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REVIEW ARTICLE

NIOSOMES –A VESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Niosomes are non-ionic surfactant based liposomes. Niosomes, the novel drug delivery system are self assembled vesicles primarily of synthetic surfactant incorporated with cholesterol as an excipient. They are the vesicles formed by hydrating the cholesterol and non-ionic surfactant. The main aim of niosome includes use of drug in efficient manner which includes reduced dose, reduced side effect, reduced dosage frequency, greater patient compliance and maximum concentration at the site of action so, that under exposure to the entire body. It includes higher therapeutic efficiency and reduced side effect. Niosomes are thought to be the better candidate's drug delivery system due to the various factor like cost, stability, etc. various types of drug delivery is possible using niosomes like targetting drug action, ophthalmic, topical, parenteral, etc. Drug delivery potential of niosomes can be enhanced by using novel concept like proniosomes, discomes and aspasomes. Niosomes serves better aid in the diagnostic imaging and as a Vaccine adjuants.this article focuses on the recent advances in niosomal drug delivery, formulation methods, and methods of characterization and current researches in the field of niosomes.

INTRODUCTION

A Niosomes are the non ionic surfactant vesicle having a bilayer structure formed by self assembly of cholesterol and non ionic surfactant. They are the ideal drug delivery system providing the targeted site of action. Targeted drug delivery is defined as the ability to direct drug on the site of action and inhibiting their action on non targeted site.[1-3] The development of the targeted drug delivery system was initiated by Paul Ehrlich, in 1909.[4-9] He pictured out a new mechanism for targeted drug delivery system. There are variety of approaches for drug delivery system which include liposomes, microsphere, microcapsule, nanotechnology, microemulsion, antibody-loaded drug delivery system implanted pumps and niosomes. Niosomes are preferred over all these dosage form for its cost and stability.[10-15] niosmes are the non-ionic surfactant vesicles of lamellar and microscopic nature. Niosomes formulated by the surfactant has been found to be biodegradable, non immunogenic and biocompatible. Incorporation of these surfactants into the niosomes increases efficiency of the drug e.g.Nimesulide, Flurbiprofen, Bleomycin, Ketoconazole, etc.[16-21]

ADVANTAGES OF NIOSOMES

The niosomes are widely used in cosmetics and for therapeutic purpose for providing wide range of applications[22-28].

- They have delayed clearance thus provides high therapeutic performance.
- The delivery in the non aqueous phase as emulsion can be regulated by dispersion of niosomes in aqueous phase.
- They are stable and impart stability to the entrapped drug.
- They do not require any special storage condition.

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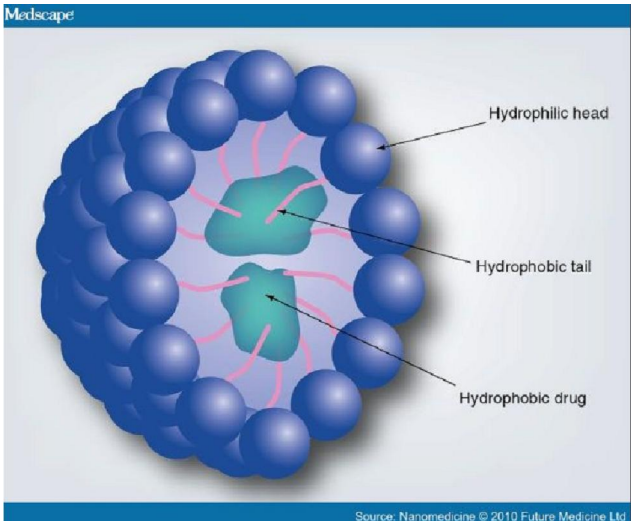

Fig. 1. Niosomes

- Targeted site of action by oral, parenteral peroral, transdermal as well as topical routes
- Parenteral route may be intra muscular and intravenous
- They are the vesicle to provide controlled release of drug.
- The vesicle suspension is water based thus provides the increased patient compliance over the oily based dosage form.
- They provide increased bioavailability.
- They can be designed based on the situation as the nisome has flexibility in their structural charecteristics.
- It protects drug from the biological environment.
- They provide wide range of solubility due to presence of hydrophilic, amphiphillic and lipophillic moieties together.
- Niosomes are osmotically active.

