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Effectual Drug delivery system of medicine- Niasomes

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Abstract- As a new system of drug delivery called Niosomes is more effective for targeted delivery of drug. In the last decade various researchers publish numbers of review and research articles on niosomes. This shows the large area of interest for researchers in niosomes because of the advantages provided by them over other vesicular carrier systems. Niosomes are formed by using non-ionic surfactant vesicles assemble themselves. There are various factors like the type of non-ionic surfactant used, the temperature of hydration, method of preparation, etc. affect formation of niasomes. this review artical covered all thus aspects regarding its merits demerits, factors affecting, composition of niosomes, method of preparation, ideal characters are covered.

Introduction

For numerous decades, drug of an acute complaint or a habitual illness has been fulfilled by delivering medicines to the cases via various pharmaceutical dose forms like tablets, capsules, capsules, creams, ointments, liquids, aerosols, injectables and suppositories as carriers. To achieve and also to maintain the attention of medicine administered within the therapeutically effective range demanded for drug, it's frequently necessary to take this type of medicine delivery systems several times in a day. This results in a changed medicine position and accordingly undesirable toxin and poor effectiveness. To minimize this fluctuation, novel drug delivery systems have been developed, which include niosomes, liposomes, nanoparticles, microspheres, microemulsions, impalatable pumps and magnetic microcapsules.[1-2]The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to get maximum efficacy of the medication. Different carriers have been used for targeting of drug, such as immunoglobulin, serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and niosomes.[3]

Niosomes are one of the stylish among these carriers. Structurally, niosomes are analogous to liposomes and also are equiactive in medicine delivery eventuality but high chemical stability and frugality makes niosomes superior than liposomes. Both correspond of bilayer, which is made up of non-ionic surfactant in the case of niosomes and phospholipids in case of liposomes. Niosomes are bit lamellar structures of size range between 10 to 1000 nm and consists of biodegradable, non-immunogenic and biocompatible surfactsnts[4]. The niosomes are ampiphillic in nature, which allows ruse of hydrophilic medicine in the core depression and hydrophobic medicines in the non-polar region present within the bilayer hence both hydrophilic and hydrophobic medicines can be incorporated into niosomes. The structure of niosomes is given below in Fig.No.1.[5]

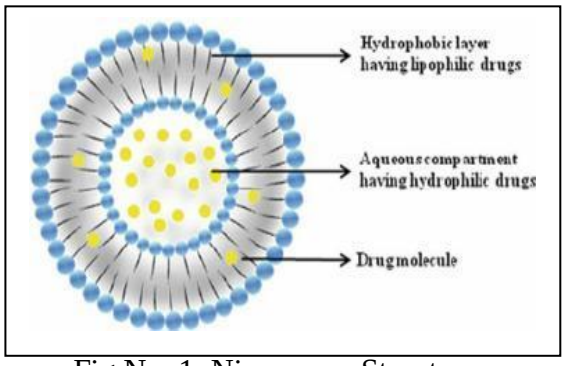

Fig.No. 1. Niaosomes Structure.

MERITS AND DEMERITS OF NIOSOMES

Merits of niosomes are following [6, 7, 8]:

- Niosomes can be novel drug dosage form for drug molecules having a wide range of solubility as their infrastructure consists of hydrophilic and hydrophobic part.
- Vesicles might be made to have different features by changing their size, composition, lamellarity, tapping volume, surface charge, and concentration.
- Since the vesicle suspension is a water-based vehicle, it offers better patient compliance than dosage forms that are oil-based. Niosomes with the desired properties can be obtained.
- By improving poorly absorbed drugs' oral bioavailability, delaying the removal of the drug from the circulation, and protecting the drug from the biological environment, they improve the therapeutic effectiveness of the drug molecules.
- They boost the stability of the medicine that has been entrapped and are osmotically active and stable. For their administration, oral, parenteral, as well as topical routes might be used.
- Niosomes are prepared using biodegradable, biocompatible, and non-immunogenic surfactants, and there are no specific handling or storage requirements for these substances.

The niosomes suffer certain demerits, which include the following[9]:

- Niosome aqueous solutions may have a short shelf life as a result of drug hydrolysis, fusion, aggregation, leakage, and leaking.
- Multilamellar vesicle preparation techniques like extrusion and sonication take time and may need specialist equipment to process.

