Review Paper

Volume : 3 | Issue : 1 | January 2014 • ISSN No 2277 - 8179

Niosomes: Layered Delivery System For Drug Targeting

Pharma

KEYWORDS : Niosomes, Thin film hydration, Rapid phase evaporation, enhancing bioavailability

Surendra Agrawal	SPPSPTM, SVKM'S NMIMS, Vile Parle (W), Mumbai, MS, India 400 056
Vaishali Londhe	SPPSPTM, SVKM'S NMIMS, Vile Parle (W), Mumbai, MS, India 400 056
Ram Gaud	SPPSPTM, SVKM'S NMIMS, Vile Parle (W), Mumbai, MS, India 400 056

ABSTRACT

The main purpose of this review is to explore and overview the existing self dispersing formulations resulting from dilution of drug into emulsions, microemulsions and surfactant dispersions. The systematic approach used in preparation of niosome and the presentation of the various physico-chemical and biopharmaceutical aspects should facilitate the comprehension of this interesting field and clarify the main considerations involved in designing and characterizing a specific self dispersing drug delivery system. These Vesicular systems act as new drug delivery systems which enhance bioavailability as well as remedial activity of encapsulated drug in controlled manner. Niosomes formed from non-ionic surfactant vesicular system which can be easily formulated in the laboratory. Method of formulation, nature of surfactant, encapsulated drug temperature at which the lipids are hydrated and the packagings of niosomes play an effective and important role in the formulation of these vesicular systems. This vesicular system has unilamellar and multilamellar structures from the non-ionic surfactants and cholesterol. These are the bilayered structures in which hydrophilic as well as lipophilic drugs can be entrapped. This review article describes all aspects of niosomes including different composition, scalable techniques. Also it focuses on strength of formulation, limitations in respect to industrial applicability and regulatory requirements concerning the drug formulation based on FDA and EMEA documents. The review also provides detailed information of the various types of niosomes formulated for successful delivery by using different encapsulated drugs.

INTRODUCTION:

Niosomes are the new vesicular drug delivery systems formed from nonionic surfactants, in which the drug is entrapped in vesicle. . These vesicles are bilayered structures of nonionic surface active agents and lipids or cholesterol. Thus they form lamellae around the encapsulated drug. The niosomes are very small and minute in size. They have a size range in nanometric scale (Makeshwar & Wasankar, 2013). Liposomes are structurally different from niosomes and have features different from lipid vesicles (Liposomes)

Salient Features of Niosomes:

- Have capacity to entrap in similar way as liposomes
- Highly osmotic and stable in nature
- Structurally constitutes of Hydrophobic and hydrophilic moieties together so that drug molecules can entrap easily.
- Have flexibility in composition, fluidity and their size that is can change according to dosage form..
- Have the ability to improve bioavailabity and therapeutic index of drug molecules.
- Protects the drug from external natural environment.
- Biodegradable, nontoxic, non immunogenic in nature.

The arrangement formed is closed bi-layers and usually involves some input of energy such as physical shakeup or heat. This results into an understanding in which the hydrophobic parts and hydrophilic parts are in maximum contact. These structures are related compounds as alternatives to phospholipids (Saini A, 2011). Niosomes were first formulated and reported in the seventies as a feature of the cosmetic industry but have since been studied as drug targeting agents. Niosome constitutes of non-ionic surfactants, formulation methodologies, toxicological studies. They are low cost, have greater stability and can be easily of stored (Tangri & Khurana, 2011).

Factors governing the self assembly of non-ionic surfactants into niosome

Non-ionic surfactant structure

Niosomal formulation whole and sole is dependent on the non ionic surfactants which are used and their properties which can entrap aqueous soluble drug; in certain cases cholesterol is required in the formulation and vesicle aggregation (Makeshwar & Wasankar, 2013).. Surfactants of all classes are classified according to important parameter the hydrophilic lipophilic balance (HLB) which acts as good indicator of the vesicle forming ability of any surfactant. With the sorbitan monostearate(Span) surfactants, a HLB number of between 4 and 8 was found to be compatible with vesicle formation. The other surfactants that can be used to formulate niosomes are ester linked surfactants, ether linked surfactants, di-alkyl chain surfactants which are totally dependent on HLB scale and the carbon bonding.