METHODS OF PREPARATION

- 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[29-34]

The preparation of niosomes includes the introduction of the solution dissolved in the solution of diethyl ether at 60^0c. They are been injected into aqueous solution by the needle of size about 14 gauze. On further vaporization of ether there forms a single layered vesicle of 50 to 1000 nm.

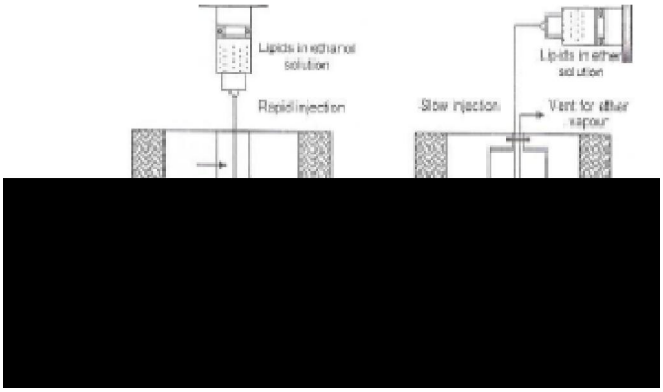

Fig. 2. Ether injection method

Thin film hydration technique (hand shaking method)[35-40]

Cholesterol, surfactant and other vesicle forming agents are dissolved in volatile organic solution (diethyl ether, chloroform and methanol). They are carried out in the round bottomed flask and the solvent is evaporated either at room temperature (20^0c) or by rotary evaporator. The dried surfactant layer being deposited on the walls of the flask which are rehydrated at 60^0C with gentle shaking. They are mainly used to form multilamellar vesicles.

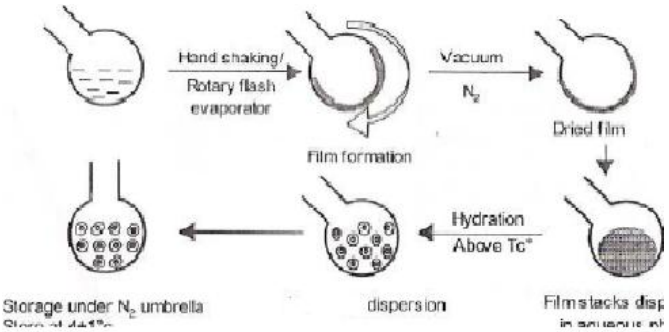

Fig 3. Thin film hydration technique (hand shaking method)

Sonification method[41-45]

It is the most prominent method where vesicles have been produced by sonification of the solution. This method was described by Cable. A small portion of drug solution in buffer is been added to either surfactant or cholesterol mixture in a 10 ml vial. The prepared mixture is probe sonicated at 60^oc for 3 min using sonicator with a titanium probe which yield niosomes.

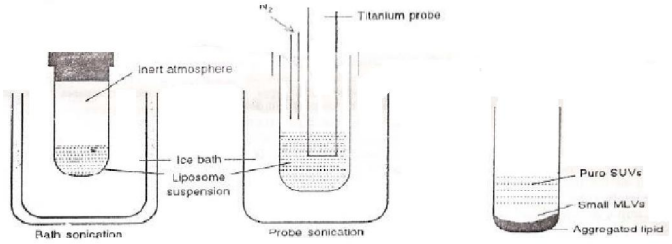

Fig 4. Sonification method

Reverse phase evaporation technique[46-47]

Cholesterol and surfactant (1:1) is added to the mixture of ether and chloroform. An aqueous phase containing drug is added to this mixture and resulting two phase are been sonicated at 4-5^{o}C , results in the formation of the clear gel they are sonicated again after the addition of aliquot of phosphate buffered saline (PBS). At 40^{o}C and reduced pressure the organic phase is removed forming a viscous suspension is diluted with PBS and heated at 60^{o}C for 10 minutes to form niosomes.

Microfluidization[48-52]

It is a recent technique to produce unilamellar vesicles of defined size distribution. The method includes the submerged jet principle in which two fludized stream interact at ultrahigh velocities, in precisely defined micro channels within the interaction chamber. They are impingemented into thin liquid sheet through a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller and better reproducibility of niosomes formed.