FACTORS GOVERNING NIOSOME FORMATION:

Composition of niosome: The presence of a specific class of amphiphile and an aqueous solvent are required for niosome formation in theory, however in some situations cholesterol is needed in the formulation to provide the niosomes stiffness, the right shape, and conformation.. Cholesterol also stabilizes the system by prohibiting the formation of aggregates by repulsive steric or electrostatic effects.

Surfactant and lipid level: To make niosomal dispersions the surfactant/lipid level is generally kept 10-30 mM (1-2.5% w/w). If the surfactant, water ratio is altered during the hydration step may affect the microstructure of the system and it's properties. If we increasing the surfactant/lipid level the total amount of drug encapsulated also increases, but the viscosity level of system also increase11.

Nature of the encapsulated drug:

The nature of encapsulated drug influences the niosomal formation, generally the physico chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The encapsulated medication interacts with the head groups of the surfactant and forms a charge that causes mutual repulsion between the surfactant bilayers, increasing vesicle size and also causing vesicle aggregation., which is prevented by using electrostatic
stabilizers like dicetyl phosphate in 5(6)-carboxyfluorescein (CF)12.

Structure of surfactants:

The geometry of vesicle to be formed from surfactants is affected by surfactant's structure, which can be defined by critical packing parameters. Geometry of vesicle to be formed can be predicated on the basis of critical packing parameters of surfactants .

Critical packing parameters can be defined using following equation,

CPP (Critical Packing Parameters) = V/ lc× a0

Where v = hydrophobic group volume,

lc = the critical hydrophobic group length,

a0= the area of hydrophilic head group.

From the critical packing parameter value type of miceller structure formed can be ascertained as given below,

If CPP < ½ formation of spherical micelles,

If ½ < CPP < 1 formation of bilayer micelles,

If CPP > 1 formation inverted micelles[11,13]

Temperature of hydration:

Hydration temperature influences the shape and size of the niosome, temperature change of niosomal system affects assembly of surfactants into vesicles by which induces vesicle shape transformation. Ideally the hydration temperature for niosome formation should be above the gel to liquid phase transition temperature of system[14,15]

COMPOSITION OF NIOSOMES

The two main ingredients utilised to prepare niosomes are cholesterol and non-ionic surfactants. Cholesterol provides shape and stiffness. The development of niosomes is greatly influenced by the surfactants. The manufacture of niosomes often involves the use of non-ionic surfactants such as spans (span 20,40,60,85,80), tweens (tween 20,40,60,80), and brij (brij 30,35,52,58,72,76).16. Few other surfactants that are reported to form niosomes are as follows[17,18]:

- Ether linked surfactant
- Di-alkyl chain surfactant
- Ester linked
- Sorbitan Esters
- Poly-sorbates

METHOD OF PREPARATION:

Preparation of small unilamellar vesicles Sonication:

It is a typical method of production of the vesicles in which a 10-ml glass vial drug solution in buffer is added to the surfactant/cholesterol mixture. Then the mixture is probe sonicated at 60°C for 3 minutes using a sonicator with titanium probe to yield niosomes. The resulting vesicles are small and unilamellar[19]**.**

Micro fluidization:

It is a relatively new method that uses the submerged jet principle. Within the interaction chamber, two fluidized streams travel forward through a carefully defined micro channel while interacting at extremely high speeds. The arrangement of the thin liquid sheet impingement along a single front ensures that the energy supplied to the system stays in the region of niosome creation, leading to increased uniformity, smaller size, and improved reproducibility of the niosomes created.[20].

Preparation of multilamellar vesicles

Hand shaking method (Thin film hydration technique):

Surfactant and the other vesicles forming ingredients like cholesterol are blended and mixture is dissolved in a volatile organic solvent like diethyl ether, chloroform or methanol in a round bottom flask. Using rotary evaporator the organic solvent is removed at room temperature (20°C), by this a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 60°C with gentle agitation results in formation of multilamellar niosomes[19].

