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NIOSOMES – NOVEL DRUG DELIVERY SYSTEM- A REVIEW

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ABSTRACT

Non-ionic surfactant vesicles or simply noisomes are synthetic vesicles made by hydrating mixture of cholesterol and non ionic surfactants. Different new approaches used for the drug delivery which include liposomes, microspheres, nanoparticles, antibody-loaded drug delivery, magnetic microspheres, implantable pumps, microemulsions and niosomes. Niosomes and liposomes are equiactive in drug delivery potential is more drug efficacy than conventional free drug delivery systems. Niosomes are more preferable over liposomes as they show high chemical stability and less toxic also more economical as they can be made with or without cholesterol. The application of these vesicular systems in cosmetics and also for therapeutic purpose may offer several advantages. As these niosomes entrap the drug to improve the solubility and therapeutic performance by delayed clearance from the circulation and protecting the drug from biological environment and restricting the effect to target cells. The article cites the recent advances in niosomal drug delivery, key advantages over other delivery systems, formulation methods, methods of characterization and applications and recent research on niosomal formulations. Also niosomes have great drug delivery potential for anti-cancer, anti-infective agents, anti-fungal agents. Drug delivery efficacy of niosomes can be enhanced by using novel concepts like proniosomes, discosomes, aposomes. Niosomes also serve as drug carriers, diagnostic imaging aids and as vaccine adjuvant. Thus there is an optimistic scope of research in the formulations of niosomes which are commercially acceptable.

KEYWORDS: Niosomes, Novel drug delivery, Non-ionic surfactant, Cholesterol.

INTRODUCTION[1,26]

Definition of niosomes

Noisomes are a novel drug delivery system, in which the drug is encapsulated in a vesicle. The vesicles are composed of a bilayer of non ionic surface active agents and hence the name niosomes. The niosomes are very small and microscopic in size lies in the nanometric scale. They are structurally similar to liposomes and also have several advantages over them. These are obtained on hydration of synthetic non-ionic surfactants with or without cholesterol or other lipids. These niosomes are used as drug carriers of both amphiphilic and lipophilic drugs. Niosomes are promoting 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. Paul Ehrlich, in 1909 developed the targeted drug delivery mechanism which directly targets the diseased cell.[2] Since then different carriers were used as carriers that carry drug to target tissues or organs these include serum proteins, synthetic polymers, immunoglobulins liposomes, erythrocytes, niosomes etc. Surfactant containing niosomes are incorporated with drugs such as gentamicin[4], oxcarbazepine[6], ketoconazole[7], lansoprazole[18], minoxidil[21], econazole[9], Cytarabine hydrochloride[10], reserveretol, nimesulide, flurbiprofen, piroxicam, bleomycin which exhibit more bioavailability than the free drug. More recently niosomes are used as an anti aging tool in cosmeceuticals. The drug tenofovir- disproxil fumerate(TDF) an anti- HIV drug is formulated as noisome.

The niosomes are formulated as topical, oral parenteral transdermal[19], vaginal mucosal, pulmonary, intranasal and ocular delivery. Noisomes and liposomes are equiactive and have same drug efficacy than compared to the free drug.niosomes are more preferred than liposomes as they exhibit more chemical stability and less toxic and more economical.[3]

Advantages of niosomes[3]

1) Improves the therapeutic efficacy of the drug molecules by delayed clearance from the circulation.
2) Protecting the drug from biological environment and restricting effects to target cells.
3) They are osmotically active and stable and increase the stability of entrapped drug.
4) Handling and storage of surfactants requires no special conditions.
5) Improve the oral bioavailability of poorly absorbed drugs and enhance the skin permeation of drugs.
6) They can be given as oral, parenteral as well as topical to reach the site of action.

7) Controlled drug delivery can be achieved by altering the vesicle size, lamellarity, volume, surface charge and concentration.
8) They have an infrastructure of hydrophilic, amphiphilic and lipophilic moieties together and as a result drug molecules with wide range of solubilities can be incorporated.

Limitations of noisomes[15]

1. Aggregation of niosomes occurs and form a mass this causes drug leakage.
2. Fusion of niosomal vesicles causes difficulties in drug entrapment or drug loading.
3. Physical instability is caused due o drug leakage and cause dosing problems.
4. Hydrolysis of drug which is encapsulated drugs limits the shelf life of niosomal dispersion and thereby cause drug degradation.