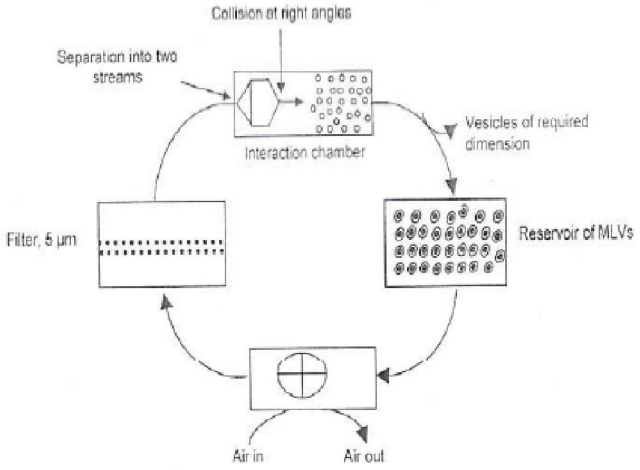

Fig 5. Microfluidization

Multiple membrane extrusion method[53-55]

Surfactant, cholesterol and diacetyl phosphate solublised in the cholesterol and evaporated to remove the solvent results to a thin film. They are hydrated using aqueous drug solution forming suspension that is excluded poly carbonate membrane. They are arranged in a passage of eight series. This method provides the production of niosomes of desired size.

Transmembrane pH gradient (inside acidic) drug uptake process (remote loading) [56-59]

In this method surfactant and cholesterol are blended to which excess cholesterol is added in the round bottomed flask container. They are evaporated under pressure using vortex motion. It is used to form the multilameller vesicles.

Bubble method[60-61]

It is a single step preparation of niosomes in the absence of organic solvent. A round bottom flask with three necks positioned in water

bath for controlling the temperature constitutes the bubbling unit. In the first neck of bubbling unit water- cooled reflex has been positioned followed by the thermometer in the second neck. Through the third neck sufficient nitrogen gas is supplied to be buffered (pH 7.4) add cholesterol and surfactants which is homogenized for 15 seconds using high shear homogenizer and soon after they have been doubled at 70^0C by inert gas nitrogen.

Formation of niosomes from proniosomes[62-64]

It is an alternative method where dry niosomes are formulated by coating a soluble carrier like sorbitol and surfactants. Each water soluble particles are coated with a thin film of dry surfactants which is known to be the proniosomes.[15]

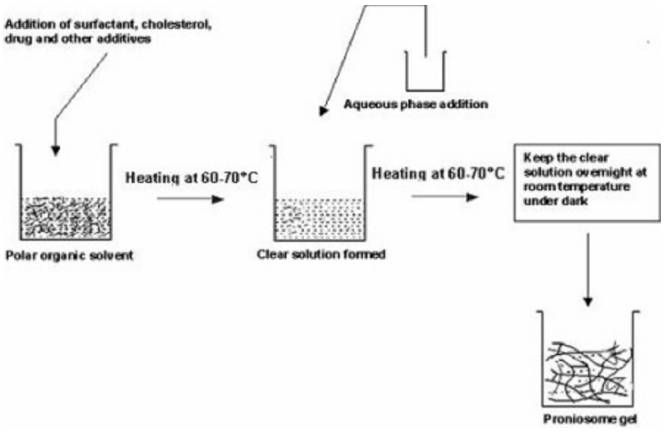

Fig 6. Formation of niosomes from proniosomes

EVALUATION

Vesicle size and morphology[65-70]

The size of niosomes range from 20 nm – 50 µm. Large niosomes with diameters above 1µm can be measured by coulter counter and light microscopy technique. To determine the vesicle size in submicron size, light scattering technique can be used further study of shape and surface of niosomes can be done by scanning electron microscopy, atomic force microscopy, cryo transmission electron microscopy.

Vesicle charge[71-72]

Vesicle surface charge has great impact niosome behavior both *in vivo* and *in vitro* the uncharge vesicle are less stable when compared to charged niosomes whereas the zeta potential can be measured by micro electrophoresis. The most recent technique used was dynamic light scattering.

Entrapment efficiency[73-79]

Dialysis, centrifugation and gel filtration are most widely used technique for the separation of untrapped drug from niosomal dispersion the complete vesicle disruption by using 0.1% TritonX-100 or 50% n-propanol, the resultant solution was homogenized, centrifuged and supernatant liquid assayed for drug after suitable dilution using following equation[18].