Trans-membrane pH gradient (inside acidic) drug uptake process (Remote Loading):
In a round-bottom flask blend of Surfactant and cholesterol are dissolved in chloroform and the chloroform is then evaporated under reduced pressure to obtain a thin film on the wall of the flask. The film is hydrated by vortex mixing with 300 mM citric acid (pH 4.0). The multilamellar vesicles are frozen and thawed three times and then sonicated. Aqueous solution containing 10 mg/ml of drug is added to this niosomal suspension and vortexed. With 1M disodium phosphate the pH of the sample is raised to 7.0- 7.2 and the mixture is then heated at 60°C for 10 minutes to produce the desired multilamellar vesicles[21, 22].

Preparation of large Unilamellar Vesicles

Reverse phase evaporation technique (REV):
In this procedure, a solution of ether and chloroform is combined with a 1:1 ratio of cholesterol and surfactant. Then, an aqueous phase containing a medication is introduced, and the two phases that arise are sonicated at 4-5°C. The transparent gel generated above is then sonicated while a little amount of phosphate buffer saline is added. The organic phase is eliminated under low pressure and 40 °C. The resulting viscous niosome suspension is diluted with phosphate buffer saline, and it is then heated in a water bath at 60°C for 10 minutes to produce niosomes.[23]

Ether injection method:
The surfactant mixture is first made as a solution, which is then gradually added to warm water kept at 60°C. A 14-gauge needle is used to inject the ether-surfactant mixture into the material's aqueous solution. The vaporisation of ether produces single-layered vesicles. Depending on the circumstances, vesicles with a diameter of 50–1000 nm can be produced. The main drawback of this approach is that a tiny amount of ether is frequently still present in the vesicle solution and might be challenging to eliminate.[24].

Miscellaneous
Multiple membrane extrusion method:
A blend of surfactant, cholesterol, and di acetyl phosphate is dissolved in chloroform and the solvent is evaporated leading to formation of thin film. Using aqueous drug solution the film is hydrated and the resultant suspension extruded through polycarbonate membranes, which are placed in a series for up to eight passages. This is a best method for controlling niosome size[24].

The "Bubble" Method:
It is one step technique by which liposomes and niosomes are prepared without the use of organic solvents. Round bottomed flask is used as bubbling unit with its 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. At 70°C Cholesterol and surfactant are dispersed together in the buffer (pH 7.4) and mixed with high shear homogenizer for 15 seconds and immediately afterwards "bubbled" at 70°C using nitrogen gas[10].

Formation of niosomes from proniosomes:
In this method of producing niosomes a water-soluble carrier such as sorbitol is coated with surfactant resulting in the formulation of dry formulation in which each watersoluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". Then proniosome powder is filled in a screw capped vial, and mixed with water or saline at 80 °C by vortexing, followed by agitation for 2 min results in the formation of niosomal suspension[25].

Emulsion method:
From an organic solution of surfactant, cholesterol, and aqueous solution of drug, oil in water (o/w) emulsion is prepared. The organic solvent is then evaporated, leaving niosomes dispersed in the aqueous phase[26,14].

Lipid injection method:
In this process, either mixture of lipids and surfactant is first melted and then injected into a highly agitated heated aqueous phase containing dissolved drug, or the drug can be dissolved in molten lipid and the mixture will be injected into agitated, heated aqueous phase containing surfactant. This method does not require expensive organic phase[22].

Niosome preparation using Micelle:
Niosomes may also be formed by the use of enzymes in a mixed micellar solution. A mixed micellar solution of C16G2, dicalcium hydrogen phosphate (DCP), polyoxyethylene cholesteryl sebacetate di ester (PCSD) when incubated with esterases converts to a noisome dispersion. PCSD is cleaved by the esterases action to yield polyoxyethylene, sebacic acid and cholesterol and then cholesterol in combination with C16 G2 and DCP then yields C16 G2 niosomes[22].

Niosome preparation using polyoxyethylene alkyl ether:
Charactersitics like the size and number of bilayers of polyoxyethylene alkyl ethers and cholestrol consisting vesicles can be changed in alternative way. Small unilamellar vesciles transforms to large multilamellar vesicles by temperature rise above 600° C, while multilamellar vesicles can be transformed into unilamellar ones by vigorous shaking at room temperature. It is the characteristics for the polyoxythelene alkyl ether surfactants to transfromation from unilamellar to multilamellar vesicles at higher temperature since it is known that polyethyleneglycol (PEG) and water at higher temperature demixes due to a breakdown of hydrogen bonding between water and PEG moieties[27].