Structure of niosomes[3]

Niosomes are microscopic lamellar vesicles their structure is similar to that of liposomes. The basic structure of niosomes consists of the following:

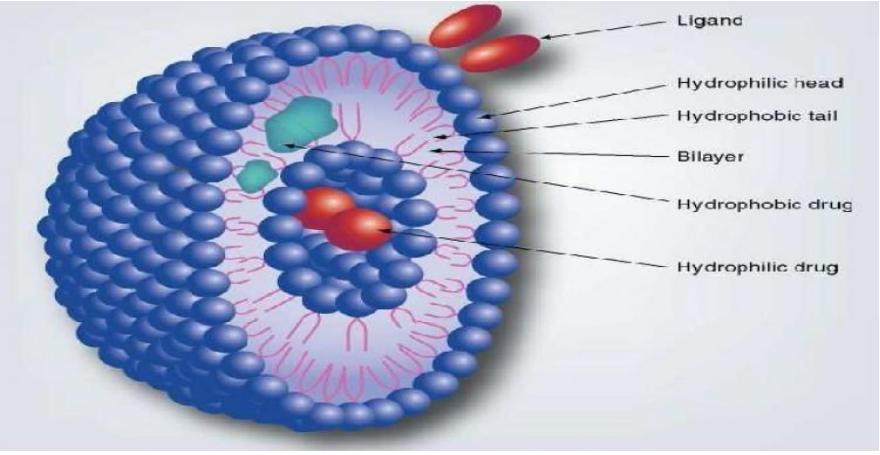

Fig. 1: Structure of noisome.

A.Non ionic surfactant B.Cholesterol or lipid layer.

C.Charge inducing molecule or ligand.

Surfactants - Non-ionic surfactants are used; they considered the important structural component. The non ionic surfactants include terpenoids, polysorbates alkyl oxyethylenes(from C12to C18), ester linked surfactants followed by birjs(poly oxyethylene e.g. birj 35) tweens(poly sorbates e.g. tween 20,40,80), spans(sorbitan esters e.g. Span 20,40,60). These are vesicle formers and relate to the vesicle stability this tendency of forming vesicles depends on the HLB of the non ionic surfactant. HLB number in between 4

and 8 is compatible for vesicle formation and more entrapment efficiency. Another important parameter is the phase transition temperature, higher temperature are more likely to form gel and thereby forming less leakage of the bilayer, hence having higher entrapment efficiency, while surfactants with lower temperature are more likely in liquid form causing instability.

Cholesterol-Cholesterol is a steroid metabolite found in the cell membrane. The inclusion of cholesterol into nisomal composition gives membrane stabilizing activity and also decreases the leaky nature of membrane. It also increases entrapment efficiency and gives rigidity to the niosomal bilayer. Cholesterol forms a lipid layer for the orientation of niosomal layers and thereby abolishing the gel to liquid phase transition of niosomal system which results in niosomes which are less leaky.

Charge inducers – These include solvents, ligands, cations or anions. The solvents act as penetration enhancer and may affect the size of the niosomal vesicle formation. Solvents such as water, ethanol, chloroform, carbapol, methanol, glycerol etc.

Classification[3]

Different types of niosomes are divided on the basis of vesicle size:

1. Small Unilamellar Vesicles (SUV, Size = 0.025 0.05μm)
2. Multilamellar Vesicles (MLV, Size = >0.05
3. Large Unilamellar Vesicles (LUV, Size = >0.10μm).

METHODS OF PREPARATION

1) Hand shaking method (Thin film hydration technique)

In this technique the surfactant and cholesterol were dissolved in a volatile organic solvent(diethyl ether, chloroform or methanol)in a round bottomed flask. The organic solvent is removed at room temperature(20°C) using rotary evaporator leaving thin layer of solid mixture deposited on the wall of the flask. the dried surfactant film is rehydrated with aqueous phase phosphate buffer saline (PBS) of ph 7.4 at 0- 60° C with gentle agitation under normal pressure. This forms typical multilamellar niosomes.[7] SB Sshirsand *et al* has reported the preparation of ketoconazole niosomal gel using tween 60 by this method.