Entrapment efficiency = $\frac{\text{amount entrapped}}{\text{Total amount added}} \times 100$

***Invitro* release study**[80-88]

Human cadaver skin (HCS) stored at 4^0C was spreaded and punched approximately 3 cm^2 area. It was sliced to 500 mm thickness using a Daw's dermatone. It was hydrated in pH 7.4 buffer for 24 hr prior to use. The skin was attached to khesary cell which is filled with 100 ml of phosphate buffer and added 10 mg of niosomal suspension. This set up was immersed in receptor compartment by the dermal surface just flash to the surface of permeation fluid and stirred by magnetic stirrer at 50 rpm. Aliquots of 10 ml were withdrawn and replaced with same volume of fresh buffer at every sampling point. The final solution was analysed spectrophotometrically by U.V Spectrophotometer.

Stability studies[89-92]

The stability studies are carried out by storing the niosomal formulation at 4^oC, 25^oC and 37^oC in thermostatic oven for three months. They are further checked by referring the *invitro* release study of the drug.

APPLICATION

Niosomes as a drug carrier [93-94]

Niosomes as liposomes are used for the treatment of cancer. The anticancer drug which is been loaded into the niosomes are anticipated to be accumulated inside the tumor. The tumoricidal and drug release activity is increased by addition of Doxorubicin and methotrexate.

Niosomes as a diagnostic agent [95]

Gadobenatedimeglcemine, PEG 4400, PEG and NPG exhibit significantly as a diagnostic agent for imaging tumor.

Niosomes as therapeutic agents [96]

Niosomes are less marketed and their uses are based on the experimental evaluation of drug. They include the

1. Anti-cancer drugs
2. Anti infective agents
3. Anti inflammatory agents

Anti cancer drugs

Daunorubicin Hcl[97]

Niosomal daunorubicin are more potent than in the free form since they destroys the Dalton's ascetic lymphomas cell present in the peritoneum in the period of three days where as the free drug requires about six days and was found to be incomplete. Niosomal formulation also achieves high efficiency.

Doxorubicin

The niosomal doxorubicin formulation includes the mixture of C16 mono alkyl glycerol ether either in the presence or absence of the cholesterol. It provides targeted action on the tumor cells, thus it has decreased proliferation and increase in the span of drug.

Anti infective agents[98]

The sodium stibogluconateare formulated as niosomal preparation for the ailment of leshmaniasis which is a protozoa diseases. They have high efficacy which is due to high levels of antimony. E.g. Niosomal rifampicim has found to exhibit the antitubercular activity.

Anti inflammatory agents[99]

Niosomal dichlofenac sodium in 70% cholesterol exerts an anti inflammatory activity.Niosomal nimesulide and flurbiprofen are also found to have anti inflammatory activity.

Niosomes in transdermal drug delivery [100]

It is used so due to its advantage over the crossing of first pass metabolism. Thus exhibits slow release into the skin. Eg. Niosomal nimesulide and dichlofenac sodium.

Niosomes used in ophthalmic drug delivery system.[101]

The tear production from eye, impermiablity of corneal epithelium, non productive absorption and transient residence decreases the bioavailability of the drug. Thus it can be overcome by the use of the niosomal acetazolamide which are bioadhesively coated and has the span of 60. The use of chitosan coated timolol sulphate as the niosomal formulation is used to decrease the intraocular pressure with reduced cardiovascular side effects.

Conclusion

Niosomes as novel drug delivery system has greater potential impact creating glorious future for pharmaceutical scientists. The convenient way of dosing medication makes a significant improvement in terms of drug release obtaining better therapeutic blood levels making it superior in comparison to other novel drug delivery system. Since, drug delivery by targeted action by niosomes is prominent, stable, it is a well preferred drug delivery system than liposomes. Thus niosomes have wide spread not only in protein endorsment and vaccines but also in encapsulating toxic drugs. Hence niosome is a boon in novel drug delivery system throwing its sparkling lights as efficient vesicular drug delivery system.

