Received: Nov 12, 2010
Accepted: Dec 6, 2010

Special Focus: Colloidal Drug Delivery (Article 2)

NIOSOMES AS COLLOIDAL DRUG DELIVERY SYSTEM: A REVIEW

Attaullah Khan*, Pramod Kumar Sharma, Sharad Visht, Rishabha Malviya

Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology,

NH-58, Baghpat By-pass Crossing, Delhi-Haridwar Highway, Meerut-250005 (India)

* Corresponding author. Tel: +91-121-2439019; Fax: +91-121- 2439058;

E mail: atta.khan0313@gmail.com

Abstract

Niosomes are microscopic lamellar structures ranging between 10 to 1000 nm constitute of non-ionic surfactant and cholesterol. Niosomes are unilamellar or multilamellar depending on method of preparation. Both hydrophilic and hydrophobic drug can be incorporated into it. Liposomes and niosomes are equally active in drug delivery system. Both have same physical properties but chemically differ in monomers units. Liposomes constitute of phospholipids were as niosomes constitute of non- ionic surfactant. Niosomes are preferred over liposome due to chemicals stability and economy. The niosomes having bilayer which is ampiphillic in nature, means that polar region which exposed outside and inside the vesicles where will be hydrophilic drug will entrapped, non-polar region present within the bilayer where hydrophobic drug entrapped. This review article deals with properties, merit and demerit, surfactant for vesicles, method of preparation, separation of unentrapped niosomes, determination of characteristics of niosomes, stability, toxicity and application of niosomes.

Key Words: Biodegradable, Colloidal drug delivery, transdermal drug delivery

Introduction

For past decades, the of acute or chronic disease mostly commonly treated by the delivery of drug to patients by using various pharmaceutical formulation such as capsules, pills, creams, tablets, suppositories, ointments, liquids, aerosols, and injections. But to maintain the drug concentration within the therapeutically effective range for treatment, it is necessary to take the dosage forms several times a day, resulting in significant fluctuations of drug levels in the body. To minimize this fluctuation, novel drug delivery systems have been developed, which include niosomes, liposomes, nanoparticles, microspheres, micro-emulsions, impalatable pumps and magnetic microcapsules.

Liposomes and niosomes are equally active as drug delivery systems. Both have chemical differences in monomer units, but have similar physical properties. Liposomes contain phospholipids, whereas niosomes contains non- ionic surfactants. Niosomes are preferred over liposomes due to chemicals stability and economy.[1] Niosomes are essentially non-ionic surfactants and are multilamellar or unilamellar vesicles depending on the preparation method. In niosomes, an aqueous solution of drug is entirely enclosed in a bilayer of non-ionic surfactant.[2,3]

Properties of Niosomes

Niosomes are microscopic lamellar structures of size range between 10 to 1000 nm and constituted from non-ionic surfactant and cholesterol.

Structurally, niosomes are similar to liposomes. Both are made up of bilayer, which is made up of non-ionic surfactant in the case of niosomes and phospholipids in case of liposomes. Both hydrophilic and hydrophobic drugs can be incorporated into niosomes. The niosomes are ampiphillic in nature, which allows entrapment of hydrophilic drug in the core cavity and hydrophobic drugs in the non-polar region present within the bilayer. The structure of niosomes is given in Fig. 1.[4]

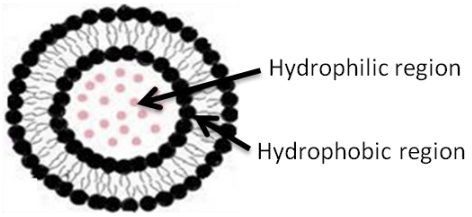

Fig. 1. Structure of niosomes

Merits and demirits of niosomes

Following are the merits of niosomes:[5,6,7]-

1. They release the drug in sustained / controlled manner.
2. They enhance the bioavailability of drug, particularly, in ocular delivery system.
3. They have stable structure even in emulsion form.
4. They do not require special conditions such as low temperature or inert atmosphere.
5. They have ability to entrap both hydrophilic and hydrophobic drugs.
6. Niosomes are non-toxic, biodegradable, and non-immunogenic.
7. They are economic for large scale production.
8. They protect the drug from enzyme metabolism.