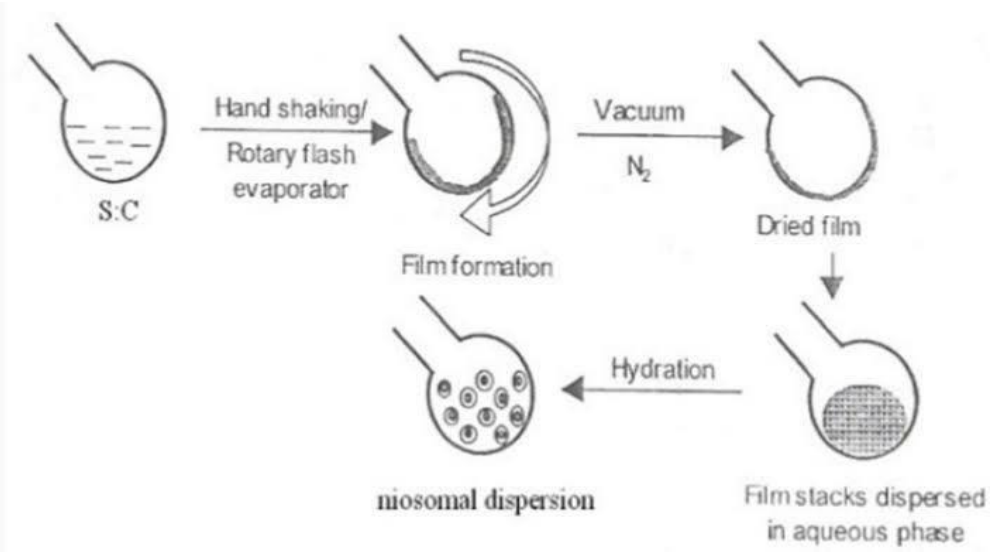

Fig. 2: Hand shaking method (Thin film hydration technique) 2)Microfluidisation.

Micro fluidization is a recent technique used for the preparation of small unilamellar vesicles. It is based on submerged jet principle in which two fluidized streams move forward thorough a precisely defined micro channel and interact at ultra high velocities within the chamber. There is a common gateway which is arranged such that the energy supplied to the system remains within the area of niosomes formation. This results in niosomes with greater uniformity and with smaller size.

3) Reverse phase evaporation (REV)technique[14]

In this method the cholesterol were taken in (1:1) ratio and are dissolved in a mixture of ether and chloroform. To this an aqueous phase containing drug is added and the resulting solution is sonicated at 4-5° C. A clear gel is made which further sonicated by the addition of little mass of phosphate buffered saline (PBS). The organic part is evaporated at 40° C under low pressure. The resulting viscous niosomal suspension was diluted with PBS and heated on a water bath at 60° C for 10 minutes to form niosomes. Large uni lammellar vesicles are formed.