REFERENCE

1. Breimer D D and Speised R. 'Topics in Pharmaceutical Sciences'. Elsevier Science Publishers, Newyork, USA. 1985; 291.
2. Handjani VRM. Dispersion of Lamellar Phases of Nonionic Lipids in Cosmetic Products. *Int J Cosmetic Sci.1979*; 30.
3. Sternberg B, Uchegbu IF, Florence AT and Murdan S. 1998
4. Theresa MA. Drugs Published by *A dis international Ltd. 1998;* 56(5):747-756.
5. Breimer DD and Speiser R. 'Topics in Pharmaceutical Sciences'. Elsevier Science Publishers, New York, USA. 1985; 291.
6. Allen TM: 'Liposomal drug formulations': Rationale for development and what we can expect for the future. Drugs, 1998, (56), 747-756.
7. Karim K. M., Mandal A. S., Biswas N., Guha A., Chatterjee S., Behera M., Kuotsu K. Niosome: A future of targeted drug delivery systems. *J Adv Pharm Tech Res. 2010*; 1: 374-380.
8. Mujoriya R. Z., Bodla R. B. Niosomes – challenge in preparation for pharmaceutical scientist*. Int J App Pharm*. 2011; 3: 11-15.
9. Arunothayanun P., Turton J.A., Uchegbu I.F., Florence A.T. Preparation and *invitro invivo* evaluation of luteinizing hormone releasing hormone (LHRH)-loaded polyhedral and spherical tubular niosomes, *J. Pharm. Sci*.1999;88: 34-38.
10. Hunter CA. Vesicular system (Niosomes and Liposomes) for Delivery of Sodium stibogluconate in Experimental murine Visceral Leishmaniasis. *J pharm Pharmacol.* (1988); 161.
11. Malhotra M., Jain N.K.Niosomes as 'Drug Carriers. Indian Drug'. 1994; 31: 81-86.
12. Girigoswami A., Das S., De S. Fluorescence and dynamic light scattering studies of niosome membrane mimetic systems. *Spectrochimica Acta Part A. 2006*; 64: 859–866.
13. Vyas SP and Khar RK. 'Targeted and Controlled Drug Delivery Novel Carrier Systems'. CBS Publishers and Distributors, New Delhi (2011) 249 -279.
14. Biju SS, Telegaonar S, Mishra PR, Khar RK: Vesicular system: an overview, *Indian J Pharm Sci, 2006*, (68) 141-153.
15. Indhu PK, Garg A, Anil KS, Aggarwal D: Vesicular system in ocular drug delivery. *Indian J Pharm Sci, 2004,* (269), 1-14.
16. Reddy DN and Udupa N. Formulation and evaluation of oral and Transdermal preparation of Flurbiprofen and piroxicam incorporated with different carrier. *Drug dev Ind Pharm, 1993*;843.
17. Udupa, N. (2004). Niosomes as drug carriers. In: N. K. Jain. 'Controlled and Novel Drug Delivery' (pp. 292-303). New Delhi: CBS Publishers & Distributors.
18. Shahiwala A., Misra A. Studies in Topical Application of Niosomally Entrapped Nimesulide. *J. Pharma. Sci. 2002;* 5:220-225. Vol. 2 (2), July-Sept, 2012.
19. Reddy D.N., Udupa N. Formulation and Evaluation of Oral and Transdermal Preparation of Flurbiprofen and Piroxicam Incorporated with Different Carriers. *Drug Dev. Ind. Pharm. 1993*; 19:843-852.
20. Satturwar P. M. Formulation and Evaluation of Ketoconazole Niosomes*. Ind. J. Pharm. Sci. 2002*; 64:155-158.
21. NareshR.A.R. Kinetics and Tissue Distribution of NiosomalBleomycin in Tumor Bearing Mice. *Ind. J. Pharm. Sci. 1996*; 58:230.
22. Malhotra M. and Jain N.K. Niosomes as Drug Carriers.' Indian Drugs' (1994), 31 (3): 81-86.
23. Blazek-Welsh A.I., Rhodes D.G.Maltodextrin-based proniosomes, *AAPS Pharm. Sci. 2001*; 3:E1.
24. Uchegbu I.F., Double J., Turton T.A., Florence A.T. Distribution, metabolism and tumoricidal activity of doxorubicin administered in sorbitanmonostearate (Span 60) niosomes in the mouse*. Pharm. Res. 1995*; 12: 1019-1025.
25. Yoshioka T., Sternberg B., Florence A.T. Preparation and Properties of Vesicles (Niosomes) of Sorbitan Monoesters (Span-20, Span-40, Span-60 and Span-80) and ASorbitanTriester (Span-85). *Int. J. Pharm. 1994*; 104: 1-6.
26. Hao Y., Zhao F., Li N., Yang Y., Li K. Studies on a high encapsulation of colchicine by a niosome system. *Int. J.Pharm. 2002;* 244: 73-80.
27. Fang J.Y., Yu S.Y., Wu P.C., Huang Y.B., Tsai Y.H. In vitro skin permeation of estradiol from various proniosomes formulations. *Int. J. Pharm. 2001;* 215: 91- 99.
28. Buckton G, Harwood. Interfacial phenomena in drug delivery and targeting. Switzerland: Academic Publishers;1995. pp.154-5.
29. Rogerson A., Cummings J., Willmott N., Florence A.T. The distribution of doxorubicin in mice followingadministration in niosomes, *J. Pharm. Pharmacol.1988*; 40: 337–342.
30. Baillie A.J.,Coombs G.H., Dolan T.F.. Non-ionic surfactant vesicles (niosomes) as delivery system for the antileishmanialdrug, sodium stibogluconate, J. *Pharm. Pharmacol. 1986*; 38: 502-505.
31. Guinedi A. S., Nahed D. M., Samar M., Rania M. H. Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide*. Int J Pharm. 2005;* 306: 71–82.
32. Yasin M. N., Hussain S., Malik F., Hameed A., Sultan T., Qureshi F., Riaz H., Perveen G., Wajid A. Preparation and characterization of chloramphenicol niosomes and comparison with chloramphenicol eye drops (0.5%w/v) in experimental conjunctivitis in albino rabbits. *Pak J Pharm Sci. 2012*; 25: 117-121.
33. 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.
34. Deamer, D and Bhangham, AD (1976), "Biochem. Biphys. Acta, 443, 629-634. YektaOzer, AtillaHinal A; Bouwstra, Joke A (1991) *Eur. J. Pharm. Biopharm*., 37(2), 75-79.
35. Bhaskaran S., PanigrahiL. Formulation and evaluation of niosomes using different non-ionic surfactant. *Ind. J.Pharm. Sci. 2002;* 64: 63-65.
36. Rogerson A., Cummings J., Willmott N. and Florence A.T. The distribution of doxorubicin in mice following administration in niosomes. *J Pharm Pharmacol. 1988*; 40(5): 337–342.
37. 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.
38. Palozza P., Muzzalupo R., Trombino S., Valdannini A., Picci N. Solubilization and stabilization of beta-carotene in niosomes: delivery to cultured cells. *ChemPhys Lipids. 2006;* 139: 32–42.

