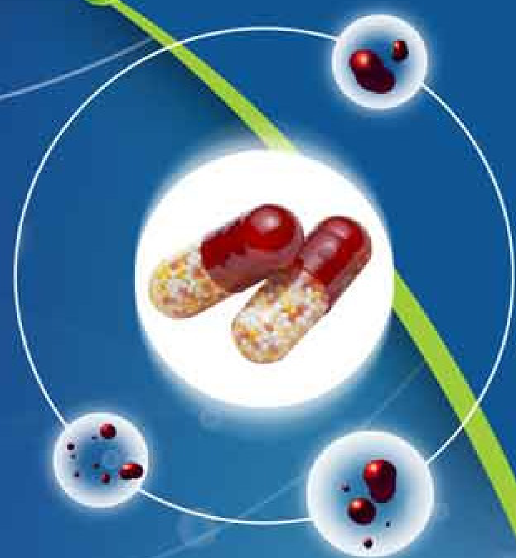
ISSN : 2320 4850

BI MONTHLY

A J P R D

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)



Volume - 01 Issue - 04 JULY-AUG 2013

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development

(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)

www.ajprd.com

ISSN 2320-4850

Review Article

A REVIEW ON NOVEL DRUG DELIVERY SYSTEM - NIOSOMES

Ruchi Maurya*, Kadambari Pathak[1], Priya Saxena, Juhi Tiwari

Department of Pharmaceutical Sciences, Jayoti Vidyapeeth Women's University, **Jaipur, Rajasthan**

Received: 25 July 2013, Revised and Accepted: 1 August 2013

ABSTRACT

Drug delivery aims at delivering the drug at a particular site. Novel drug delivery is a recent system that promotes easy and convenient route of administration and are also advantageous over conventional dosage form. Niosomes are novel drug delivery that promotes formations of vesicles by hydrating the mixture of cholesterol and non-ionic surfactants. Targeted drug delivery can also be achieved using niosomes where the drug is directly delivered to the body part where the therapeutic effect is required. Thereby reducing the dose required to be administered to achieve the desired effect. The therapeutic efficacy of the drugs is improved by reducing the clearance rate, targeting to the specific site and by protecting the encapsulated drug. Drug targeting reduces the dose which leads to subsequent decrease in the side effects.

KEY WORDS*: Novel drug delivery, Niosome, Drug targeting.*

INTRODUCTION

Novel drug delivery system promotes the ease and convenience of administration, deliverance of accurate dose as well as to prolong residence time of drug in contact with skin membrane. NDDS delivers the drug at a rate directed by the needs of the body during the period of treatment of a disease, and reach the active ingredient to the site of action. A number of NDDS have been reported through various routes of administration, to achieve controlled and targeted drug delivery. A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structures is one such system, which can be expected to prolong the duration of the drug in systemic circulation, and to reduce the toxicity by selective up taking. NDDS has an object to deliver the drug at a rate directed by the needs of the body during the period of treatment of a disease, and reach the active ingredients to the site of action. Consequently a number of vesicular drug delivery systems such as liposomes, niosomes, transferosomes, and pharmacosomes were developed [1].

*For correspondence:
Ruchi Maurya
Department of Pharmaceutical Sciences
Jayoti Vidyapeeth Women's University, Jaipur
Email id: ruchimaurya11@gmail.com

Novel drug delivery is a vital research area which strives to solve the problems of conventional drug delivery system and aim to achieve a programmed delivery of the therapeutic substances for the optimal beneficial effects while avoiding the side effect of drugs. A novel drug delivery system is a system that offers multiple drug delivery solutions such as:

- Oral Drug Delivery Systems and Materials
- Parenteral and Implant Drug Delivery Systems
- Pulmonary and Nasal Drug Delivery

- Transmucosal Drug Delivery
- Transdermal and Topical Drug Delivery Delivery of Proteins and Peptides
- Drug Delivery Pipelines

The main goal of a site specific drug delivery system is not only to increase the selectivity and drug therapeutic index, but also to reduce the toxicity of the drug. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulin's, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc. Among different carriers liposomes and niosomes are well documented drug delivery. In general, Vesicular systems are a novel means of drug delivery that can enhance bioavailability of encapsulated drug and provide therapeutic activity in a controlled manner for a prolonged period of time [2].