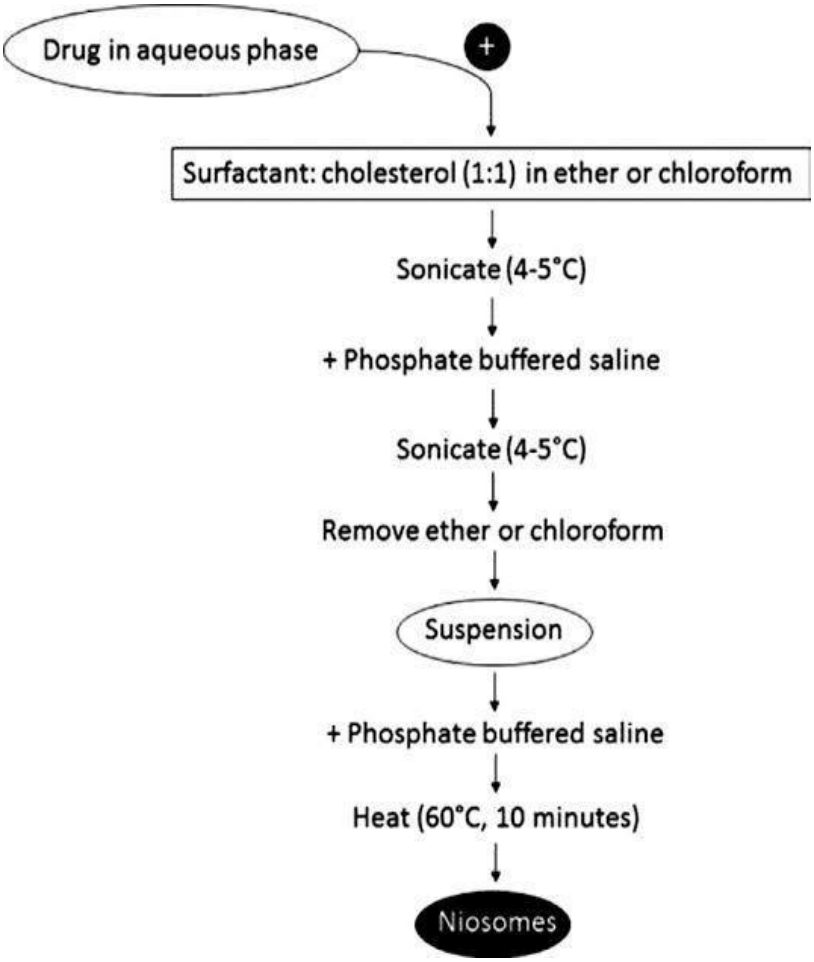

Fig. 3: Reverse phase evaporation technique.

4) Ether injection method

This method gives the means of preparing niosomes by slowly injecting a solution of surfactant which is dissolved in di ethyl ether into a warm water which is maintained at 60° C. the surfactant mixture is injected through a 14- gauge needle into the aqueous solution. Then vaporization of ether leads to the formation of unilamellar vesicles. Depending on the conditions the diameter of vesicle may range from 50-1000nm.

5) Trans membrane pH gradient drug Uptake Process (Remote Loading)

Surfactant and cholesterol are taken in 1:1 ratio in the chloroform and the organic phase was evaporated under reduced pressure and a stream of nitrogen to get a thin film on the wall of the RBF. The lipid film obtained is hydrated with an acidic compound (usually citric acid). The resulting multilamellar vesicles are freeze thawed three times and later sonicated. To this niosomal suspension the aqueous solution containing drug is added and vortexed. The pH of the solution is raised to 7.0-7.2 with 1M disodium phosphate. The mixture is then heated later at 60°C for 10 minutes to yield niosomes.[17] Bhaskaran and lasshmi reported that niosomes

with high entrapment efficiency (EE=87.5%) can be prepared by this method.

