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NIOSOME: A NANO-TARGETED DRUG DELIVERY SYSTEM

Sadhana Noothi*

India.

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***Corresponding Author**
Sadhana Noothi
India.

INTRODUCTION

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.

Niosomes are one of the best among these carriers. The self-assembly of non-ionic surfactants into vesicles was first reported in the 70s by researchers in the cosmetic industry. Niosomes (non-ionic surfactant vesicles) obtained on hydration are microscopic lamellar structures formed upon combining non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class with cholesterol.

The non-ionic surfactants form a closed bilayer vesicle in aqueous media based on its amphiphilic nature using some energy for instance heat, physical agitation to form this structure. In the bilayer structure, hydrophobic parts are oriented away from the aqueous solvent, whereas the hydrophilic heads remain in contact with the aqueous solvent. The properties of the vesicles can be changed by varying the composition of the vesicles, size, lamellarity, tapped volume, surface charge and concentration. Various forces act inside the vesicle, eg, van der Waals forces among surfactant molecules, repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc.

These forces are responsible for maintaining the vesicular structure of niosomes. But, the stability of niosomes are affected by type of surfactant, nature of encapsulated drug, storage temperature, detergents, use of membrane spanning lipids, the interfacial polymerisation of surfactant monomers *in situ*, inclusion of charged molecule. Due to presence of hydrophilic, amphiphilic and lipophilic moieties in the structure, these can accommodate drug molecules with a wide range of solubility. These may act as a depot, releasing the drug in a controlled manner. The therapeutic performance of the drug molecules can also be improved by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells. Noisome made of alpha, omega-hexadecyl-bis-(1-aza-18-crown-6) (Bola-surfactant)-Span 80-cholesterol (2:3:1 molar ratio) is named as Bola-Surfactant containing noisome. The surfactants used in niosomes preparation should be biodegradable, biocompatible and non-immunogenic.

A dry product known as proniosomes may be hydrated immediately before use to yield aqueous niosome dispersions. The problems of niosomes such as aggregation, fusion and leaking, and provide additional convenience in transportation, distribution, storage, and dosing Niosomes behave *in vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. As with liposomes, the properties of niosomes depend on the composition of the bilayer as well as method of their production. It is reported that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation, and thus entrapment efficiency.

However, differences in characteristics exist between liposomes and niosomes, especially since niosomes are prepared from uncharged single-chain surfactant and cholesterol, whereas liposomes are prepared from double-chain phospholipids (neutral or charged). The concentration of cholesterol in liposomes is much more than that in niosomes. As a result, drug entrapment efficiency of liposomes becomes lesser than niosomes. Besides, liposomes are expensive, and its ingredients, such as phospholipids, are chemically unstable because of their predisposition to oxidative degradation; moreover, these require special storage and handling and purity of natural phospholipids is variable.

APPLICATIONS

The application of niosomal technology is widely varied and can be used to treat a number of diseases. Niosomes as.

Drug Carriers

Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for X-ray imaging. Topical niosomes may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

Drug Targeting

One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticuloendothelial system. The reticulo-endothelial system (RES) preferentially takes up niosome vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infections of the liver. Niosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to niosomes (as immunoglobulin's bind readily to the lipid surface of the niosome) to target them to specific organs.

Anti-neoplastic Treatment

Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half-life of the drug, thus decreasing the side effects of the drugs. Niosomes are decreased rate of proliferation of tumor and higher plasma levels accompanied by slower elimination.

Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment.

Delivery of Peptide Drugs

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in vitro study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.

Use in Studying Immune Response

Due to their immunological selectivity, low toxicity and greater stability; niosomes are being used to study the nature of the immune response provoked by antigens. Nonionic surfactant vesicles have clearly demonstrated their ability to function as adjuvant following parenteral administration with a number of different antigens and peptides.

Niosomes as Carriers for Haemoglobin

Niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anaemic patients.

Other Applications

a) Sustained Release

Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation.

b) Localized Drug Action

Drug delivery through niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration.

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 Table1. The self-assembly of nonionic surfactants in aqueous media results in closed bilayer structures (Figure1). 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 surfactants ensure that hydrophilic termini point outwards and are in contact with water. The assembly into closed.