Membrane additives:

The most common stabilizer found in niosomal systems is cholesterol or Fatty acids. Thus in cases where a mixture of surfactants or cholesterol is used to prepare niosome, the bi-layer membrane is in ordered structure and may exist in the gel state or the liquid crystalline state, called the lamellar phase (Saini A, 2011)**.** For any system the liquid crystalline state exists at a higher temperature than the gel state systems. Surfactant niosomes prepared without adding cholesterol, forms a gel and only after the addition of cholesterol, niosome dispersion can be obtained. Cholesterol is thus usually included in a 1:1 molar ratio in most formulations. However even after the addition of cholesterol, the intrinsic phase transition behaviour of vesicle forming surfactants still influences the properties of the dispersion: notably the membrane permeability, encapsulation efficiency, bilayer rigidity, ease of rehydration of freeze dried niosomes, toxicity (Tangri & Khurana, 2011).

Encapsulated drug's nature:

The most important factor which is considered is the nature of encapsulated drug whether it is amphilic or not. To determine encapsulation efficiency of the niosomal aqueous suspension, suspension is ultracentrifuged, supernatant is removed and residue is washed twice with ethanol or n-propyl alcohol. Entrapment of drug in niosomes increase vesicle size, most likely by interaction of solute with surfactant by increase its size and charge and mutual repulsion of the surfactant bilayers (Tangri & Khurana, 2011). .

Surfactant and lipid levels:

The mean size of niosomes increases with increase in the HLB value of surfactants because the surface free energy decreases with an increase in hydrophobicity of surfactant.Depending on the temperature these vesicles are in liquid state or in gel state the type of surfactant which is used.In the gel state alkyl chains are framed in a well ordered structure and in the liquid state the structure of the bilayers is more disordered (Biswal *et al.,* 2008).

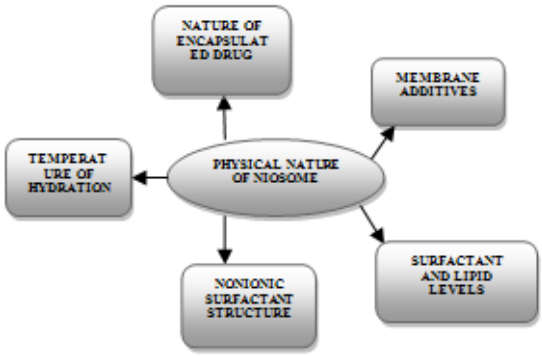

Figure: Factors influencing physical nature of niosome

Temperature of Hydration:-
The hydrating temperatures are required for formation of niosomes and are above the gel to liquid phase change of the system. Normally hydration of the thin film is formed from cholesterol and surfactant on the sides of round bottom flask is hydrated by using phosphate buffer (pH 7.4) for 60 °C on water bath. Then further they are sonicated and the film gets hydrated (Biswal *et al*., 2008).

SURFACTANT USED IN THE FORMATION OF NIOSOMES:
Niosomes are non-ionic surfactant unilamellar, multilamellar vesicles formed from artificial non-ionic surfactants (Biswal *et al*., 2008). These surfactants are observed according to their HLB scale (hydrophilic-lipophilic balance), thus it is the good indicator of the vesicle forming ability of any surfactant. Vyas US (1998) reported the surfactants which can be commonly used are:-

- Ether linked surfactants
- Di alkyl chain surfactant
- Ester linked surfactant
- Sorbitan Esters

NIOSOME PREPARATION:
The formation of the vesicular assemblies requires some form of energy and all experimental methods consist of hydration of mixture of the surfactant/lipid at elevated temperature followed by size reduction thus obtains a colloidal dispersion (Makeshwar & Wasankar, 2013; Saini A, 2011). Method involves addition of aqueous solvent to a solid mixture of lipids and surfactant is commonly used in laboratory and most suitable method. Drug loading in vesicular systems are done and are listed in table no 1.

Ether injection: Surfactant and cholesterol is dissolved in diethylether and then later on injected in aqueous solution of drug. 14 gauge needle is used for formulation.