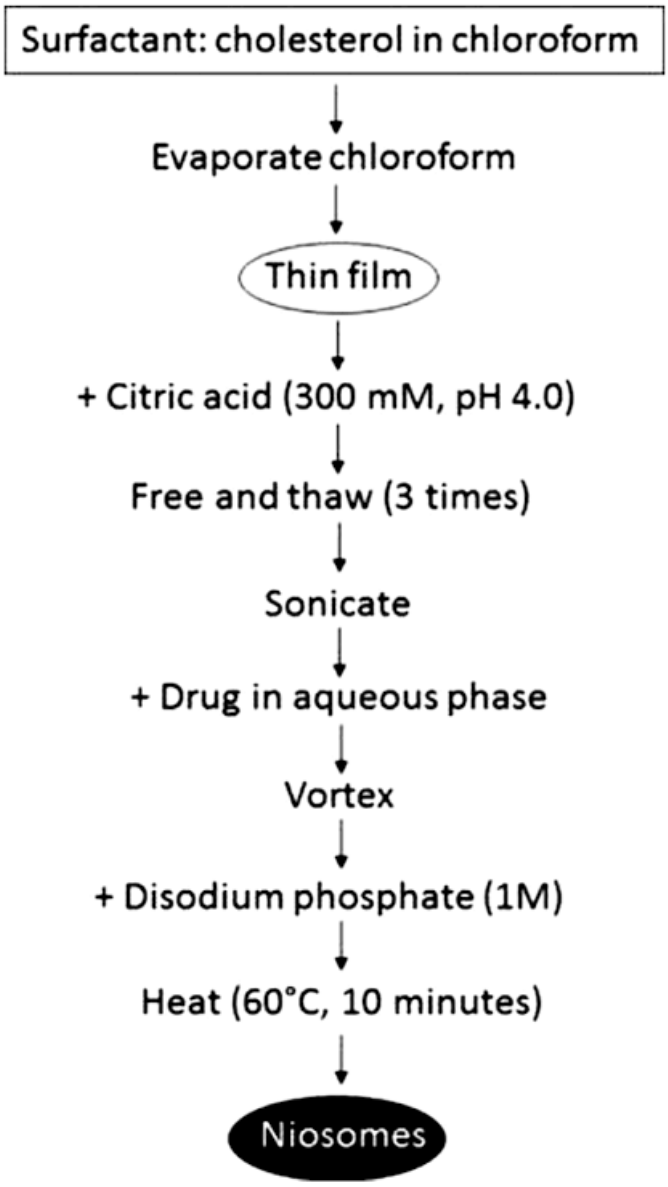

Fig. 4: Trans membrane pH gradient drug uptake process.

6) Sonication

It is a typical method of producing niosomal vesicles by sonication of the solution. In this method a mixture of drug solution in buffer is added to the surfactant or cholesterol mixture in a 10ml glass vial. The mixture is sonicated at 60°Cfor 3 minutes using a sonicator with a titanium probe to form niosomes.[16]

7) The "Bubble" Method

This is a new technique for single step preparation method of niosomes without the use of organic solvents. The bubbling unit consists of round bottomed flasks with 3 necks positioned

in controlled water bath (constant temperature). The first two necks are placed in water cooled reflux with thermometer to control temperature. The nitrogen gas was passed from the third neck. Surfactant and cholesterol are dispersed in buffer (pH7.4) at 70°C which is homogenised for 15 seconds and immediately the nitrogen gas is bubbled at70°C this results in the formation of small unilamellar vesicles.

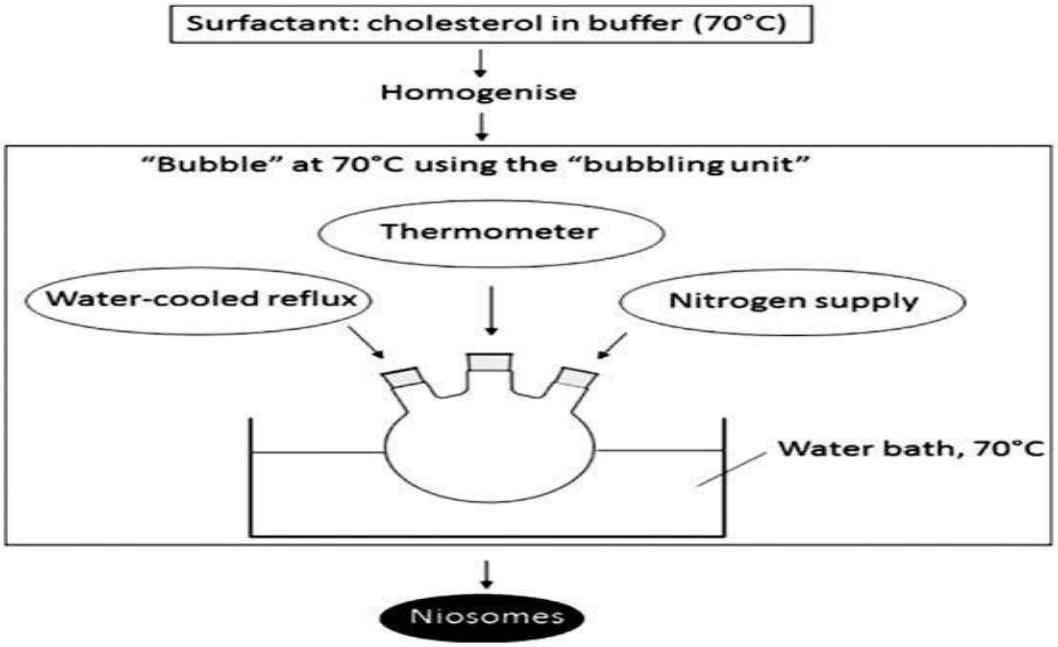

Fig. 5: Bubble method.

8) Formation of Niosomes from Proniosomes

Proniosomes are the water soluble carriers such as sorbitol which are coated with dry surfactants. The niosomes are formed by the addition of aqueous phase at T > Tm and with brief agitation. Where T= temperature Tm=mean transition temperature.

