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A RECENT AND INNOVATIVE TREND OF DRUG DELIVERY SYSTEM IN FORM OF NIOSOMES: AS A REVIEW ARTICLE

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ABSTRACT

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayers of non-ionic surface active agents and hence the name niosomes. Structurally, niosomes are similar to liposomes, in that they are also made up of bilayers. However, the bilayers of niosomes are made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Niosome are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or their lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Noisome are promising vehicle for drug delivery and being non-ionic; and Niosomes are biodegradable, biocompatible non-immunogenic and exhibit flexibility in their structural characterization. Niosomes have been widely evaluated for controlled release and targeted delivery for the treatment of cancer, viral infections and other microbial diseases. Niosomes can entrap both hydrophilic and lipophilic drugs and can prolong the circulation of the entrapped drug in body. Encapsulation of drug in vesicular system can be predicted to prolong the existence of drug in the systemic circulation and enhance penetration into target tissue, perhaps reduce toxicity if selective uptake can be achieved. Niosomes present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosomes ability to encapsulate different type of drugs within their multi environmental structure. This review article focuses on the advantages, Disadvantages, preparation methods, factors affecting, characterizations, in vitro methods, drug release kinetics, and applications.

KEYWORD: Niosomes, Methods of Preparation, Encapsulation, Compositions, Vesicles andApplications Surfactants.

INTRODUCTION

An ideal drug delivery system delivers drug at rate dictated by the need of the body over the period of treatment and it channels the active entity solely to the site of action.

Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with nontarget tissue[1] Different novel approaches used for delivering these drugs include liposomes, microspheres, nanotechnology, micro emulsions, antibody- loaded drug delivery, magnetic microcapsules, implantable pumps and noisome. Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. Niosomes have recently been shown to greatly increase Tran's dermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery.

Noisomes are formations of vesicles by hydrating mixture of cholesterol and nonionic surfactants.[2] These are formed by self-assembly of non- ionic surfactants in aqueous media as spherical, unilamellar, multilamellar system and polyhedral structures in addition to inverse structures which appear only in non- aqueous solvent.[3]

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. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with non target tissue.[4,5]

In niosomes drug delivery system the medication is encapsulated in a vesicle.[6] The vesicle is composed of

a bilayer of non-ionic surface active agents and hence the name noisomes. In noisomes, the vesicles forming amphiphilic is a non-ionic surfactant such as Span- 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate.[6] Various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parental, etc.

The first niosomes formulations were developed and patented by L'Oreal in 1975. Niosomes were first utilized in drug delivery for anticancer drugs. The developed niosomes formulations were capable of altering the pharmacokinetic profile, organ distribution and metabolism of methotrexate in mice. Niosomes are versatile in structure, morphology and size; they can entrap hydrophilic drugs in aqueous compartments orlipophilic drugs by partitioning of these molecules into bilayers domain. Furthermore, they can be formulated as unilamellar, oligolamellar or multilamellar vesicle. Niosomes also possess good physical stability, are cost-effective, and are relatively straight forward for routine and large-scale production.

Surfactant forming niosomes are biodegradable, non-immunogenic and biocompatible. Incorporating them into niosomes enhances the efficacy of drug, such as nimesulide, flurbiprofen, piroxicam, ketoconazole and bleomycin exhibit more bioavailability than the free drug.[7, 8, 9,]

Ideal properties of niosomes

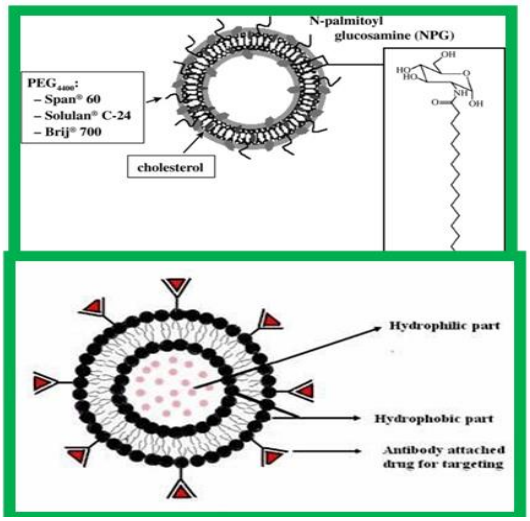
- Better availability to the particular site, just by protecting the drug from biological environment.
- Niosomes possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecules with a wide range of solubility.
- Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
- Niosomes can entrap solutes in a manner analogous to liposomes.
- Niosomes are osmotically active and stable.
- Niosomes can improve the performance of the drug molecules.
- Niosomes surfactants are biodegradable, biocompatible and non-immunogenic.
- The surfactants are biodegradable, biocompatible, and non-immunogenic.
- Improve 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.
- The niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug and administer normal vesicles in external non-aqueous phase.[10]

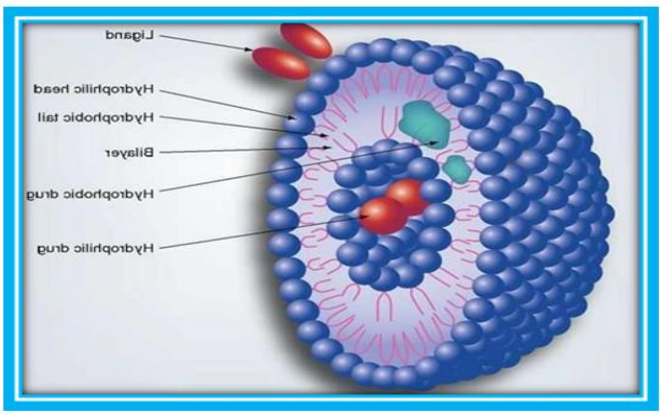
Structure of Niosomes

A typical niosomes vesicle would consist of a vesicle forming amphiphilic i.e. a non-ionic surfactant such as Span-60, which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle. Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures however some surfactants can yield bilayer vesicles which are niosomes.