NIOSOMES

Niosomes are novel drug delivery system in which serves as drug depots in the body which release the drug in a controlled manner through its bilayer providing sustained release of the enclosed drug. Niosomes are non-ionic surfactant vesicles obtained by hydration of synthetic non-ionic surfactants, with or without incorporation of cholesterol or other lipids. The niosomes are very small, and microscopic in size [3]. Their size lies in the nanometric scale. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. One of the reasons for preparing niosomes is assumed higher chemical stability of the surfactants than that of phospholipids, which are used in the preparation of liposomes. Due to the presence of ester bond, phospholipids are easily hydrolysed [4].

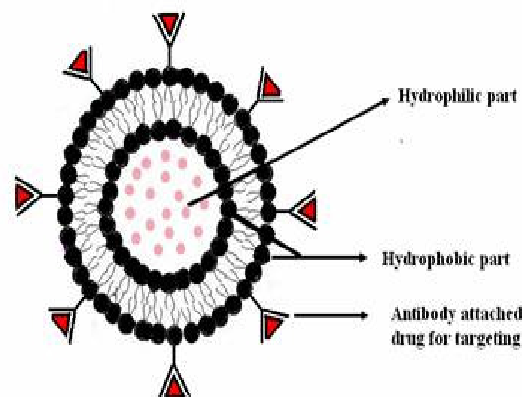


Figure 1: Structure of Niosomes

Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as span 60 which is usually stabilised by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate.Major component of niosomes is non-ionic surfactant which give it an advantage of being more stable when compared to liposomes thus overcoming the problems associated with liposomes i.e. susceptibility to oxidation, high price and the difficulty in procuring high purity levels which influence size, shape and stability. Niosomes can entrap hydrophilic drugs and other bio actives upon encapsulation or hydrophobic material by partitioning of these molecules into hydrophobic domains. These vesicles can be formulated either unilamellar or multilamellar in structure. Moreover, niosomes possess great stability, cost-effectiveness, and simple methodology for the routine and large-scale production without the use of hazardous solvents.

ADVANTAGES OF NIOSOMES

Niosomes was first used in cosmetics by Loreal as the vesicle suspension being water based offers greater patient compliance over oil based systems.

It offers place to accommodate a variety of drugs such as hydrophilic, lipophilic as well as ampiphilic drug moieties.

The vesicle size and lamellarity etc can be varied according to the requirement.

They increase the stability of the entrapped drug.

It enhance the skin penetration of the drug.

It improves the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug [5].

DISADVANTAGES OF NIOSOMES

The aqueous suspensions of niosomes may have limited shelf life due to fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs

The methods of preparation of multilamellar vesicles such as extrusion, sonication, are time consuming and may require specialized equipments for processing [6].

TYPES OF NIOSOMES

Bola surfactant containing niosomes

Bola surfactant containing niosomes are the surfactants that are made of omega hexadecylbis-(1-aza-18 crown-6) (bola surfactant): span- 80/cholesterol in 2:3:1molar ratio [7].

Proniosomes

Proniosomes are the niosomal formulation containing carrier and surfactant, which requires to be hydrated before being used. The hydration results in the formation of aqueous noisome dispersion. Proniosomes decreases the aggregation, leaking and fusion problem associated with niosomal formulation [8].

Proniosome-derived niosomes are superior to conventional niosomes in convenience of storage, transport and dosing. Stability of dry proniosomes is expected to be more stable than a pre-manufactured niosomal formulation. In release studies proniosomes appear to be equivalent to conventional niosomes. Size distributions of proniosome-derived niosomes are somewhat better than those of conventional niosomes so the release performance in more critical cases turns out to be superior [9-10].