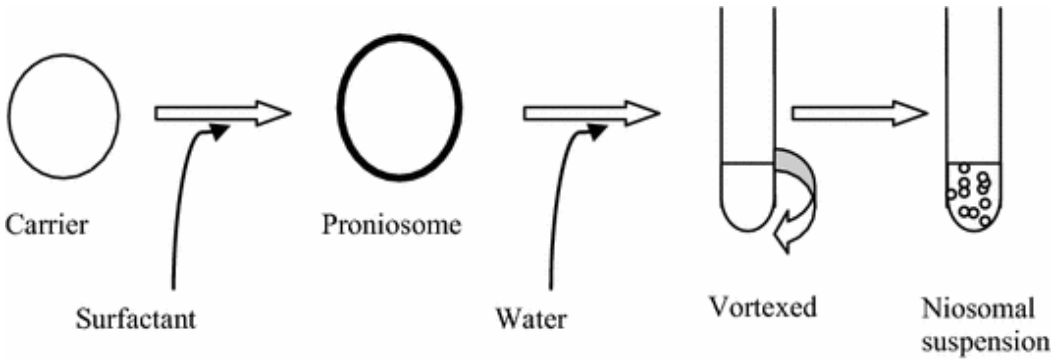

Fig. 6: Preparation of niosomes from proniosomes.

The Multilamellar niosomal vesicles are formed from the hydration of proniosomes.

Separation of Unentrapped drug[3] During the formation of niosomal vesicles some amount of drug remains unentrapped which should be separated for the preparation of stable niosomal formulation. This separation is accomplished by various techniques which include:

1) Dialysis - done by using dialyzing tube against phosphate buffer or normal saline solution.
2) Gel filtration – the drug un entrapped is removed by gel filtration of niosomal suspension though Shephadex-G-50 column and eluting it with phosphate buffer or normal saline.
3) Centrifugation - the centrifugation of niosomal suspension is done by centrifuge and the supernatant liquid is separated and the pellet is washed and re suspended to get a niosomal suspension free from unentraped drug.

CHARACTERIZATION AND FACTORS AFFECTING FORMATION OF NIOSOMES

Nature of surfactants[1] A non ionic surfactant used for preparation of niosomes must have a hydrophilic head and hydrophobic tail. The hydrophobic tail should consist of one or two alkyl or perfluoroalkyl groups or a single steroidal group. The ether type surfactants with single chain alkyl as hydrophobic tail is more toxic than corresponding dialkylether chain .The ester type surfactants are chemically less stable than ether type surfactants and the ester type is less toxic than the ether. Surfactants with alkyl chain length from C12 to 18 are more suitable for the preparation of niosomes.

Type of non-ionic surfactant	Examples
Fatty alcohol	Cetyl alcohol, stearyl alcohol, cetostearyl alcohol, oleyl alcohol
Ethers	Brij, Decyl glucoside, Lauryl glucoside, Octyl glucoside, Triton X-100, Nonoxynol-9
Esters	Glyceryl laurate, Polysorbates, Spans
Block copolymers	Poloxamers

Fig. 7: Different nonionic surfactants used.

Membrane composition[15]**:** The stable niosomes can be prepared by addition of different additives along with surfactants and drugs. Niosomes formed have a range of forms and their permeable nature and stability properties may be differed by manipulating membrane characteristics by completely different additives.

Nature of encapsulated drug

The physico-chemical properties of entrapped drug influence charge and rigidity of the niosomal bilayer. The drug interacts with surface active agent head groups and builds the charge that creates mutual repulsion between surfactant bilayer and hence increases vesicular size.

Routes of drug administration	Examples of Drugs
Intravenous route	Doxorubicin, methotrexate, sodium stibogluconate, iopromide, vincristine, diclofenac sodium, flurbiprofen, centchroman, indomethacin, colchicine, rifampicin, tretinoin, transferrin and glucose ligands, zidovudine, insulin, cisplatin, amarogentin, daunorubicin, amphotericin B, 5-fluorouracil, camptothecin, adriamycin, cytarabine hydrochloride
Peroral route	DNA vaccines, proteins, peptides, ergot alkaloids, ciprofloxacin, norfloxacin, insulin
Transdermal route	Flurbiprofen, piroxicam, estradiol, levonorgestrol, nimesulide, dithranol, ketoconazole, enoxacin, ketorolac
Ocular route	Timolol maleate, cyclopentolate
Nasal route	Sumatriptan, influenza viral vaccine
Inhalation	All-trans retinoic acids

Fig. 8: Different drugs encapsulated as niosomes.