39. 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.
40. Azmin, MN; Florence, AT; Handajani, VR; Stuart, JFB; Vanlerberghe, G and Wittakar, JS (1985), "The effect of nonionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice", *J. Pharm. Pharmacol.*, 37,237-242.
41. Baillie A.J., Coombs G.H. and Dolan T.F. Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmanial drug, sodium stribogluconate*J.Pharm.Pharmacol. 1986;* 38: 502-505.
42. Carter K.C.The therapeutic effect of sodium stibogluconate in BALB: c mice infected with Leishmaniadonobani is organ dependent. *J Pharm Pharmacol. 1988*; 40: 370–373.
43. Hofland H. E. J. Safety aspects of non-ionic surfactant vesicles-a toxicity study related to the physicochemical characteristics of non-ionic surfactants. *J Pharm Pharmacol.* 1992; 44:287-294.
44. Bhaskaran S., PanigrahiL. Formulation and evaluation of niosomes using different non-ionic surfactant. *Ind. J.Pharm. Sci. 2002;* 64: 63-65.
45. Rogerson A, Cummings J, Willmott N and Florence AT. The Distribution of Doxorubicin in Mice Following Administration in Niosomes. *J Pharm Pharmacol. 1988*; 40(5):337–342.
46. 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
47. Guinedi A. S., Nahed D. M., Samar M., Rania M. H. Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. *Int J Pharm. 2005;* 306: 71–82.
48. 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.
49. Khandare JN, Madhavi G, Tamhankar BM. Niosomes: Novel drug delivery system. *The Eastern Pharmacist. 1994*; 37:61-4.
50. Mayer LD, Bally MB, Hope MJ, Cullis PR: Uptake of antineoplastic agents into large unilamellar vesicles in response to a membrane potential. *BiochemBiophysActa, 1985,* (816), 294-302.
51. Khandare J. N., Madhavi G., Tamhankar B. M. Niosomes novel drug delivery system. The *Eastern Pharmacist. 1994;* 37: 61-64
52. Cook E.J., Lagace A.P.' Apparatus for forming emulsions'.US Patent. 4254553, 1985.
53. 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.
54. 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.
55. Suggy S, Murrari CR, Ahmed Niosomes (a review) *Biopharm.2004*, 24-37
56. Chauhan S and Luorence MJ and Cullis PR. *BiochemBiophysActa. 1985;* 816:294-302.
57. Maver LD, Bally MB, Hope MJ and Cullis PR. *BiochemBiophysActa.*1985; 816:294-302.
58. KaziMasudKarim, AsimSattwaMandal, Nikhil Biswas, ArijitGuha, Sugata Chatterjee, MamataBehera: Niosome: A future of targeted drug delivery systems. *J Adv Pharm Tech Res, 2011,* (62), 122.
59. 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.
60. Blazek-Walsh AI, Rhodes DG. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes. *Pharm. Res. 2001;*18:656-61
61. Chauhan S, Luorence MJ. The preparation of polyoxyethylene containing non-ionic surfactant vesicles. *J. Pharm. Pharmacol. 1989*; 4:6.
62. Blazek Welsh AI, Rhodes DG: SEM Imaging Predicts Quality of Niosomes from Maltodextrin-Based Proniosomes. *Pharm Res, 2001*, (18), 656-661.
63. Baidya S, Gupta BK, High Technology site-specific approach through niosomes drug delivery system. Indian *J Pharm. Pharmacol. 40*, 1988, 32:39-42.