Thin Film Hydration (Hand shaking Method): Cholesterol and surfactant are mixed into the mixture of organic solvents and then evaporated under low pressure. Film formed is hydrated by using buffer which is used as media, vortexed and sonicated (Kumar & Rajeshwarrao, 2011).

Rapid Phase Evaporation Method: oil in water mixture is prepared by adding organic solvent to surfactants and cholesterol and then further aqueous solution of drug is added and it is evaporated under low pressure and then sonicated.

Sonication: One of typical method of production of vesicles is by sonication of that solution. An aliquot of drug solution is added to the mixture of surfactants and cholesterol film in 10 ml glass vial. The mixture is probe sonicated at 60ºC for 3 minutes using a sonicator with a titanium probe to yield niosomes.

Microfluidization: Recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on jet principle in which two fluidized streams act together at ultra high velocities in defined micro channels within interaction chamber.

Bubbling Method: The homogenisation of a surfactant/lipid mixture followed by the bubbling of nitrogen gas through this mixture. This is new technique and one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round bottomed flask. The dispersal formed is mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70ºC using nitrogen gas.

Table No 1: Preparative Methods of niosomes:

Surfactant Used	Drug (API)	Methods of preparation	Entrapment efficiency	Ref.
Span 60,Tween 61	Diclofenac diethyl ammonium elastic niosomes	Thin Film Hydration with sonication	64% but was improved to 93% (elastic niosomes formed)	Mansoroi & Jantrawut, 2008
Bola – surfactant α,w-hexadecyl-bis-(1-aza-18-crown-6-), Span 80	5-fluorouracil niosomes	Thin Film hydration	By centrifugation method 45.2± 2.2% and by GPC was 44.1± 1.6% and sonicated niosomes were 40.7±3.1% and by GPC were 39.5%	Paolino et al., 2008
Span 20,Span 40,Span 60,Span 80	Flurbiprofen Niosomes formed from Proniosomes	Thin Film Hydration	By exhaustive dialysis and freeze thawing, 41.05± 0.91 (span 20) 42.79± 0.24 (span 40) 44.69±1.04 (span 60) 37.74 ± 0.87 (span 80) and when concn of flurbiprofen improved efficiency 55,67 and 72%	Mokhtar et al., 2008
Span 40 & Span 60	Acetazolamide Multilamellar vesicles	Reverse phase Evaporation, Thin Film Hydration	Entrapment efficiency of span 40 by REV increased from 16.81% to 18.49% & by thin film hydration MLVs were formed and the efficiency increased from 18.21% to 20.74% in molar ratio (7:4 & 7:6)	Guinedi et al., 2005