Separation of Unentrapped Drug
Various techniques can be accomplished for the removal of unentrapped solute from the vesicles which include[25]:

- Dialysis
- Gel Filtration
- Centrifugation

CHARACTERISATION OF NIOSOMES Size:
Shape of niosomal vesicles is assumed to be spherical, and various techniques can be used for determination of their mean diameter like laser light scattering method, electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy and optical microscopy and freeze fracture electron microscopy[13,28,29,.]

Bilayer formation, Membrane rigidity and Number of lamellae:
Bilayer vesicle formation by assembly of non-ionic surfactants is characterized by X-cross formation under light polarization microscopy and membrane rigidity can be measured by means of mobility of fluorescence probe as function of temperature. NMR spectroscopy, small angle X-ray scattering and electron microscopy are used determine the no of lamellae[30,31.]

Entrapment efficiency:
As described above after preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation or gel filtration and/ or complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 is done for the estimation of the drug remained entrapped in niosomes and then analyzing the resultant solution by appropriate assay method for the drug.
Where, Entrapment efficiency (EF) can be defined by[11]:
Entrapment efficiency (EF) = (Amount entrapped/ total amount) x100.

***In vitro* Release Study**

Dialysis:
With the help of dialysis tubing *in vitro* release rate study can be done. A dialysis sac was washed and soaked in distilled water. The suspension of vesicle was pipetted into a bag made up of the tubing and then sealed and placed in 200 ml buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. The buffer was analysed at various time intervals, for the drug content by an appropriate assay method [32].

Reverse dialysis:
In this technique, niosomes are placed in a number of small dialysis tubes containing 1 mL of dissolution medium and the niosomes are then displaced from the dissolution medium[35].

Franz diffusion cell:
In a Franz diffusion cell, the cellophane membrane is used as the dialysis membrane. The niosomes are dialyzed through a cellophane membrane against suitable dissolution medium at room temperature. The samples are withdrawn at suitable time intervals and analyzed for drug content[37.]

***In vivo* Release Study**
For *in vivo* study niosomal suspension was injected intravenously (through tail vein) to the albino rats using appropriate disposal syringe. These rats were subdivided into groups[35].

FACTORS AFFECTING VESICLES SIZE, ENTRAPMENT EFFICIENCY, AND RELEASE CHARACTERISTICS:

Drug:
Vesicle size increases by entrapment of drug in niosomes, probably by increasing the charge and mutual repulsion of the surfactant bilayers or interaction of solute with surfactant head groups. But some drug is entrapped in the long PEG chains In case of polyoxyethylene glycol (PEG)-coated vesicles, thus tendency to increase the size reduces. The degree of entrapment is affected by hydrophilic lipophilic balance of the drug[23].

Amount and type of surfactant:
With increase in the hydrophilic-lipophilic balance (HLB) of surfactants such as Span 85 (HLB 1.8) to Span 20 (HLB 8.6) the mean size of niosomes increases proportionally, because with an increase in hydrophobicity of surfactants the surface free energy decreases. Depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol the bilayers of the vesicles are either in the so called liquid state or in gel state. When the structure of the bilayers is disordered it will be in liquid state and if alkyl chains are present in a well ordered structure it will be in the gel state. Entrapment efficiency is also affected by phase transition temperature of surfactants, for example Span 60 having higher phase transition temperature provides better entrapment[20].

Cholesterol content and charge:
Cholesterol increases the chain order of liquid state bilayers and also it decreases the chain order of gel state bilayers. The gel state is transformed to a liquid-ordered phase at a high cholesterol concentration. An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material, and therefore an increase in the rigidity of the resulting bilayers. The interlamellar distance between successive bilayers in multilamellar vesicle tends to increase due to presence of charge and leads to greater overall entrapped volume[34].

Methods of Preparation:
Ether injection method (50-1,000 nm) forms vesicles with small diameter than vesicles formed by Hand shaking method (0.35-13 nm). By Reverse Phase Evaporation (REV) method small-sized niosomes can be produced while by microfluidisation greater uniformity and smallsized vesicles are obtained[20].