The niosomes suffer certain demerits, which include the following:[8]

1. The aqueous suspensions of niosomes may undergo fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs, which lead to limited shelf life.
2. The methods of preparation of multilamellar vesicles such as extrusion, sonication, are time consuming and may require specialized equipments for processing.

Preparation of niosomes

Vesicles of niosomes are prepared using surfactants. The surfactants used in the preparation of niosomes include alkyl and dialkyl polyglycerol ethers, PEG–polyglycerol and dialkylpolyethylene ethers, dialkylpolyglycerol and polyoxyethylene ethers. Other bilayer forming amphiphilic substances are steroidal oxyethylene ethers, laurate ethers, alkyl galactosides, sorbitan monooleate and polyoxyethylated hydrogenated castor oil.

Different methods used for the preparation of niosomes are described below:[2,3,15-22]

Ether injection

This method is essentially based slow injection of surfactant: cholestrol solution in ether through a suitable needle at approximately 0.25 mL/min into preheated aqueous phase maintained at 60 °C, where vaporization leads to formation of unilamellar vesicles.

Hand shaking

This is also known as thin film hydration technique. In this method, a mixture of surfactant and cholesterol are dissolved in volatile organic solvent such as diethyl ether, chloroform, methyl alcohol, in a round bottom flask. The organic solvent is removed by using rotary evaporator at room temperature, which leaves behind a thin layer of solid deposited on wall of the flask. After gentle agitation, the surfactant is rehydrated with aqueous phase at 0-60 °C. This method forms multilamellar noisomes.

Thermo sensitive noisomes are prepared at 60 °C by evaporating organic solvent and leaving a thin film of lipid of on the wall of rotary flask evaporator. The aqueous phase containing drug is added slowly by shaking at room temperature followed by sonication.

Reverse phase evaporation

The surfactant is dissolved in choloroform and phosphate buffer is added, followed by emulsification and sonication under reduced pressure.

Bubbling of inert gas

It is a novel technique for the preparation of niosomes and liposomes without use of organic solvents. The bubbling units consist of round bottom flask with three necks. The first neck is meant for water cooled reflux, the second neck is for thermometer, and the third neck is for nitrogen gas supply. Surfactant and cholesterol are dispersed together in buffer (pH 7.4) at 70 °C for 15 sec with high shearing homogenizer and immediately

nitrogen gas at 70 °C is bubbled, which forms vesicles.

Sonication

Niosomes are prepared by using sonication method, in which mixture of surfactant and cholesterol is dispersed in aqueous phase in a vial. Then this dispersion is subjected to ultrasonic vibration for 30 min at 60 °C, which leads to formation of multilamellar vesicles.

Micro fluidization

It technique is based on submerged jet containing micro channels with interaction chamber in which two fluidized streams interact with each other at ultra velocities. The impingement of thin liquid sheet along with common front are arranged in such a way that the energy supplied for the formation of niosomes remains same. This forms unilamellar niosomes with better reproducibility and size uniformity.

Multiple membrane extrusion

Niosomes can be chemically prepared by extrusion through polycarbonate membrane (0.1 µm nucleophore) by using C16 G12. By this method, a desired size of the vesicles can be obtained.

Transmembrane pH gradient drug uptake

Surfactant and cholesterol are dispersed into chloroform in a round bottom flask followed by solvent evaporation under reduced pressure leading to the formation of thin film on the wall of the flask. This film is hydrated with 300 mM citric acid by using vortex mixing. This forms multilamellar vesicles, which are frozen and sonicated to get niosomes. To this niosomal suspension, aqueous solution of drug containing is added and mixed by vortexing, after which, phosphate buffer treatment is done to maintain pH between 7.0 and 7.2 and the mixture is heated at 60 °C for 10 minutes to produce vesicles.

Formation of niosomes from proniosomes

Proniosome powder is filled in a screw capped vial, in which water or saline at 80 °C is added and mixed by vortexing, followed by agitation for 2 min results in the formation of niosomal suspension (Fig. 2).

Aqueous dispersion

It is based on micro dispersion of surfactant in aqueous media containing active drug for entrapment or encapsulation. The method is represented in Fig. 3.