Temperature of hydration: Hydration temperature influences the form and size of the noisome. For ideal condition it should be higher than the gel to liquid phase transition temperature of system. Temperature change of niosomal system affects arrangement of surfactants into vesicles and also induces vesicle morphology.

Bilayer formation: Aggregation of non-ionic surfactants to form bilayer vesicle is characterized by X-cross formation under light polarization microscopy.

Number of lamellae: It is determined by using NMR spectroscopy and small angle X-ray scattering and electron microscopy.

Membrane rigidity: Membrane rigidity can be measured by using mobility of fluorescence probe as function of temperature.

Entrapment efficiency (EE)[3]

The entrapment efficiency (EE) or encapsulation efficiency is expressed as

$$EE = amount\ entrapped/total\ amount\ drug \times 100$$

It is determined after separation of unentrapped drug, then vesicles were digested by suitable organic solvents such as 50% *n* –propanol or 0.1% triton-X-100 and 1ml of 2.5% sodium lauryl sulphate, briefly homogenized and centrifuged and supernatant is analysed for drug by suitable method.

Entrapment efficiency is affected by following factors.

a. Surfactants: The length of chain and hydrophilic head of non-ionic surfactants affect entrapment efficiency, for example stearyl chain C18 non-ionic surfactant vesicles have higher entrapment efficiency than lauryl chain C12 non-ionic surfactant vesicles. The tween series surfactants having a long alkyl chains well as more hydrophilic heads in combination with cholesterol at1:1 ratio have highest entrapment efficiency for hydrophilic drugs. HLB value of surfactants also affects entrapment efficiency, such as HLB value of 14 to 17 is not suitable for niosomes but HLB value of 8.6 has highest entrapment efficiency and entrapment efficiency decreases with decrease in the HLB value from 8.6 to 1.7.

Cholesterol: The incorporation of sterol into bilayer composition of niosomes produces membrane stabilising activity and thereby decreasing the leaky nature of membrane and provides membrane rigidity thereby increasing the entrapment efficiency and also increases the permeability.

APPLICATIONS[11, 12]

Niosomes as Drug Carriers in cancer chemotherapy.

Immunological application of noisomes Niosomes have been used for immunostimulatory actions by vaccine delivery.

Noisome formulation as a brain targeted delivery system to target the blood brain barrier.

Niosomes as carriers for Haemoglobin. Niosomes are often used as a carrier for hemoglobin. It performs as a transporter for haemoglobin.

Niosomes are used as anti-aging tools in cosmeceuticals and also topical delivery.

For the delivery of peptide drugs hormonal drugs are entrapped niosomes.

Ophthalmic drug delivery formulation of gentamicin for controlled drug delivery.

Trans dermal delivery of drugs by niosomes to increase the penetration rate due to slow penetration of drug through skin.[19]

Diagnostic imaging with niosomes as diagnostic agents in in targeting the tumours which are accessed by MR imaging.

Pulmonary delivery for asthmatic patients by sustained and targeted niosomal formulations.

Marketed products of niosomes

Lancome foundation cream noisome – anti aging [8] cosmetic product by L'Oreal. Niosomal gel of meloxicam is marketed.

CONCLUSION

Niosomes a novel drug delivery system are more preferable over the liposomes as they are being stable and more economic. The niosomes are having a great drug delivery potential for the delivery of anticancer, anti- infective[13], anti-tubercular anti-leishmanial[16], anti-inflamatory and anti-fungal agents.[7] Recently the anti HIV drug also formulated as niosomes.[20] The delivery of niosomes can be improved by using modified niosomes such as proniosomes, discosomes and aposomes. Niosomes have a wide range of applications in diagnostic, therapeutic as well as in cosmeceuticals. They are widely used as carriers for drugs, hormones, peptides, proteins and haemoglobin transporters. The niosomes are structurally similar to liposomes and hence they are used as alternative vesicular systems for the drug entrapment. The niosomes or liposomes are better used for targeting the tumours and work effectively. The niosomes are delivered through oral, parenteral, topical, and nasal intranasal and also used sustained and controlled drug delivery. Thus there is a lot of scope of research in the production of niosomes for increasing the utility and produce more commercially accepted niosomal formulations with more increased novelty.

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