Span 60 & Tween 60	Ellagic acid niosomes	Reverse phase evaporation by adding solubilizers as Polyethylene glycol (PEG 400 10 & 15% & Methanol was also added	Niosomes prepared with methanol gave lowest entrapment efficiency (% EE = 1.35-3.48) although the solubility is more than PEG or PG.For PEG 400 in 2:1 ratio of span 60:tween 60 in 15% gave the maximum EE that is from 21.27%±1.96 to 26.75 % ± 0.58	Junyaprasert et al., 2012
Span 20, Span 40 , Span 60 , Span 80	Salicylic Acid and p-Hydroxyl benzoic acid	Thin film Hydration	Span 60 > span 40>span 20> span 80 and % E.E was much higher in p-Hydroxyl benzoic acid than Salicylic acid.	Hao & Li., 2012
Span 20, Span 40, Span 60	Diallydisulfide Niosomes	Sonication	In span 20 & 40 % E.E was very low of the molar ratios of constituents used. The maximum entrapment efficiency was observed in Span 80 in (47.5:47.5) molar ratio that is 74.5 ± 3.2%	Alam et al., 2013
Span 60	Aceclofenac Niosomes	Thin Film hydration, Reverse phase Evaporation, Ethanol injection, Sonication,Ether injection	EE of TFH:89.52 %, Reverse phase evaporation: 91.70 %, Ether injection: 86.89 %, Ethanol injection: 68.53 %, Sonication: 71.33 %	Srinivas & Anandkumar, 2010
Span 60	Lansoprazole Niosomes	Reverse Phase Evaporation	% EE of lansoprazole observed was 57.21% initially drug was taken 4.62 mg and the drug after lysis was found 4.01 mg.	Ahuja et al., 2008
Span 80	Acyclovir niosomes	Hand shaking /Thin film hydration and Ether injection	% EE in Hand shaking Method / TFH is in 1:1 -56.12% 1:2 -65.26% 1:3 84.22 and in Ether injection method 1:1 – 45.16% 1:2- 53.44% 1:3- 69.72%	Rangasamy et al., 2008
Span 60, Span 20' Span 40, Tween 20, Brij 76,Brij 78,Brij 72	Paclitaxel Niosomes	Thin Film Hydration	The higher values of % EE was obtained with thosehaving lower HLB values. EE was improved from (12.51 to 96.61%) and it was observed highest in span 40	Bayindir & Yuksel, 2010
Span 60	Orlistat Niosomes	Thin Film Hydration	Among all the formulations the highest entrapment efficiency is 55.90%	Rani & Hari, 2011
Span 20 span 40 span 60 span 80 span 85	Rifampicin loaded niosomes	Hand shaking	Entrapment efficiency decreased progressively for various sorbitan esters used in the order of span 85> span 80 > span 60 > span 40 > span 20	Jatav et al, 2011
Tyloxapol surfactant used and PEG 2000	Formulation of tyloxapol niosomes	Sonication	% EE was higher in antitubercular drugs that are Rifampicin 97± 0.2%, Isoniazide 98.89% and Pyrazinamide 99.5%	Mehta & Jindal, 2013

SEPERATION OF UNENTRAPPED DRUG:

The analysis entrapped drug and the parting from the unentrapped solute can be done by various techniques which include:

- Dialysis
- Gel filtration
- Centrifugation

Although a number of methods are used for this purpose, each method has certain advantages and disadvantages associated with them as listed in table no 2.

Table No 2: Advantages and disadvantages of different methods of separation of entrapped drug from the unentrapped drug

Separation Method	Advantages	Disadvantages
Dialysis	Suitable for large vesicles >10µm,Suitable for highly viscous system, Inexpensive	Extremely slow (5-24 hrs), Dilutes the niosome dispersion, Large volumes of dialysate required
Centrifugation (below 7000 x g	Quick (~ 30 min),Inexpensive instrumentation Concentrates niosome dispersion	Fails to sediment the sub micron niosomes, May lead to the destruction of fragile systems
Ultracentrifugation (15,000×g)	Sediments all size populations, Concentrates the niosome dispersion	Expensive instrumentation, Long centrifugation times (1-1.5 h) , May lead to destruction of fragile systems, May lead to formation of aggregates
Gel Filtration	Quick (4-5 min) with sephadex G50)	Slow (1-2 h) when using Sepharose for macromolecule separation Gels are expensive when not used. Not suitable for high viscous formulations.

The studies for the evaluation involve characterization of niosomes. This characterization includes:

Size, shape and morphology:
Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) is used to determine the mean diameter of the vesicles. The size of niosomes are ranging from 0.5 – 10 µm in size (Kumar & Rajeshwarrao, 2011).

Size distribution, Polydispersity index :
Laser beam is used for mean surface diameter, size distribution and mass distribution of niosomes. Polydispersity index is a measure of the different sizes of molecules or particles in a mixture. A collection of objects is called monodisperse or uniform if the objects have the same size, shape, or mass. A sample of objects that have an inconsistent size, shape and mass distribution is called polydisperse or non-uniform. Polydispersity index is determined by Dynamic light scattering method (Kumar & Rajeshwarrao, 2011).

Viscosity:-
Viscosity is measured with various types of viscometers as well as rheometers. Viscosity is defined as the measurement of fluid resistance to gradual deformation by shear stress or tensile stress. Viscosity in evaluation of niosomes is measured by Ostwald viscometer. Thus the temperature maintained is at 25 ± 0.5 ºC and 35 ± 0.5ºC).