Advantages of proniosomes over the niosomes

Avoiding problem of physical stability like aggregation, fusion, leaking.

Avoiding hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.

Aspasomes

Combination of acorbyl palmitate, cholesterol and highly charged lipid diacetyl phosphate leads to the formation of vesicles called aspasomes. Aspasomes are first hydrated with water/aqueous solution and then sonicated to obtain the niosomes. Aspasomes can be used to increase the transdermal permeation of drugs. Aspasomes have also been used to decrease disorder caused by reactive oxygen species as it has inherent antioxidant property [11].

Niosomes in carbopol gel

Niosomes were prepared using drug, spans and cholesterol. The niosomes thus obtained were then incorporated in carbopol-934 gel (1%w/w) base containing propylene glycol (10% w/w) and glycerol (30% w/w). Using human cadaver skin, in vitro diffusion studies of such niosomal gel, plain drug gel and marketed gel were carried out in diffusion cell. It was observed that the mean flux value and diffusion co-efficient were 5 to 7 times lower for niosomal gel as compared to plain drug gels [12].

Vesicles in water and oil system (v/w/o):

It has been reported that the emulsification of an aqueous niosomes into an oil phase form vesicle in water in oil emulsion (v/w/o). This can be prepared by addition of niosomes suspension formulated from mixture of sorbitol monostearate, cholesterol and solulan C24 (Poly- 24-Oxyethylene cholesteryl ether) to oil phase at 60 0C. This results in the formation of vesicle in water in oil (v/w/o) emulsion which by cooling to room temperature forms vesicle in water in oil gel (v/w/o gel) [13]. The v/w/o gel thus obtained

can entrap proteins/ proteinous drugs and also protect it from enzymatic degradation after oral administration and controlled release.

Niosomes of hydroxyl propyl methyl cellulose

In this type, a base containing 10% glycerine of hydroxyl propyl methyl cellulose was first prepared and then niosomes were incorporated in it. The bioavailability and reduction of paw edema induced by carrageenan was found to be higher by this niosomal system than the plain formulation of drugs [14-15].

FACTORS AFFECTING THE FORMATION OF NIOSOMES

Type of surfactant

Type of the surfactants influences encapsulation efficiency, toxicity, and stability of niosomes. The first niosomes were formulated using cholesterol and single-chain surfactants such as alkyl oxyethylenes. The alkyl group chain length is usually from C12–C18. The hydrophilic- lipophilic balance (HLB) is a good indicator of the vesicle forming ability of any surfactant.

Cholesterol

The incorporation of cholesterol into bilayer composition of niosome induces membrane stabilizing activity and decreases the leakiness of membrane. Hence, incorporation of cholesterol into bilayer increases entrapment efficiency. The permeability of vesicle bilayer to 5, 6-carboxy flourescein (CF) is reduced by 10 times due to incorporation of cholesterol [16].

Nature of 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 [17-18]. The hydrophilic lipophilic balance of the drug affects degree of entrapment.

Method of preparation

Method of preparations can also affect the niosomal properties. Different type of methods like ether injection, hand shaking; sonication etc. has been reviewed by Khandare et al., 1994. The average size of acyclovir niosomes prepared by hand-shaking process was larger (2.7μm) as compared to the average size of niosomes 1.5μm prepared by ether injection method which may be attributed to the passage of cholesterol and span-80 solution through an orifice into the drug solution. Reverse phase evaporation can be used to produce smaller size vesicles. Vesicles with smaller size and greater stability can be produced by micro fluidization method. Niosomes obtained by transmembrane pH gradient (inside acidic) drug uptake process showed greater entrapment efficiency and better retention of drug [19-20].

METHOD OF PREPARATION OF NIOSOMES

Various methods are reported for the preparation of niosomes such as:

- Ether injection method
- Thin film hydration technique
- Sonication method
- Reverse phase evaporation technique (REV)
- Micro fluidization
- Multiple membrane extrusion method
- Trans membrane pH gradient (inside acidic) drug uptake process (remote loading)
- Bubble method

Formation of niosomes from proniosomes

Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether (volatile organic solvent) into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14- gauge needle into an aqueous solution of material. Vaporization of ether (volatile organic solvent) leads to formation of single layered vesicles.

Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm [21-22].

Thin Film Hydration

All vesicles forming Components i.e. surfactant, cholesterol and charge inducers are dissolved in a volatile organic solvent in a round bottom flask. Using rotary evaporator the organic solvent is evaporated at room temperature forming a thin dry film of dissolved components. The dried thin film is hydrated with aqueous phase with gentle agitation which leads to formation of niosomes. The drug can be added to the aqueous phase if hydrophilic and can be dissolved in organic solvent with other components if hydrophobic [23-24].

Sonication method

In this method at first the surfactant-cholesterol mixture is dispersed in the aqueous phase. This dispersion is then probe sonicated for 10 minute at 60oC, which leads to the formation of multilamellar vesicles (MLV). These MLVs are further ultrasonicated either by probe sonicator or bath sonicator, which in turn leads to the formation of unilamellar vesicles [25].

Reverse phase evaporation technique (REV)

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4- 5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes [26].

Microfludisation

This is a recent technique to prepare small multi lamellar vesicles. A microfludizer is used to pump the fluid at a very high pressure (10,000 psi) through a 5 pm screen. Thereafter; it is forced along defined micro channels, which direct two streams of fluid to collide together at right angles, thereby affecting a very efficient transfer of energy. The lipids can be introduced into the fluidizer. The fluid collected can be recycled through the pump until vesicles of spherical dimensions are obtained. This method resulted in niosomes with greater uniformity and small size which shows better reproducibility [27-28].

Multiple membrane extrusion method

In membrane extrusion method, the size of niosomes is reduced by passing them through membrane filter. This method can be used for production of multi lamellar vesicles as well as large unilamellar vesicles. It is found as a good method for controlling niosomal size [29].

Transmembrane pH gradient (inside acidic) drug uptake process (remote loading)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes [30].

The "Bubble" Method

It is novel technique for the one step preparation of liposome and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas [31].

Formation of niosomes from Proniosomes

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating

process is a dry formulation [32]. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes".

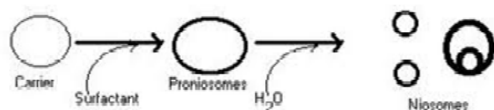


Figure 2: Formation of Niosomes from proniosomes

DRUG RELEASE KINETICS

The release patterns can be divided into those that release drug at a slow zero or first order rate and those that provide an initial rapid dose, followed by slow zero or first order release of sustained component [33]. The purpose of the controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible34. In other words, they are able to exert a control on the drug release rate and duration35. For this purpose, generally, controlled release system initially release part of the dose contained in order to attain rapidly the effective therapeutic concentration of the drug. Then, drug release kinetics follows a well defined behaviour in order to supply the maintenance dose enabling the attainment of the desired drug concentration.

Zero-order model

Drugs that do not disaggregate or release slowly from the dosage form can be represented by this equation:

$$Q0 - Qt = K0t \quad (1)$$

Rearrangement of equation (1) yields:

$$Qt = Q0 + K0t \quad (2)$$

where Qt is the amount of drug dissolved in time t, Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and K0 is the zero order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time [36-37].

First order model

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

$$-\frac{dc}{dt} = -Kc \quad (3)$$

where K is first order rate constant expressed in units of time -1.

Equation (3) can be expressed as:

$$\log C = \log C0 - Kt / 2.303 \quad (4)$$

where C0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a [38]

$$\text{slope} = - k/2.303 \quad (5)$$

Higuchi model

Higuchi proposed this model in 1961.This mathematical model is used to describe drug release from matrix system. This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than system thickness; (iv) matrix swelling and dissolution are negligible; (v) drug diffusivity is constant; and (vi) perfect sink conditions are always attained in the release environment. Accordingly, model expression is given by the equation:

$$ft = Q = A \sqrt{D}(2C - Cs) Cs\ t \quad (6)$$

where Q is the amount of drug released in time t per unit area A, *C* is the drug initial concentration, *Cs* is the drug solubility in the matrix media and *D* is the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance.