Resistance to osmotic stress:
If in a suspension of niosomes hypertonic salt solution is added, reduction in diameter occurs. In hypotonic salt solution, probably due to inhibition of eluting fluid from vesicles, there is initial slow release with slight swelling of vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress.[3]

Applications
Numerous pharmacological treatments for the treatment of different diseases may be able to use niosomal drug delivery. Few of their therapeutic applications are as follows:
Targeting of bioactive agents

1. To reticulo-endothelial system (RES)
The vesicles occupy RES cells more frequently than other cell types. It results from circulating opsonins in the serum.which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver[35].

2. To organs other than reticulo-endothelial system (RES)

By use of antibodies, carrier system can be directed to specific sites in the body. Immunoglobulins seem to have affection to the lipid surface, thus providing a convenient means for targeting of drug carrier. Many cells have the intrinsic ability to recognize and bind particular carbohydrate determinants and this property can be used to direct carriers system to particular cells[36, 37].

Neoplasia

The anthracyclic antibiotic Doxorubicin, with broad spectrum anti tumour activity, shows a dose dependant irreversible cardio toxic effect. The half-life of the drug increased by its niosomal entrapment of the drug and also prolonged its circulation and its metabolism altered. If the mice bearing S-180 tumour is treated with niosomal delivery of this drug it was observed that their life span increased and the rate of proliferation of sarcoma decreased[38]. Methotrexate entrapped in niosomes if administered intravenously to S-180 tumour bearing mice results in total regression of tumour and also higher plasma level and slower elimination[39, 40].

Delivery of peptide drugs

Niosomal entrapped oral delivery of 9-desglycinamide, 8- arginine vasopressin was examined in an in-vitro intestinal loop model and reported that stability of peptide increased significantly[41].

Immunological applications of niosomes

For studying the nature of the immune response provoked by antigens niosomes have been used. Niosomes have been reported as potent adjuvant in terms of immunological selectivity, low toxicity and stability[42].

Niosome as a carrier for Hemoglobin

Niosomal suspension exhibits a visible spectrum that may be superimposed onto that of free haemoglobin and is therefore suitable for use as a haemoglobin carrier. Vesicles are also permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin[43].

Transdermal delivery of drugs by niosomes

An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes as slow penetration of drug through skin is the majordrawback of transdermal route of delivery for other dosage forms. The topical delivery of erythromycin from various formulations including niosomes has studied on hairless mouse and from the studies, and confocal microscopy, it was found that non-ionic vesicles could be formulated to target pilosebaceous glands[24].

Diagnostic imaging with niosomes

Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglcemine with [N-palmitoylglucosamine(NPG)],PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging[44].

Leishmaniasis therapy

Derivatives of antimony are most commonly prescribed drugs for the treatment of leishmaniasis. These drugs in higher concentrations – can cause liver, cardiac and kidney damage. Use of niosomes as a drug carrier showed that it is possible to overcome the side effects at higher concentration also and thus showed greater efficacy in treatment[34].

Niosome formulation as a brain targeted delivery system for the vasoactive intestinal peptide (VIP)

Radiolabelled (I125) VIP-loaded glucose-bearing niosomes were injected intravenously to mice. Encapsulated VIP within glucose-bearing niosomes exhibits higher VIP brain uptake as compared to control[45].

Ophthalmic drug delivery

From ocular dosage form like ophthalmic solution, suspension and ointment it is difficult to achieve excellent bioavailability of drug due to the tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But niosomal and liposomal delivery systems can be used to achieve good bioavailability of drug. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span

60, cholesterol stearylamine or dicetyl phosphate exhibits more tendencies for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide) [46].

Other Applications

a) Sustained Release

Drugs with low therapeutic index and low water solubility could be maintained in the circulation via niosomal encapsulation, through niosomes sustained release action can be obtained. Azmin *et al* 30 suggested the role of liver as a depot for methotrexate after niosomes are taken up by the liver cells.

b) Localized Drug Action

To achieve localized drug action, niosomal dosage form is one of the approaches because of the size of niosomes and their low penetrability through epithelium and connective tissue the drug localized at the site of administration. This results in enhancement of efficacy and potency of the drug and also reduces its systemic toxic effects e.g. Antimonials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity[10,34.]