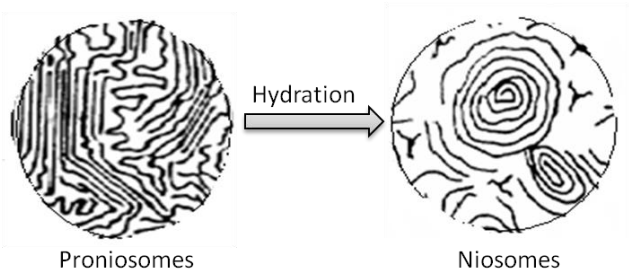

Fig. 2. Preparation of niosomes from proniosomes

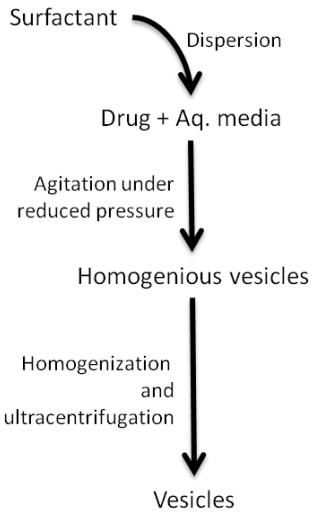

Fig. 3. Preparation of niosomes by aqueous dispersion method

Separation of unentrapped drug

The removal of unentrapped drug from the vesicles can be done by various techniques.

1. *Dialysis*: The aqueous niosomal dispersion is dialyzed using cellophane tubing against phosphate buffer or saline. [24, 25]
2. *Column chromatography*: The free drug from niosomal dispersion can also be removed by passing through sephadex G50 column and eluting using phosphate buffer. The free drug gets retained on column and vesicles percolate down. [26, 27]
3. *Centrifugation*: The niosomal dispersion is subjected to centrifugation in water or saline, where niosomes get sedimented down and the supernatant containing free drug is separated.[21,28]

Characterization of niosomes

The parameters for characterization of niosomes include size, shape, morphology and entrapment

efficiency. The vesicles can be visualized by using freeze fracture electron microscopy; photon spectroscopy is used for determination of mean diameter of vesicles; electron microscopy is used for determination of morphological characters of vesicles; laser scattering is used for size distribution and mean diameter of niosomes.[6]

The entrapment efficiency is determined by using carboxy fluorescein as marker.[30] Generally, carboxy fluorescein (CF) is used at 200 mM concentration for hydration. At this concentration inside the vesicles, it exhibits self quenching and does not give fluorescence. Another method is by disruption of vesicles using hydrophilic surfactants, which releases carboxy fluorescein and hence, fluorescence is observed.
Entrapment efficiency (%) = (Amount of CF before disruption / amount of CF after disruption) × 100

In vitro drug release

In vitro drug release can be determined by the following methods:[31]

Dialysis
Niosomes are placed in dialysis tubing, which would be hermetically sealed and dialyzed against a suitable dissolution medium at room temperature. Samples are withdrawn from medium at suitable intervals, centrifuged and analyzed for drug content by a suitable method.

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

Franz diffusion cell
In a Franz diffusion cell, 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.

Stability of niosomes

Stable niosomes suspension should have a constant concentration of entrapped drug and constant particle size. Stability of niosome is enhanced by entrapped drug. The stability is also dependent on concentration and type of surfactant used along with cholesterol content.[27] For example, sonicated cholesterol rich spherical/tabular C16G2 niosomes are stable at room temperature, whereas, sonicated polyhedral niosomes are stable at temperatures above the phase transition temperature, but are instable at room temperature.

Toxicity of niosomes

The toxicity of CxEOy surfactants has been studied using cilio toxicity model on nasal mucosa.[32] The results suggest that increase in alkyl chain length of surfactant leads to decrease in toxicity, whereas, increase in the polyoxyethylne chain length increases ciliotoxicity. It has been found that increase in alkyl chain length of surfactant leads to formation of gel, on the other hand as increase in polyoxyethylene chain length leads to formation of liquid state. By this study, it is clear that the liquid state is more toxic than gel state[32] In a toxicity study involving human keratocytes, it has been reported that the surfactant-linked-esters exhibit less toxicity than surfactant-linked-ethers. In another study, it has been reported that vincristine encapsulated in niosomes is less toxic than free drug.[33]

Pharmacokinetics of Niosomes[34]

The bioavailability of drug from niosomes is dependent on the extent of release of entrapped drug at target tissues. Liver is the only organ which has been extensively and quantitatively analyzed using physiological models for targeted drug availability. A three compartment physiological model has been used for studying kinetics of uptake and degradation of niosomes in liver. Based on this model, the measurable variables can be estimated as:

1. Percentage of injected intact niosomes that remained in liver.
2. Percentage of injected intact niosomes that remained in blood.
3. Percentage of injected intact niosomes that degraded in liver.