This relation is valid during all the time, except when the total depletion of the drug in the therapeutic system is achieved. In a general way it is possible to simplify the Higuchi model as (generally known as the simplified Higuchi model):

$$f_t = Q = K_H \times t^{1/2} \quad (7)$$

where, K_H is the Higuchi dissolution constant. The data obtained were plotted as cumulative percentage drug release versus square root of time [39-40].

Hixson-Crowell model

Hixson and Crowell (1931) recognized that the particles regular area is proportional to the cube root of its volume. They derived the equation:

$$W_0^{1/3} - W_t^{1/3} = \kappa t \quad (8)$$

where W_0 is the initial amount of drug in the dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface area and volume relation. The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cube root of drug percentage remaining in matrix *versus* time [41].

Korameyer-Peppas model

Korameyer et al. in 1983 derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korameyer - Peppas model.

$$M_t / M_\infty = K t^n \quad (9)$$

where M_t / M_∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. In this model, the value of *n* characterizes the release mechanism of drug.

To find out the exponent of *n* the portion of the release curve, where $M_t / M_\infty < 0.6$ should only be used. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release *versus* log time [42].

APPLICATIONS OF NIOSOMES

- **Niosomes as carriers**

Niosomes can be used as a carrier for haemoglobin. Niosomal suspension shows a visible spectrum superimposable onto that of free haemoglobin. Vesicles are permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non-encapsulated haemoglobin [43-44]. Chandraprakash *et al* [45] reported the formation and pharmacokinetic evaluation of methotrexate niosomes in tumour bearing mice.

- **Transdermal delivery of drugs by niosomes**

One of the most useful spects of niosomes is that they greatly enhance the uptake and penetration rate of drug through the skin. TDD utilising niosomal technology is used in cosmetics. Recently, transdermal vaccines utilising niosomal technology is also being researched.

- **Delivery of peptide drugs**

Oral peptide drug delivery has been faced with a challenge of bypassing the enzymes which would breakdown the peptide. use of niosomes successfully protected the peptides from gastrointestinal peptide breakdown [46].

- **Anti-neoplastic treatment**

Most anti-neoplastic drugs causes severe side effects thus the use of niosomes can alter the metabolism, prolong circulation and half life drug, thus decreasing the side effect. Niosomal entrapment of methotrexate showed improved effects such as decreased rate of proliferation of the tumour and high plasma levels.

Immunological application

Niosomes have been used for studying the nature of immune response provoked by antigens. Brewer and Alexander have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability [47]

CONCLUSION

Niosomes are novel drug delivery system which offers a large number of advantages over other

conventional and vesicular delivery systems. Namely targeted delivery, reduction of dose, stability and compatibility of non-ionic surfactants, easy modification, delayed clearance, suitability for a wide range of Active Pharmaceutical Agents etc. Drug delivery potential of niosomes can enhance by using novel concepts like proniosome, discomes and aspasome. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant.