64. Lassic D. Niosomes: from Physics to application. 'Amsterdam Elsevier': 1993.
65. Carter, KC, Baillie AJ, Alexander J, Dolan TF. The therapeutic effect of sodium stibogluconate in BALB: c mice infected with Leishmaniadonoani are organ dependant. *J. Pharm. Pharmacol.40, 1988*, 370-373.
66. Chauhan S. and Luorence M.J. The preparation of polyoxyethylene containing non-ionic surfactant. Vesicles. *J. Pharm. Pharmacol. 1989*; 41: 6p.
67. Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F: Vesicles of Non-ionic Surfactants (Niosomes) and Drug Delivery Potential. *Int J of Pharm Sci and Nanotechnology, 2008, (1*), 1-8.
68. Almira I, Blazek-welsh IA, Rhodes GD: Maltodextrin –Based proniosomes. *AAPS Pharm Sci Tech, 2001,* (3), 1-8.
69. Manosroi A: Characterization of Vesicles Prepared with Various Nonionic Surfactants mixed with Cholesterol. *Colloids and surfaces Biointerfaces, 2003.P.129.*
70. Malhotra M., Jain N.K. Niosomes: A Controlled and Novel Drug delivery System.' Indian Drugs. 1994'; 31: 81-86
71. Khan A., Sharma P. K., Visht S., Malviya R. Niosomes as colloidal drug delivery system: *A review. Journal of Chronotherapy and Drug Delivery.* 2011; 2: 15-21.
72. Desai A.R., Raghuveer I., Chitme H.R., Chandra R. Niosomes: A Controlled and Novel Drug delivery System. *Drug Invention Today. 2010*; 2: 325- 327.
73. Balasubramanyan A. Formulation and *invivo* evaluation of noisome encapsulated daunorubicin hydrochloride. *Drug Dev and Ind Pharm. 2002;* 1181.
74. Chauhan S, Luorence MJ, The preparation of poly-oxyethylene containing non-ionic surfactant vesicles, *J. Pharm. Pharmacol, 41,* 1989, 6.
75. Yoshioka T, Sternberg B, Florence AT, Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60, and 80) and a sorbitantriester (Span 85), *IntJ. Pharm, 105,* 1994, 1-6.
76. AlemayehuTarekegn, Nisha M Joseph, S Palani, AnishZacharia, ZelalemAyenew: niosomes in targeted drug delivery: some recent advances. *IJPSR, 2010,* (9), 1-8.
77. Yoshida H., Lehr C.M., Kok W., Junginger H.E., Verhoef J.C., BouwistraJ.A.. Niosomes:
78. Gayatri D.S., Venkatesh P., UdupaN.Niosomalsumatriptan succinate for nasal administration. *Int. J. Pharm. Sci. 2000*; 62: 479-481.
79. Silver B.L.The physical chemistry of membranes'. Unwin and Soloman Press, New York, USA, 1985.]
80. A Controlled and Novel Drug delivery System. *J.Control Rel. 1992*; 21: 145-153.
81. Szoka FJR, Papahadyopoulos D, comparative properties and methods of preparation of lipid vesicle (liposomes), *Ann.Rev. Biophys. Bioeng, 9, 1980,* 467-500.
82. Szoka FJR, Papahadyopoulos D, Comparative properties and methods of preparation of lipid vesicles (liposomes), *Ann. Rev. Biophys. Bioeng, 9, 1980*, 501-508.
83. Sattuwar PM, Khandare JN, Nahde VS, Niosomal delivery of Ketoconozole, *Indian Drugs, 38(12), 2001*, 620-623.
84. Yoshioka T, Sternberg B, Florence AT: Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60, and 80) and a sorbitantriester (Span 85). Int*J Pharm, 1994,* (105),1-6
85. Malhotra M, Jain NK: Niosomes as Drug Carriers. *Indian Drugs, 1994, (31),* 81-86.