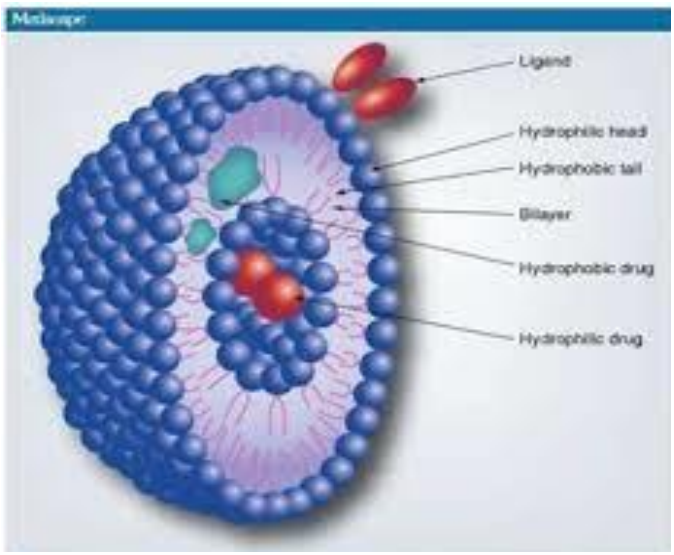

Figure1: Structure of niosomes.

Bilayers usually require 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)(10–100nm)
Large unilamellar vesicles(LUV) (100–3000nm),
Multilamellar vesicles (MLV)
where more than one bilayers are present.

1. Nonionic Surfactants

Nonionic surfactants are a class of surfactants, which have no charged groups in their hydrophilic heads. They are more stable and biocompatible and less toxic compared to their anionic, amphoteric, or cationic counterparts. Therefore, they are preferred for formation of stable niosome for in vitro and in vivo applications Nonionic surfactants are amphiphilic molecules that comprise two different regions: one of them is hydrophilic (water-soluble) and the other one is hydrophobic (organic soluble). Alkyl ethers, alkyl esters, alkyl amides, fatty acids are the main nonionic surfactant classes used for niosome production. The hydrophilic-lipophilic balance (HLB) and critical packing parameter (CPP) values play a critical role in the selection of surfactant molecules for niosome preparation.

1.1. Hydrophilic-Lipophilic Balance (HLB). HLB is a dimensionless parameter, which is the indication of the solubility of the surfactant molecule. The HLB value describes the balance between the hydrophilic portion to the lipophilic portion of the nonionic surfactant. The HLB range is from 0 to 20 for nonionic surfactants. The lower HLB refers to more lipophilic

surfactant and the higher HLB to more hydrophilic surfactant. Surfactants with a HLB between 4 and 8 can be used for preparation of vesicle. Hydrophilic surfactants with aHLBvalueranging from 14 to 17 arenotsuitabletoforma bilayer membrane due to their high aqueous solubility. However, with the addition of an optimum level of cholesterol, niosomes are indeed formed from polysorbate 80 (HLB value = 15) and Tween 20 (HLB value = 16.7). Tween20 forms stable niosome in the presence of equimolar cholesterol concentration. The interaction occurs between the hydrophobic part of the amphiphile next to head group and the 3-OH group of cholesterol at an equimolar ratio and this interaction could explain the effect of cholesterol on theformationandhydrationbehaviorofTween20niosomal membranes. Drug entrapment efficiency of the niosomes is also affected by HLB value of surfactant. Shahiwala et al. have incorporated nimesulide in to niosomes using lipid film hydration technique by changing the HLB. They found that as the HLB value of surfactant decreases from 8.6 to 1.7, entrapment efficiency decreases.

1.2. Critical Packing Parameter(CPP). During the niosomal preparation, the geometry of the vesicle depends upon the critical packing parameter. On the basis of the CPP of a surfactant, the shape of nano structures formed by self-assembly of amphiphilic molecules can be predicted. Critical packing parameter depends on the symmetry of the surfactant and can be defined using following equation:

$$\text{CPP} = \frac{v}{lc \times ao} \quad (1)$$

Where V is hydrophobic group volume, lc is the critical hydrophobic group length, and $a0$ is the area of hydrophilic head group. If CPP ≤ 1/3 corresponding, for example, to a bulky head group, small hydrophobic tail spherical micelles may form. Non-spherical micelles may form if 1/3 ≤ CPP ≤ 1/2, and bilayer vesicles can occur if 1/2 ≤ CPP ≤ 1. Inverted micelles form if CPP ≥ 1 when the surfactant is composed of a voluminous tail and a small hydrophobic tail. CPP could be considered as a tool for realizing, rationalizing and predicting the self-assembled structure and its morphological transition in amphiphilic solutions.