REFERENCES

1. *Manosroi A., Chutoprapat R., Abe M., Manosroi J. Characteristics of niosomes prepared by supercritical carbon dioxide (scCO2) fluid. Int. J. Pharm. 2008; 352: 248-255.*
2. *Kaparissides C, Alexandridou S, Kotti K and Chaitidou S, Recent advances in novel drug delivery. J of nanotech. 2006.*
3. *Handjani Vila. Dispersion of lamellar phases of non ionic lipids in cosmetic products. Int.j.Cos.Sci.1:1979;303-314.*
4. *Kemps j. and Crommelin D.A. Hydrolyse van fosfolipiden in watering milieu. Pharm Weekbl. 1988; 123:355-363.*
5. *Buckton G., harwood, Interfacial phenomena in drug delivery and targeting Academic Publishers, Switzerland. 1995.*
6. *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.*
7. *Yoshida H., Lehr C.M., Kok W., Junginger H.E., Verhoef J.C., Bouwistra J.A.. Niosomes: A Controlled and Novel Drug delivery System. J.Control Rel. 1992; 21: 145-153.*
8. *Jadon P.S., Gajbhiye V., Rajesh S.J., Kavita R., Narayanan G.. A Controlled and Novel Drug Delivery System. AAPS Pharm.Sci.Tech. 2009; 10: 1187-1192.*
9. *Ismail A. Attia., Sanaa A.,El-Gizawy., Medhat A. Fouda., Ahmed M. Donia.Influence of a niosomal formulation on the oral bioavailability of acyclovir in rabbits. AAPS PharmSciTech. 2007; 8 (4): 1061-1068 .*
10. *Agarwal,R., Katare,O., Vyas P. Preparation and in vitro evaluation of liposomal/nioosmal delivery systems for antipsoriatic drug dithranol. Int. J. Pharm. 2001; 228: 43–52.*
11. *Bhaskaran S., Lakshmi P.K. Niosomes: A Controlled and Novel Drug delivery System. Acta Pharmaceutica Sciencia. 2009; 51: 27-32.*
12. *Yoshida H., Lehr C.M., Kok W., Junginger H.E., Verhoef J.C., Bouwistra J.A.. Niosomes: A Controlled and Novel Drug delivery System. J.Control Rel. 1992; 21: 145-153.*
13. *Bhaskaran S., Lakshmi P.K. Niosomes: A Controlled and Novel Drug delivery System. Acta Pharmaceutica Sciencia. 2009; 51:27-32.*
14. *Hu C., Rhodes D.G. Proniosomes As Drug Carriers. Int. J. Pharm.1999; 185:23–35.*
15. *Uchegbu I. F., Vyas S. P. Challenges and strategies in novel drug delivery technologies. Int. J. Pharm.1998; 172: 33–70.*
16. *Weissman G., Bloomgarden D., Kaplan R., Cohen C., Hoffstein S., Collins T., Gotlieb A., Nagle D. A general method for the introduction of enzymes, by means of immunoglobulin- coated liposomes, into lysosomes of deficient cells. Proc. Natl. Acad. Sci. 1975;72:88-92.*
17. *Gayatri D.S., Venkatesh P., Udupa N. Niosomal sumatriptan succinate for nasal administration. Int. J. Pharm. Sci. 2000; 62: 479-481.*
18. *Silver B.L. The physical chemistry of membranes. Unwin and Soloman Press, New York, USA, 1985.*
19. *Verma A.K., Bindal J.C. A vital role of niosomes on Controlled and Novel Drug delivery. Indian Journal of Novel Drug delivery. 2011; 3: 238-246.*
20. *Aggarwal D., Garg A., Kaur I.P. Niosomes: A Controlled and Novel Drug delivery System . J. Pharm. Pharmacol. 2004; 56: 1509-1517.*
21. *Rogerson A., Cummings J., Willmott N., Florence A.T. The distribution of doxorubicin in mice following administration in niosomes, J. Pharm. Pharmacol. 1988;40: 337–342.*
22. *Baillie A.J.,Coombs G.H., Dolan T.F. Non-ionic surfactant vesicles (niosomes) as delivery system for the antileishmanial drug, sodium stribogluconate, J. Pharm. Pharmacol. 1986;38: 502-505.*
23. *Palozza P., Muzzalupo R., Trombino S., Valdannini A., Picci N. Solubilization and stabilization of beta-carotene in niosomes: delivery to cultured cells. Chem. Phys. Lipids. 2006; 139: 32–42.*
24. *Arunothayanun P., Bernard M. S., Craig D. Q. M., Uchegbu I. F., Florence A. T. Someproperties of extruded non-ionic surfactant micro-tubes . Int. J. Pharm. 2000; 201: 7-11.*
25. *Bhaskaran S., Panigrahi L. Formulation and evaluation of niosomes using different non-ionic surfactant. Ind. J. Pharm. Sci. 2002; 64: 63-65.*
26. *Raja Naresh R.A., Chandrashekhar G., Pillai G.K., Udupa N. Antiinflammatory activity of Niosome encapsulated diclofenac sodium with Tween -85 in Arthitic rats. Ind. J. Pharmacol. 1994; 26: 46-48.*
27. *Cook E.J., Lagace A.P. Apparatus for forming emulsions.US Patent. 4254553, 1985.*
28. *Khandare J.N., Madhavi G., Tamhankar B. M. Niosomes novel drug delivery system. The East Pharmacist. 1994; 37: 61-64.*
29. *Junyaprasert V.B., Teeranachaideekul V., Supaperm T. Effect of Charged and Non-ionic Membrane Additives on Physicochemical Properties and Stability of Niosomes. AAPS PharmSciTech. 2008; 9: 851-859.*
30. *Mayer L.D., Bally M.B., Hope M.J., Cullis P.R. Uptake of antineoplastic agents into large unilamellar vesicles in response to a membrane potential. Biochem. Biophys. Acta. 1985; 816: 294-302.*
31. *Chauhan S., Luorence M.J. The Preparation of Polyoxyethylene Containing Non-Ionic Surfactant Vesicles. J. Pharm. Pharmacol. 1989; 1:6.*
32. *Blazek-Walsh A.I., Rhodes D.G. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes, Pharm. Res. 2001;18: 656-661.*
33. *Anonymous: Fed. Register 42, 1642 (1977).*
34. *Medical applications of controlled release, applications and evaluation, Langer R.S., Wise D.L. CRC Press, Boca Raton 1984;1-2.*
35. *Controlled drug delivery, Robinson J.R., Lee, V.H.L. Eds., Marcel Dekker, Inc. New York, Basel 1987.*
36. *Release kinetics, data interpretation. in: Encyclopedia of Controlled Drug Delivery. Narashimhan B., Mallapragada S.K., Peppas N.A. John Wiley and Sons, Inc, New York 1999.*
37. *Quantitative calculations in pharmaceutical practice and research. Hadjiioannou T.P., Christian G.D., Koupparis MA. Eds., VCH Publishers Inc., New York 1993.*
38. *Bourne D.W.: Pharmacokinetics. in: Modern pharmaceutics. Banker GS, Rhodes CT, Eds., Marcel Dekker Inc, New York, 2002;4.*