Drug Analysis :
Free and entrapped drug is been determined by UV spectrophotometer or HPLC. That is done by supernatant and residue method. Free drug is subtracted from the total amount of drug taken for the formulation. Then the analysis is done at specific wavelength of drug. In residue method, lysis of entrapped drug is done by n-propanol or ethanol (99.9%).

Entrapment Efficiency:
The drug entrapped in vesicle form it is being determined by entrapment efficiency. Thus how much drug is entrapped in supernatant as well as residue method is compared. Entrapment efficiency is determined as

Entrapped drug = Total drug taken – Free drug calculated (From supernatant method).

Entrapment efficiency can be determined by Dialysis, Centrifugation, and Gel filtration method. Ultracentrifugation method is used for large particle size and is performed at around 20000 rpm. Sometimes, during washing there is drug loss so direct lysis by adding ethanol is done and analysis is done by suitable analytical technique. The other method is Dialysis method by using dialysis bag and thus keeping it for 24 hrs against phosphate buffer saline (pH 7.4). Also Gel chromatography is being done and these are not done for high viscous formulation.

The characterization of samples for above mentioned parameters can be frequently done by various techniques as listed in table no 3.

Table No 3: Methods for evaluation of niosomes

Evaluation parameter	Method
Morphology	SEM ,TEM, freeze fracture technique
Size distribution, Polydispersity index	Dynamic light scattering, particle size analyser
Viscosity	Ostwald viscometer, Brookfield Viscometer
Drug Analysis	UV diode array Spectrophotometer
Entrapment efficiency	Centrifugation,Dialysis,Gel chromatography
In-vitro release study	Dialysis membrane
Permeation study	Franz diffusion cell

***In vitro* release study & Permeation study:**
In vitro release study & Permeation study can be performed by Dialysis membrane and Franz diffusion cell. In *in-vitro* release study of niosomal formulation, disperse in 1ml of phosphate buffer saline and place in dialysis bag. Immerse under release medium keep for 24 hours. At various time intervals, the buffer aliquot is taken and replaced with fresh buffer solution. Later on aliquot should be analyzed for the drug content by appropriate assay method.

MARKETED NIOSOMES:
Lancome is the antiageing marketed product which is based on niosomes formulation (Pola et al, 2012). L'Oreal is also undertaking research on antiageing cosmetic products. Niosomal preparation in the market is – Lancome (www.lancome.com)

APPLICATIONS:
The applications of niosome technology can be used to treat a number of diseases. Kamboj et al (2013) listed drug targeting for Antineoplastic treatment, Leishmaniasis, carriers of Haemoglobin, ophthalmic drug delivery, Transdermal drug delivery.

CONCLUSION:
Drug merging in the niosomes is to target drug to the specific site is newly promising delivery model. Niosomes have a structure similar to liposomes and hence they can represent another vesicular system with respect to liposomes. This is due to their ability to encapsulate different type of drugs. Niosomes are considered to be better for drug delivery as compared to liposomes due to various factors like cost, stability (Alhat et al, 2013). These advantages over the liposomes make it a better target agent. They can be given ophthalmic, topical, parenteral route mainly for better effectiveness. Finally drug in liposomes/ niosomes demonstrate reduces toxicities and retained the enhanced efficacy compared with free complements. However we can say that niosomes will be promising drug delivery systems, these areas need further research and study so as to develop and bring out commercially available niosomal preparation.

