005.
23. Buckton G., Harwood, Interfacial phenomena in Drug Delivery and Targeting Academic Publishers, Switzerland. 1995; 154-155.
24. Suzuki K., Sokan K., The Application of Liposome's to Cosmetics. Cosmetic and Toiletries. 1990; 105: 65-78.
25. Pape WJ, Pfannenbecker U. Hoppe U. Validation of the red blood cell test system as in vitro assay for the rapid screening of irritation potential of surfactants. *Mol Toxicol*. 1987; 1: 525–536.
26. Handjani-Vila RM, Riber A, Rondot B, Valenberghe G. Aqueous dispersion. *Int J Cosmet Sci*. 1979; 1: 303–314.
27. Barel A, Paye M, Maibach HI. *Handbook of Cosmetic Science and Technology*. New York, NY, USA: Marcel Dekker Inc.; 2001.
28. Singh S. Niosomes: a role in targeted drug delivery system. *Int J Pharm Sci Res*. 2013; 4: 550–557.
29. Sahin NO. Niosomes as nanocarrier systems. In: Mozafari MR, editor. *Nanomaterials and Nanosystems for Biomedical Applications*. New York, NY, USA: Springer; 2007.
30. Hofland HE, Bouwstra JA, Verhoef JC, et al. Safety aspects of non-ionic surfactant vsicles: a toxicity study related to the physicochemical characteristics of non-ionic surfactants. *J Pharm Pharmacol*. 1992; 44: 287–294.

31. Tavano L, Infante MR, Abo Riya M, et al. Role of aggregate size in the hemolytic and antimicrobial activity of colloidal solutions based on single and gemini surfactants from arginine. *Soft Matter*. 2013; 9: 306–319.