CONCLUSION:

Neosomal drug delivery system is one of the examples of great evolution in drug delivery technologies. The concept of drug incorporation in the niosomes and to target the niosomes to the specific site is widely accepted by researchers and academicians. They represent alternative vesicular systems with respect to liposomes also having various advantages over liposomes like cost, stability etc. Niosomes represent a promising drug delivery technology and much research has to be inspired in this to juice out all the potential in this novel drug delivery system.

REFERENCES:

1. Yie W Chien: Concepts and System Design for Rate- Controlled Drug Delivery. Chapter 1 in Novel Drug Delivery
System, Marcel Dekker, Inc, New York, 2nd Edition 1992.P. l-42.
2. Yie W Chien: Rate-controlled Drug Delivery Systems. Ind J Pharm Sci 1988.P. 63-65.
3. Allen TM: Liposomal drug formulations: Rationale for development and what we can expect for the future. Drugs, 1998, (56), 747-756.
4. Handjani-vila RM: Dispersion of lamellar phases of nonionic lipids in cosmetic products. Int J Cosmetic Sci, 1979; 1**:** 303.
5. Mehta A: Niosomes. www.pharmainfo.net. 2009.
6. Biju SS, Telegaonar S, Mishra PR, Khar RK: Vesicular system: an overview, Indian J Pharm Sci, 2006, (68) 141- 153.
7. Vyas SP, Khar RK: Controlled drug delivery system: concept and advances.CBS Publishers and Distributors New Delhi, 2002.
8. Indhu PK, Garg A, Anil KS, Aggarwal D: Vesicular system in ocular drug delivery. Indian J Pharm Sci, 2004, (269), 1- 14.
9. Verma S, Singh SK, Navneet S, Mathur P, Valecha V: Nanoparticle vesicular systems: a versatile tool for drug delivery. J Chem Pharm Res, 2010.P.496-509.
10. Chauhan S, Luorence MJ, The preparation of polyoxyethylene containing non-ionic surfactant vesicles. J Pharm Pharmacol, 1989, (41), 6.
11. Alemayehu Tarekegn, Nisha M Joseph, S Palani, Anish Zacharia, Zelalem Ayenew: niosomes in targeted drug delivery: some recent advances. IJPSR, 2010, (9), 1-8.
12. Stafford S, Ballie AJ, Florence AT: Drug effect on the size of chemically defined nonionic surfactant vesicles. J Pharm Pharmacol, 1988, (26), 40.
13. Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F: Vesicles of Non-ionic Surfactants (Niosomes) and Drug Delivery Potential. International Journal of Pharmaceutical Sciences and Nanotechnology, 2008, (1), 1-8.
14. Uchegbu FI, Vyas PS, Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm, 1998, (33), 172.
15. Arunothayanun P *et al*: The effect of processing variables on the physical characteristics of nonionic surfactant vesicles (niosomes) formed from hexadecyl diglycerol ether. Int J Pharm, 2000, (7), 201.
16. Parthasarathi G, Udupa N, Umadevi P, Pillai GK: Niosome encapsulated of vincristine sulfate: improved anticancer activity with reduced toxicity in mice. J Drug Target,1994, (2), 173-182.
17. Rogerson A, Cummings J, Willmott N and Florence AT: The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol, 1988, (40), 337-342.