Volume : 3 | Issue : 1 | January 2014 • ISSN No 2277 - 8179

REFERENCE

Ahuja, N., Saini, V., Bishnoi, V., Garg, A., Historia, M., Sharma, J., & Nepali K. (2008). Formulation and evaluation of Lansoprazole Niosome. Rasayan Journal of chemistry, 1(3): 561-563. | Alam, M., Zubair, S., & Farazuddin, M. (2013). Development, characterization and efficacy of niosomal diallyldisulfide in treatment of disseminated murine candidiasis. Nanomedicine, Nanotechnology, Biology & Medicine, 9, 247-256. | Alhat, B., & Rukari, T. (2013). Niosomal Drug Delivery System-Promising Drug Carriers. International Journal for inventions in Pharmaceutical Sciences, 1(1), 19-26. | Bayindir, ZS., & Yuksel N. (2010). Characterization of niosomes prepared with various Non ionic surfactants for Paclitaxel oral delivery. J Pharm Sci. 99 (4), 2049-60. | Biswal, S., Murthy, P., Sahoo, P., Sahu, J., & Amir F. (2008). Vesicles of non-ionic surfactants (Niosomes) and drug delivery potential. International Journal of Pharmaceutical Sciences and Nanotechnology, 1(3), 1-8. | Guinedi, A., Mortada, N., Mansour, S., & Hathout, R. (2005). Preparation and evaluation of reverse phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. International Journal of Pharmaceutics, 306, 71-82. | Hao, Y., & Li, K. (2011). Entrapment and release difference resulting from hydrogen bonding interactions in niosome. International Journal of Pharmaceutics, 403, 245-253. | Jatav, V., Singh, S., & Khatri, P. (2011). Formulation and in vitro evaluation of Rifampicin-Loaded Niosomes. Journal of Chemical and Pharmaceutical Research, 3(2), 199-203. | Junyaprasert, V., Singhsa, P., & Chantasart, D. (2012). Physico-chemical properties and skin permeation of span 60/Tween 60 niosomes of ellagic acid. International Journal of Pharmaceutics, 423, 303-311. | Kamboj, S., Saini, V., Magon, N. Bala, S., & Jhawat, V. (2013). Vesicular drug delivery systems: A Novel approach for drug targeting. International Journal of drug delivery, 5, 121-130. | Kumar, G., & Rajeshwarrao, P. (2011). "Non-ionic surfactant vesicular systems for effective drug delivery – an overview. Acta Pharmaceutica Sinica B, 1 (4), 208-219. | Makeshwar, K., & Wasankar, S. (2013). "Niosomes: a novel drug delivery system". Asian Journal of Pharma Research, 3 (1), 16-20. | Mansoroi, A., & Jantrawut, P. (2008). Anti-inflammatory activity of gel containing novel elastic niosomes entrapped with diclofenac diethylammonium, 360, 156-163. | Mokhtar, M., Sammour, O., Hmmad, M., & Megrab, N. (2008). Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes. International Journal of Pharmaceutics, 361, 104-111. | Nasir, A., SL, H., & Kaur, A. (2012) Niosomes: An Excellent Tool for Drug Delivery. International Journal Research in Pharmacy and Chemistry, 2(2), 479-487. | Paolino, D., Cosco, D., Muzzalupo, R., Trapasso, E., Picci, N., & Fresta, M. (2008). Innovative bola-surfactant niosomes as topical delivery systems of 5-fluorouracil for the treatment of skin cancer. International Journal of pharmaceutics, 353, 233-242. | Pola, V., Arunachalam, A., Jeganath, S., Yamini, K., Tharangini, K., & Chaitanya, G. (2012) Nisomes: A Novel drug delivery system. International Journal of Trends in Pharmaceutical Sciences, 2(1), 25-31. | Rangasamy, M., Ayyasamy, B., & Raju, S. (2008) Formulation and in vitro evaluation of niosome encapsulated Acyclovir. Journal of Pharmacy Research, 1(2), 163-166. | Rani, S., & Hari V. (2011). Niosomal formulation of Orlistat. Formulation and In-vitro Evaluation. International Journal of Drug development & Research, 3 (3), 300-311. | Mehta, SK., & Jindal, N. (2013). Formulation of Tyloxapol niosomes for encapsulation, stabilization and dissolution of anti-tubercular drugs. Colloids and Surfaces B: Bio interfaces, 101: 434-441. | Saini, A. (2011). Niosomes: A Novel drug delivery system. International journal of Research in pharmacy and chemistry, 1(3), 498-511. | Srinivas, S., & Anandkumar, Y. (2010). Preparation and evaluation of niosomes containing 3 Aceclofenac. Digest Journal of Nanomaterials and Biostructures, 5 (1): 249-254. | Tangri, P., & Khurana S. (2011). Niosomes: Formulation and Evaluation. International Journal of Biopharmaceutics, 2 (1), 47-53. | Vyas, US. (1998). "Non-ionic surfactant based vesicles (niosomes) in drug delivery". International journal of pharmaceutical sciences, 172, 33-70. |