Applications of niosomes

Leishmaniasis therapy
Leishmaniasis is a disease caused by parasite genus *Leishmania* which invades the cells of the liver and spleen. Most Commonly prescribed drugs for the treatment are the derivatives of antimony – which, in higher concentrations – can cause liver, cardiac and kidney damage. Use of niosomes as a drug carrier showed that it is possible to administer the drug at high levels without the triggering the side effects, and thus showed greater efficacy in treatment.[1]

Niosomes in oncology

Intravenous administration of noisome loaded with methotrexate, did not lead to increased accumulation of the drug in the liver compared to administration of free drug. This may be due to difference in the size of the niosomal vesicles used in the two studies or by a modification of the drug in the liver as compared to administration of free drug. It is clear that the charge, size, and hydrophilicity of the vesicles can change the distribution of encapsulated drug when administered intravenously. Also, drug accumulation in the tumor was found to increase when administered in cholesterol containing niosomes.[34]

Niosomes containing doxorubicin prepared from C16 monoalkyl glycerol ether with cholesterol led to increased level of doxorubicin in tumor cells, lungs and serum, but not in spleen and liver. But, doxorubicin loaded niosomes without cholesterol exhibited reduced rate of tumor proliferation in mice. The life span of tumor bearing mice was increased. The cardio toxicity of doxorubicin was reduced with niosomal formulation. Also, in the form of niosomes, there was a change the general metabolic pathway of doxorubicin.[35]

Niosomes containing bleomycin formulated using 47.5% cholesterol exhibited higher level of drug in the spleen, liver and tumor as compared to free drug solution when administered to tumor bearing mice. There was reduced accumulation of drug in kidney and gut in case of niosomal formulation.[16] Niosomes containing vincristine exhibited higher tumoricidal efficacy as compared to free drug formulation.[33] Niosomes with carboplatin also showed higher tumoricidal efficacy in S180 lung carcinoma-bearing mice as compared to free drug solution and decreased bone marrow toxic effects.[36]

Anti-inflammatory niosomes

Diclofenac sodium loaded niosomes with 70% cholesterol showed greater anti-inflammatory activity than free drug.[38] Similarly, nimesulide and flurbiprofen loaded niosomes have exhibited greater anti-inflammation activity than free drug.[39]

Niosomes in ophthalmic drug delivery

It is difficult to achieve good bioavailability of drug in ocular formulations due to the tear production, non productive absorption, impermeability of corneal epithelium and transient residence time. But, the bioavailability can be enhanced by use of vesicular systems such as niosomes.[39] Bioadhesive-coated niosomes of acetazolamide prepared using span 60, cholesterolstearylamine or dicetyl phosphate have exhibited better efficacy in reducing the intraocular pressure than other ocular formulations. Chitosan-coated niosomal formulation of timolol maleate also showed higher efficacy in the reduction of intraocular pressure than other formulations Such formulations also have reduced cardiovascular side effects.

Niosomes in transdermal drug delivery

Administration of drugs trough transdermal route has advantage of avoidance of first pass metabolism. But, it suffers a drawback of slow penetration of drugs through the skin. One of the approach to enhance the penetration rate is formulation of niosomes. Transdermal delivery ketorolac prepared as pro-niosomal formulation with span-60 exhibited a higher effect than the pro-niosomes prepared with tween-20.[40] It has been reported that the therapeutic efficacy and bioavailability of drugs like flurbiprofen, diclofenac and nimesulide have been increased with niosomal formulations.[41]

Niosomes for Diagnosis

Niosomes can be used as diagnostic agents. Conjugated niosomal formulations with gadobenate dimeglcemine with [N-palmitoyl-glucosamine] (NPG), PEG-4400, and both PEG and NPG significantly improved tumor targeting of encapsulated paramagnetic agent which was assessed with MR imaging.[42]