1.2. Cholesterol

In the bilayer structure of niosomes, cholesterol forms hydrogen bonds with hydrophilic head of a surfactant. Cholesterol content of niosomes thereby influences the structures of niosomes and physical properties such as entrapment efficiency, long time stability, release of payload, and biostability. Cholesterol improves the rigidity of vesicles and stabilizes niosomes towards

destabilizing effects induced by plasma and serum components and decreases the permeability of vesicles for entrapped molecules thus inhibiting leakage. Drug entrapment efficiency plays an important role in niosomal formulations and it can be altered by varying the content of cholesterol.

Agarwal et al. demonstrated that cholesterol improves the stability of enoxacin loaded niosome with increasing cholesterol content, resulting in increases of entrapment efficiency. The effect of cholesterol on flurbiprofen entrapment was studied by Mokhtar et al. and cholesterol was found to have little effect on the flurbiprofen entrapment into Span 20 and Span 80 niosomes. However, a significant increase in entrapment efficiency of flurbiprofen was obtained when 10% of cholesterol was incorporatedinto niosomes prepared from Span 40 and Span 60 followed by a decrease in encapsulation efficiency of the drug upon further increase in cholesterol content. According to the reported results, the addition of cholesterol and its amount needs to be optimized depending on the physical-chemical characteristic of surfactants and loaded drugs.

1.3. Charged Molecule

Charged molecules increase the stability of the vesicles by the addition of charged groups to the bilayer of vesicles. They increase surface charge density and thereby prevent vesicles aggregation. Dicetyl phosphate and phosphatidic acid are most used negatively charged molecules for niosome preparation and, similarly, stearylamine and stearyl pyridinium chloride are well known positively charged molecules used in niosomal preparations. Normally, the charged molecule is added in niosomal formulation in an amount of 2.5–5mol%. However, increasing the amount of charged molecules can inhibit niosome formation.

Methods of Preparation

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. Multi lamellar niosomes are formed by this method.

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.

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.

Micro fluidization Method

The micro fluidization method is based on submerged jet principle. In this method, the drug and the surfactant fluidized streams interact at ultra-high 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.

Supercritical Carbon Dioxide Fluid(scCO2)

Manosroi et al. have described the supercritical reverse phase evaporation technique for noisome formation. 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. This method enables one step production and easy scale-up.

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.

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 around 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 noisome 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. According to this method, the interior of noisome has a more acidic pH value than the outer medium. The added unionized drug passes through the noisome membrane and enters into the noisome. The drug ionizes in an acidic medium and cannot escape from the niosomal bilayer.

Heating Method

This is a patented method which was created by Mozafarietal. 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.

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 thebubblingofnitrogengasat70◦C. Nitrogen gas is passed through a sample of homogenized surfactants resulting in formation of large unilamellar vesicles.

Niosomes as Nano- Drug Carriers

Targeted Delivery

The efficiency and particularly the specificity of cellular targeting of niosomal drug delivery systems can be further improved by active targeting for tumor therapy, by using a ligand coupled to the surface of niosomes, which could be actively taken up, for example, via a receptor-mediated endocytosis. Niosome surfaces can be conjugated with small molecules and/or macromolecular targeting ligands to enable cell specific targeting. Proteins and peptides, carbohydrates, aptamers, antibodies, and antibody fragments are the most

commonly used molecules that bind specifically to an overexpressed target on the cell surface.

Bragagni et al. developed brain targeted niosomal formulation using with the glucose derivative as a targeting ligand. They formulated niosomal doxorubicin composed of span:cholesterol:solulan: Npalmitoyl glucosamine. Preliminary in vivo studies in rats showed that intravenous administration of a single dose of the developed targeted-niosomal formulation with respect to the commercial one was able to significantly reduce the hearth accumulation of the drug and to keep it longer in the blood circulation and also to allow the achievement of well detectable doxorubicin brain concentrations.

Moreover, an efficient tumor-targeted niosomal delivery system was designed by Tavano et al. Niosomes were prepared from a mixture of Pluronic L64 surfactant and cholesterol and doxorubicin was entrapped into the noisome. After the preparation, transferrin was conjugated to niosomessurfaceusingEDC(N-[3-(dimethylamino)propyl]-Nethylcarbodiimide hydrochloride) chemistry. Doxorubicin loaded noisome anticancer activity was achieved against MCF-7andMDA-MB-231tumor cell lines, and a significant reduction in viability in a dose and time related manner was observed.

Targeted to reticulo-endothelial system (RES)

The vesicles occupy preferentially to the cells of RES. It is due to circulating serum factors known as opsonins, 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.

To organs other than reticulo-endothelial system(RES)

16,17 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.