86. Weismann G *et al*: General method for the introduction of enzymes, by means of immunoglobulin coated liposomes, into lysosomes of deficient cells. *ProcNatlAcadSci, 1975, (72)*, 88-92
87. Keservani R.K., Sharma A.K., Ayaz1 M., KesharwaniR.K. Novel drug delivery system for the vesicular delivery of drug by the niosomes. *Int J of Research in Controlled Release. 2011*; 1: 1-8.
88. Karki R, Mamatha GC, Subramanya G, Udupa N. Preparation, characterization and tissue disposition of niosomes containing isoniazid. *Rasayan J Chem 2008;* 1:224-7.
89. Balasubramanium A, Dasaratha DM, Vangala AK, Formulation and *In-vitro* evaluation of niosomes encapsulated Daunorubicin hydrochloride ,*Indian Drugs, 39(1), 2002*, 27-31
90. Muller D., Foulon M., Bonnemain B., Vandamme T. F. Niosomes as carriers of radiopaque contrast agents for X-ray imaging. *J. Microencapsul. 2000*; 17: 227-243.
91. Erdogan S., Ozer A.Y., BilgiliH. Niosomes: A Controlled and Novel Drug delivery System. *Intl J of Pharmaceutics. 2005;* 295: 1-6.
92. Rogerson A, Cummings J, Florence AT. Adriamycin-loaded niosomes: *Drug entrapment, stability and release. J. Microencap. 1987;* 4:321.
93. Malhotra M. and Jain N.K. Niosomes as Drug Carriers. *Indian Drugs (1994), 31 (3)*: 81-86.
94. Gregoriadis G: Targeting of drugs: implications in medicine. *Lancet, 1981, (2),* 241-246.
95. Luciani A. Glucose Receptor MR Imaging of Tumors: Study in Mice with PEGylated Paramagnetic Niosomes. *J Radiology. 2004*; 135.
96. Moser Niosomesd' hémoglobine, Preparation, proprieties physicochimiquesoxyphoriques, stabilite. *PharmaActaHelv, 1989,* (64), 192-202.
97. Zhang M., Kataoka K. Nano-structured composites based on calcium phosphate for cellular delivery of therapeutic and diagnostic agents. *Nanotoday. 2009;* 4: 508-517.
98. Carter KC, Dolan TF, Baillie AJ and MacColgan C. Visceral Leishmaniasis Drug Carrier System Characteristics and the Ability to clear Parasites from the Liver, Spleen and Bone Marrow in LeishmaniaDonovani Infected BALB/c Mice. *J Pharm Pharmcol.1989;41(2)*:87-91
99. Malhotra M. and Jain N.K. Niosomes as Drug Carriers. *Indian Drugs (1994), 31 (3*): 81-86.
100. Gregoriadis G. Targeting of drugs: implications in medicine. *Lancet. 1981; 2(8240):* 241-246.
101. Suzuki K. and Sokan K. The Application of Liposomes to Cosmetics. *Cosmetic and Toiletries. 1990*; 105: 65-78.

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