Conclusion

The niosomes are better carriers for targeting of the drug at appropriate tissue. Niosomes can encapsulate different type of drugs within their multi environmental structure. Niosomes are preferred to liposomes due to low cost, chemical stability and such other factors. Niosomes are useful in the delivery of anti-infective agents, anti-inflammatory agents, anti-cancer agents, and recently use as vaccine adjuvants and diagnostic imaging agents. Hence, niosomes appear to be the most sought after carriers for a variety of drugs.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

References

1. Hunter CA, Dolan TF, Coombs GH, Baillie AJ. Vesicular systems (niosomes and liposomes) for

delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. J Pharm Pharmacol. 1988; 40: 161-165.
2. Baillie AJ, Florence AT, Hume LR, Muirhead GT, Rogerson A. The preparation and properties of niosomes--non-ionic surfactant vesicles. J Pharm Pharmacol. 1985; 37: 863–868.
3. Stafford S, Baillie AJ, Florence AT. Drug effects on the size of chemically defined non-ionic surfactant vesicles. J Pharm Pharmacol. 1988; 40: 26.
4. Mehta A. Niosomes. www.pharmainfo.net. 17 Dec. 2009.
5. Biju SS, Telegaonar S, Mishra PR, Khar RK. Vesicular system: an overview. Indian J Pharm Sci. 2006; 68: 141-153.
6. Vyas SP, Khar RK. Controlled drug delivery system: concept and advances. New Delhi: CBS Publishers and Distributors; 2002.
7. Indhu PK, Garg A, Anil KS, Aggarwal D. Vesicular system in ocular drug delivery. Indian J Pharm Sci. 2004; 269: 1-14.
8. Verma S, Singh SK, Navneet S, Mathur P, Valecha V. Nanoparticle vesicular systems: a versatile tool for drug delivery. J Chem Pharm Res. 2010; 496-509
9. Tanaka M, Fukuda H, Horiuchi T. Phase behaviour of polyoxyethylene hydrogenated castor oil in oil/water system. J Am Oil Chem Soc. 1990; 67: 55.
10. Mueller-Goymann CC. The influence of the microstructure on consistency and physical stability of an o/w cream. Acta Pharm Technol. 1987; 33: 60-66.
11. Vanlerberghe G, Handjani-vila RM. Non-ionic vesicles as drug delivery systems. French Patent Journal. 1978; 358: 991.
12. Echegoyen LE, Hernandez JC, Kaifer A, Gokel GW, Echegoyen L. Aggregation of steroidal lariat ethers. The first example of nonionic liposomes (niosomes) formed from neutral crown ether compounds. J Chem Soc Chem Commun. 1988: 836-837.
13. 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.
14. Chandraprakash KS, Udupa N, Devi PU, Pillai GK. Effect of niosome encapsulation of methotrexate. Macrophage activation on tissue distribution of methotrexate and tumour size. Int J Pharm. 1993; 1: 133-137.
15. Manconi M, Valenti D, Sinico C, Lai F, Loy G, Anna MF. Niosomes as carriers for tretinoin II. Influence of vesicular incorporation on tretinoin photostability. Int J Pharm. 2003; 260: 261–272.
16. Palozza P, Muzzalupo R, Trombino S, Valdannini A, Picci N. Solubilization and stabilization of beta -carotene in niosomes: delivery to cultured cells. Int J Pharm. 2006; 139: 32–42.
17. Naresh RAR, Udupa N. Kinetics and tissue distribution of niosomal bleomycin in tumor bearing mice. Indian J Pharm Sci. 1996; 58: 230.
18. Balasubramaniam, Kumar VA, Pillai KS. Formulation and in-vivo evaluation of niosome encapsulated daunorubicin hydrochloride. Drug Dev Ind Pharm. 2002; 28:118.
19. Patel RP. Niosome: a unique drug delivery system. www.pharmainfo.net. 21 Dec. 2009
20. Baillie AJ, Coombs GH, Dolan TF. Non-ionic surfactant vesicles: niosomes as delivery system for the anti-leishmanial drug as sodium stribogluconate. J Pharm Pharmacol. 1986; 38: 502-505.
21. Guinedi AS, Nahed DM, Samar M, Rania MH. Preparation and evaluation of reverse phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. Int J Pharm. 2005; 306: 71–82.
22. Welsh BAI, Rhodes DG. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes. AAPS Pharm. 2001; 3: 1-8.
23. Handjani-vila RM, Riber A, Randot B, Valenberge G. Aqueous dispersion. Int J Cosmo Sci. 1979; 303
24. Hao Y, Zhao F, Li N, Yang Y, Li K. Studies on a high encapsulation of colchicine by a noisome System. Int J Pharm. 2002; 244: 73–80.
25. Muzzalupo R, Trombino S, Iemma F, Puoci F, Mesa CL, Picci N. Preparation and characterization of bolaform surfactant vesicles. Colloids and Surfaces B. Biointerfaces. Int J Pharm. 2005; 46: 78–83.
26. Tabbakhian M, Tavakoli N, Jaafari MR, Daneshamouz S. Enhancement of follicular delivery of finasteride by liposomes and niosomes; *in vitro* permeation and *in vivo* deposition studies using hamster flank and ear models. Int J Pharm. 2006; 323: 1–10.
27. Arunothayanun P, Bernard MS, Craig DM, Uchegbu IF, Florence AT. The effect of processing variables on the physical characteristics of non-ionic surfactant vesicles (niosomes) formed from a hexadecyl diglycerol ether. Int J Pharm. 2000; 201: 7–14.