Delivery of peptide drugs

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

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.

Niosome as a carrier for Hemoglobin

Niosomal suspension shows a visible spectrum super imposable onto that of free hemoglobin so can be used as a carrier for hemoglobin. Vesicles are also permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin.

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 major drawback of transdermal route of delivery for other dosage forms.

The topical delivery

Of erythromycin from various formulations including niosomes has studied on hair less mouse and from the studies, and confocal microscopy, it was found that nonionic vesicles could be formulated to target pilosebaceous glands.

Diagnostic imaging with niosomes

Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenatedimeglcemine with[N-palmitoyl glucosamine (NPG)], PEG4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.

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. Bio adhesive-

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).

CONCLUSIONS

Niosomes may enable targeting certain areas of the mammalian organisms and may be exploited as diagnostic imaging agents. Niosomes are superior systems when compared to other carriers with respect to stability, toxicity and cost-effectiveness. The problem of drug loading remain to be addressed and although some new approaches have been developed to overcome this problem, it is still necessary to increase encapsulation efficiencies as it is important to maintain the biological potential of the formulations. As type of surfactant is the most important parameter affecting the formation of the vesicles, as well as their toxicity and stability, the surfactants with the higher phase transition should be selected as they yield more desirable permeability and toxicity profiles.

Niosomal drug delivery system is one of the examples of great evolution in drug delivery technologies. Niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. The concept of incorporating the drug into niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers. Niosomes represent a promising drug delivery module. They present a structure similar to liposome. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral.

REFERENCES

1. Malhotra M, Jain NK. Niosomes as drug carriers. Indian Drugs., 1994; 31: 81–6.
2. Udupa N. Niosomes as drug carriers. In: Jain NK, editor. Controlled and novel drug delivery. 1st edition. New Delhi: CBS Publishers and Distributors; 2002.
3. Hu C, Rhodes DG. Proniosomes: A Novel Drug Carrier Preparation. Int J Pharm., 1999; 185: 23–35.
4. Baillie AJ, Coombs GH, Dolan TF, Laurie J. Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmanial drug, sodium stibogluconate. J Pharm Pharmacol., 1986; 38: 502–5.

5. Jayaraman SC, Ramachandran C, Weiner N. Topical delivery of erythromycin from various formulations: An *in vivo* hairless mouse study. J Pharm Sci., 1996; 85: 1082–4.
6. Uchegbu IF, Vyas SP. Non-ionic surfactant-based vesicles (niosomes) in drug delivery. Int J Pharm., 1998; 172: 33–70.
7. L. Tavano, L. Gentile, C. Oliviero Rossi, and R. Muzzalupo, "Novel gel-niosomes formulations as multi component systems for transdermal drug delivery," Colloids and Surfaces B: Bio-interfaces, 2013; 110: 281–288.
8. K.B. Bini, D. Akhilesh, P. Prabhakara, and K. Jv, "Development and characterization of non-ionic surfactant vesicles (niosomes) for oral delivery of lornoxicam, International Journal of Drug Development and Research, 2012; 4(3): 147–154.
9. Q. Li, Z.Li, W. Zengetal., "Proniosome-derived niosomes for tacrolimus topical ocular delivery: in vitro cornea permeation, ocular irritation, and in vivo anti-allograft rejection," European Journal of Pharmaceutical Sciences, 2014; 62: 115–123.
10. Z. S. Bayindir, A. Be¸ sikci, and N. Y¨uksel, "Paclitaxel-loaded niosomes for intravenous administration: pharmacokinetics and tissue distribution in rats," Turkish Journal of Medical Sciences, 2015; 45(6): 1403–1412.
11. C. Marianecci, F. Rinaldi, M. Mastriotaetal., "Anti-inflammatory activity of novel ammonium glycyrrhizinate/niosomes delivery system: human and murine models," Journal of Controlled Release, 2012; 164(1): 17–25.
12. S.K. Mehtaand N. Jindal, "Tyloxapol niosomes as prospective drug delivery module for antiretroviral drug nevirapine," AAPS Pharm Sci Tech, 2014; 16(1): 67–75.
13. P. Arunothayanun, M.-S. Bernard, D.Q.M.Craig, I.F.Uchegbu, and A. T. Florence, "The effect of processing variables on the physical characteristics of non-ionic surfactant vesicles (niosomes) formed from a hexa-decyl di -glycerol ether," International Journal of Pharmaceutics, 2000; 201(1): 7–14.
14. A. Pardakhty, J.Varshosaz, and A.Rouholamini, "Invitro study of poly oxyethylene alkyl ether niosomes for delivery of insulin," International Journal of Pharmaceutics, 2007; 328(2): 130– 141.
15. M. Manconi, D. Valenti, C. Sinico, F. Lai, G. Loy, and A. M. Fadda, "Niosomes as carriers for tretinoin:II. Influence of vesicular incorporation on tretinoin photostability," International Journal of Pharmaceutics, 2003; 260(2): 261–272.
16. Z. S. Bayindir and N. Yuksel, "Characterization of niosomes prepared with various nonionic surfactants for paclitaxel oral delivery," Journal of Pharmaceutical Sciences, 2010; 99(4): 2049–2060.