39. Higuchi T.: J. Pharm. Sci. 1963; 84: 1464.
40. Silvina A., Bravo M., Lamas C., Claudio J.: J. Pharm. Pharm. Sci. 2002; 5: 213.
41. Hixson A.W., Crowell J.H.: Ind. Eng. Chem. 1931; 23: 923.
42. Korameyer R.W., Gurny R., Doelker E., Buri P., Peppas N.A.: Int. J. Pharm. 1983; 15: 25.
43. Moser P., Marchand-Arvier M., Labrude P., Handjani-Vila R.M., Vignerson C. Preparation, physico-chemical properties, oxyphoric, and stability. Pharma. Acta. Helv. 1989;64:192-202.
44. Moser P., Arvier M.M., Labrude P., Vignerson C. Beginnings of hospital pharmacy with the civil hospices of Nancy and the first pharmacist-chiefs. Pharm. Acta. Helv. 1990;65:82.
45. Chandraprakash K.S., Udupa N., Umadevi P., Pillai G.K. Formulation and Evaluation of Methotrexate Niosomes. Ind. J. Pharm. Sci. 1992;54:197.
46. Pardakhty A., Varshosaz J., Rouholamini A. In vitro study of polyoxyethyleneealkyl ether niosomes for delivery of insulin. Int. J .Pharm. 2007; 328:130–141.
47. Brewer J.M., Alexander J.A. The adjuvant activity of non-ionic surfactant vesicles (niosomes) on the BALB/chumoral response to bovine serum albumin. Immunology. 1992; 75: 570-575.