28. Yoshida H, Lehr CM , Kok W , Junginger HE, Verhoef JC, Bouwstra JA. Niosomes for oral delivery of peptide drugs. J Control Release. 1992; 21: 145-154
29. Wagh VD, Deshmukh OJ. Niosomes as ophthalmic drug delivery systems. J Pharm Res. 2010; 3: 1558-1563
30. Gregoriadis G, Florence A. T. In: Liposome technology. Vol.II. CRC Press, Boca Raton, 1993; 165.
31. Muller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv. 2002; 54: 131-155.
32. Hofland HEJ, Bouwstra JA, Spies F, Bodde HE. Safety aspect of nonionic surfactant vesicles- a toxicity study related to the physicochemical characteristics of nonionic surfactants. J Pharm Pharmacol. 1992; 44: 287-292.
33. Parthasarathi G, Udupa N, Umadevi P, Pillai GK. Formulation and *in vitro* evaluation of vincristine encapsulated niosomes. Indian J Pharm Sci. 1994; 56: 90-93.
34. Uchegbu IF, Vyas SP. Nonionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm. 1998; 172: 33-70.
35. Rogerson A, Cummings J, Willmott N, Florence AT. The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol. 1988; 40: 337.
36. Zhang JQ, Lu B. Studies on lung targeted niosomes of carboplatin. Euro J Pharm Sci. 2001; 36: 303-306.
37. Shahiwala A, Misra A. Studies in topical application of niosomally entrapped nimesulide. J Pharm Sci. 2002; 5: 220-225.
38. Aggarwal D, Garg A, Kaur IP. Development of topical niosomal preparation of acetazolamide. preparation and evaluation. J Pharm Pharmacol. 2004; 56: 1509-1513.
39. Arunothayanun P, Bernard MS, Craig DM, Uchegbu IF, Florence AT. Investigation into the *in vitro*/*in vivo* behaviour of polyhedral niosomes. J Pharm Pharmcol. 1998; 50: 1169-1173.
40. Raja Naresh RA, Chandrashekhar G, Pillai GK, Udupa N. Antiinflamatory activity of niosome encapsulated diclofenac sodium in rats. Indian Drugs.1993; 30: 275-280.
41. Reddy DN, Udupa N. Formulation and evaluation of oral and transdermal preparation of flurbiprofen and piroxicam incorporated with different carriers. Drug Dev Ind Pharm. 1993; 19: 843-847.
42. Luciani, Olivier JC, Clement O, Siauve N, Brillet PY, Bessoud B, Gazeau F, Uchegbu IF, Kahn E, Frija G. Glucose receptor MR imaging of tumors: study in mice with PEGylated paramagnetic niosomes. J Radiology. 2004; 231: 135-139.

This page is intentionally left blank