17. C. P. Jain and S. P. Vyas, “Preparation and characterization of niosomes containing rifampicin for lung targeting,” Journal of Microencapsulation, 1995; 12(4): 401–407.
18. S. Mandal, C. Banerjee, S. Ghosh, J. Kuchlyan, and N. Sarkar, “Modulation of the photophysical properties of curcumin in nonionic surfactant (Tween-20) forming micelles and niosomes: a comparative study of different microenvironments,” The Journal of Physical Chemistry B, 2013; 117(23): 6957– 6968.
19. L. Di Marzio, C. Marianecci, M. Petrone, F. Rinaldi, and M. Carafa, “Novel pH-sensitive non-ionic surfactant vesicles: comparison between Tween 21 and Tween 20,” Colloids and Surfaces B: Bio-interfaces, 2011; 82(1): 18–24.
20. M. Imran, M.R. Shah F. Ullahetal., “Glycoside-based niosomal nanocarrier for enhanced in-vivo performance of Cefixime,” International Journal of Pharmaceutics, 2016; 505(1-2): 122– 132.
21. M. Manconi, C. Sinico, D. Valenti, F. Lai, and A. M. Fadda, “Niosomes as carriers for tretinoin: III. A study into the in vitro cutaneous delivery of vesicle-incorporated tretinoin,” International Journal of Pharmaceutics, 2006; 311(1-2): 11–19.
22. P. Bandyopadhyayand M. Johnson, “Fatty alcohols or fatty acids as niosomal hybrid carrier: effect on vesicle size, encapsulation efficiency and in vitro dye release,” Colloids and Surfaces B: Biointerfaces, 2007; 58(1): 68–71.
23. L. Tavano, R. Muzzalupo, L. Mauro, M. Pellegrino, S. And`o, and N. Picci, “Transferrin-conjugated Pluronic niosomes as a new drug delivery system for anticancer therapy,” Langmuir, 2013; 29(41): 12638–12646.
24. R. Muzzalupo, L. Tavano, R.Cassano, S. Trombino, T.Ferrarelli, and N. Picci, “A new approach for the evaluation of niosomes as effective transdermal drug delivery systems,” European Journal of Pharmaceutics and Biopharmaceutics, 2011; 79(1): 28–35.
25. M. Bragagni, N. Mennini, S. Furlanetto, S. Orlandini, C. Ghelardini, and P. Mura, “Development and characterization of functionalized niosomes for brain targeting of dynorphin-B,” European Journal of Pharmaceutics and Biopharmaceutics, 2014; 87(1): 73–79.
26. S.P. Vyas, R.P. Singh, S. Jainetal., “Non-ionic surfactant based vesicles (niosomes) fornon-invasivetopical geneticimmunization againsthepatitis B,” International Journal of Pharmaceutics, 2005; 296(1-2): 80–86.
27. A. Sankhyan and P. Pawar, “Recent trends in noisome as vesicular drug delivery system,” Journal of Applied Pharmaceutical Science, 2012; 2(6): 20–32.

28. V. B. Junyaprasert, V. Teeranachaideekul, and T. Supaperm, “Effect of charged and non-ionic membrane additives on physicochemical properties and stability of niosomes,” AAPS Pharm Sci Tech, 2008; 9(3): 851–859.
29. M. Bragagni, N. Mennini, C.Ghelardini, and P. Mura, “Developmentand characterization of niosomal formulations of doxorubicin aimed at brain targeting,” Journal of Pharmacy and Pharmaceutical Sciences, 2012; 15(1): 184–196.
30. C. Dufes, F. Gaillard, I. F. Uchegbu, A. G. Sch¨atzlein, J.-C. Olivier and J.-M. Muller, “Glucose-targeted niosomes deliver vasoactive intestinal peptide (VIP) to the brain,” International Journal of Pharmaceutics, 2004; 285(1-2): 77–85.