18. Pranshu Tangri, Shaffi Khurana; Niosomes: formulation and evaluation. International Journal of Biopharmaceutics, 2011, (2), 47-53.
19. Baillie AJ, Coombs GH, Dolan TF: Non-ionic surfactant vesicles, niosomes, as delivery system for the antileishmanial drug, sodium stribogluconate. J Pharm Pharmacol, 1986, (38), 502-505.
20. Khandare JN, Madhavi G, Tamhankar BM: Niosomes Novel Drug Delivery System. The Eastern Pharmacist, 1994, (37), 61-64.
21. Mayer LD, Bally MB, Hope MJ, Cullis PR: Uptake of antineoplastic agents into large unilamellar vesicles in response to a membrane potential. Biochem Biophys Acta, 1985, (816), 294-302.
22. Kazi Masud Karim, Asim Sattwa Mandal, Nikhil Biswas, Arijit Guha, Sugata Chatterjee, Mamata Behera: Niosome: A future of targeted drug delivery systems. J Adv Pharm Tech Res, 2011, (62), 122.
23. Raja Naresh RA, Chandrashekhar G, Pillai GK, Udupa N: Antiinflammatory activity of Niosome encapsulated diclofenac sodium with Tween -85 in Arthitic rats. Ind J Pharmacol, 1994, (26), 46-48.
24. Jayaraman SC, Ramachandran C, Weiner N: Topical delivery of erythromycin from various formulations: An *in vivo* hairless mouse study. J Pharm Sci, 1996, (85), 1082-1084.
25. Blazek Welsh AI, Rhodes DG: SEM Imaging Predicts Quality of Niosomes from Maltodextrin-Based Proniosomes. Pharm Res, 2001, (18), 656-661.
26. Hao Y, Zhao F, Li N, Yang Y, Li K: Studies on a high encapsulation of colchicines by a noisome system. Int J Pharm, 2002, (244), 73-80.
27. Kaneshina S, Shibata O, Nakamura M: The effect of pressure on the mutual solubility of anonionic surfactant water system. Bull Chem Soc Japan, 1982, (55), 951-952.
28. Almira I, Blazek-welsh IA, Rhodes GD: Maltodextrin – Based proniosomes. AAPS Pharm Sci Tech, 2001, (3), 1-8.
29. Manosroi A: Characterization of Vesicles Prepared with Various Nonionic Surfactants mixed with Cholesterol. Colloids and surfaces Biointerfaces, 2003.P.129.
30. Azmin MN, Florence AT, Handjani-Vila RM, Stuart JF, Vanlerberghe G, Whittaker JS: The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. J Pharm Pharmacol, 1985, (37), 237-242.
31. Kreuter J: Colloidal Drug Delivery System of Niosome, Dekker series, Dekker publication .P.66-73.
32. Yoshioka T, Sternberg B, Florence AT: Preparation and properties of vesicles (niosomes) of sobitan monoesters (Span 20, 40, 60, and 80) and a sorbitan triester (Span 85). Int J Pharm, 1994, (105),1-6.
33. Attaullah Khan, Pramod Kumar Sharma, Sharad Visht, Rishabha Malviya: Niosomes as colloidal drug delivery system: a review. Journal of Chronotherapy and Drug Delivery, 2011, (40), 15-21.
34. Hunter CA, Dolan TF, Coombs GH and Baillie AJ: Vesicular systems (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. J Pharm Pharmacol, 1988, (40), 161-165.
35. Malhotra M, Jain NK: Niosomes as Drug Carriers. Indian Drugs, 1994, (31), 81-86.
36. Gregoriadis G: Targeting of drugs: implications in medicine. Lancet, 1981, (2), 241-246.
37. Weissman G *et al*: General method for the introduction of enzymes, by means of immunoglobulincoated liposomes, into lysosomes of deficient cells. Proc Natl Acad Sci, 1975, (72), 88-92.
38. Cummings J, Staurt JF, Calman KC: Determination of adriamycin, adriamycinol and their 7-deoxyaglycones in human serum by high performance liquid chromatography. J Chromatogr, 1984, (311), 125-133.
39. Chandraprakash KS *et al*: Formulation and evaluation of Methotrexate niosomes. Ind J Pharm Sci, 1992, (54), 197.
40. Suzuki K, Sokan K: The Application of Liposomes to Cosmetics. Cosmetic and Toiletries, 1990,(105), 65-78.
41. Yoshida H *et al*: Niosomes for oral de-livery of peptide drugs. J Control Rel, 1992, (21), 145–153.
42. Brewer JM and Alexander JA: The adjuvant activity of nonionic surfactant vesicles (niosomes) on the BALB/c humoral response to bovine serum albumin. Immunology, 1992, (75), 570-575.
43. Moser P *et al*: Niosomes d'hémoglobine, Preparation, proprietes physicochimiques oxyphoriques, stabilite. Pharma Acta Helv, 1989, (64), 192-202.
44. Luciani A: Glucose Receptor MR Imaging of Tumors: Study in Mice with PEGylated Paramagnetic Niosomes. J Radiology, 2004, (2), 135.
45. Dufes C *et al*: Glucose-targeted niosomes deliver vasoactive intestinal peptide (VIP) to brain. Int J of Pharm, 2004, (285), 77.
46. Aggarwal D *et al*: Development of topical niosomal preparation of acetazolamide: preparation and evaluation. J Pharm Pharmacol, (2004), 56: 1509.