Niosomes may be unilamellar multilamellar depending on the method used to prepare them. The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer. Hence, the vesicle holds hydrophilic drugs within the space enclosed in the vesicle, while hydrophobic drugs are embedded within the bilayer itself.[11,12]

Advantage of Niosomes





Niosomes may act as a depot, releasing the drug in a controlled manner.
It improves permeability of drugs through skin.
It can be administered through parenteral route.
It increases the oral bioavailability of drugs.
It provides targeted drug delivery, enhanced cellular uptake and protection to drugs.
It offers greater patient compliance over oil based systems
They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation.
Niosomal formulation in aqueous phase can be emulsified in a non aqueous phase to regulate the delivery rate of drug.
Niosomes are biodegradable, biocompatible and non immunogenic
It can accommodate drug molecules with a wide range of solubility's.
They are osmotically active and stable; hence they increase the stability of entrapped drug.[13,14,15]

Disadvantage of Niosomes

- Physical instability
- Aggregation
- Fusion
- Leaking of entrapped drug
- Hydrolysis of encapsulated drugs which limiting theshelf life of the dispersion[16,17,18,19,20]

Types of niosomes

The niosomes are classified on the basis of following way

- On the basis of the number of bilayer (Example. MLV, SUV)
- On the basis of size (Example LUV, SUV)
- On the basis of the method of preparation (Example. REV, DRV).

i) Multi lamellar vesicles (MLV)
ii) Large unilamellar vesicles (LUV)
iii) Small unilamellar vesicles (SUV)

1. Multilamellar vesicles (MLV).

It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. Multilamellar vesicles are the most widely used niosomes. It is simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.

2. Large unilamellar vesicles (luv)

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

3. Small unilamellar vesicles (suv)

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.[21]

Composition of niosomes

The two major components used for the preparation of niosomes are following.

- ❖ Cholesterol
- ❖ Nonionic surfactants

Cholesterol

Cholesterol is used to provide rigidity and proper shape, conformation to the niosomes preparations.

Nonionic surfactants

The surfactants play a major role in the formation of niosomes.
The following non-ionic surfactants are generally used for the preparation of niosomes.
1. Spans (span 60, 40, 20, 85, 80)
2. Tweens (tween 20, 40, 60,80).
3. Brijs (brij 30, 35, 52, 58, 72, 76).
The non ionic surfactants possess a hydrophilic head and ahydrophobic tail.[21]

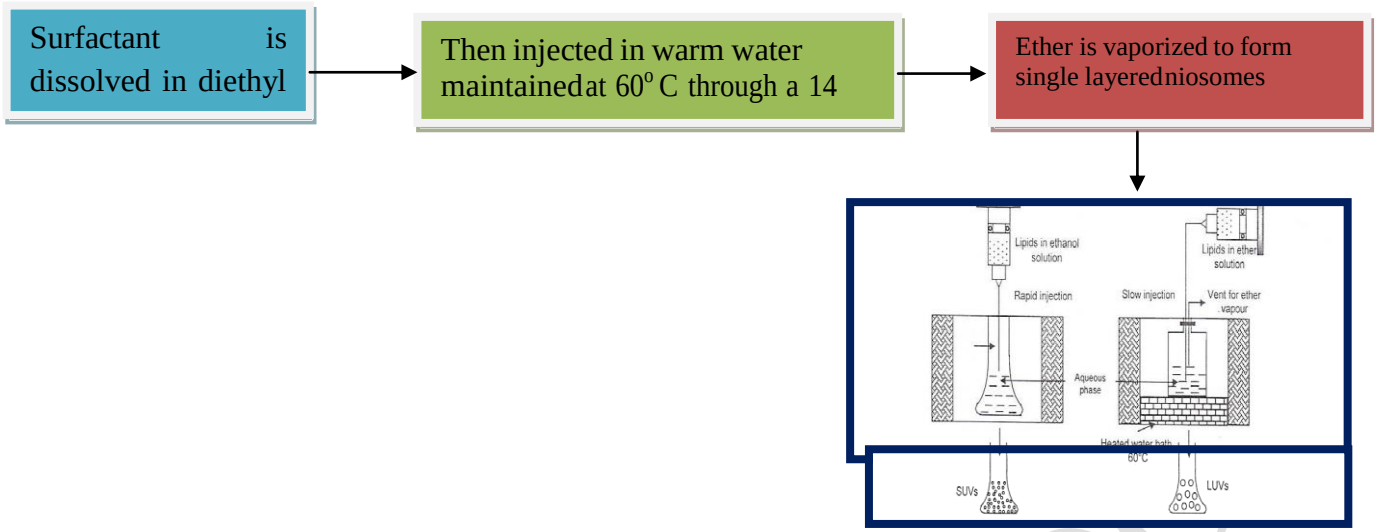
Method of preparation of niosomes

The method of preparation influences the size, size distribution and number of bilayers, entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles.

A. Ether injection method
B. Hand shaking method/thin film hydration method
C. Micro fluidization
D. Multiple membrane extrusion method
E. Reverse phase evaporation technique
F. Sonication
G. Trans membrane P^H gradient drug uptake
H. The bubble method
I. Formation from pro-niosomes

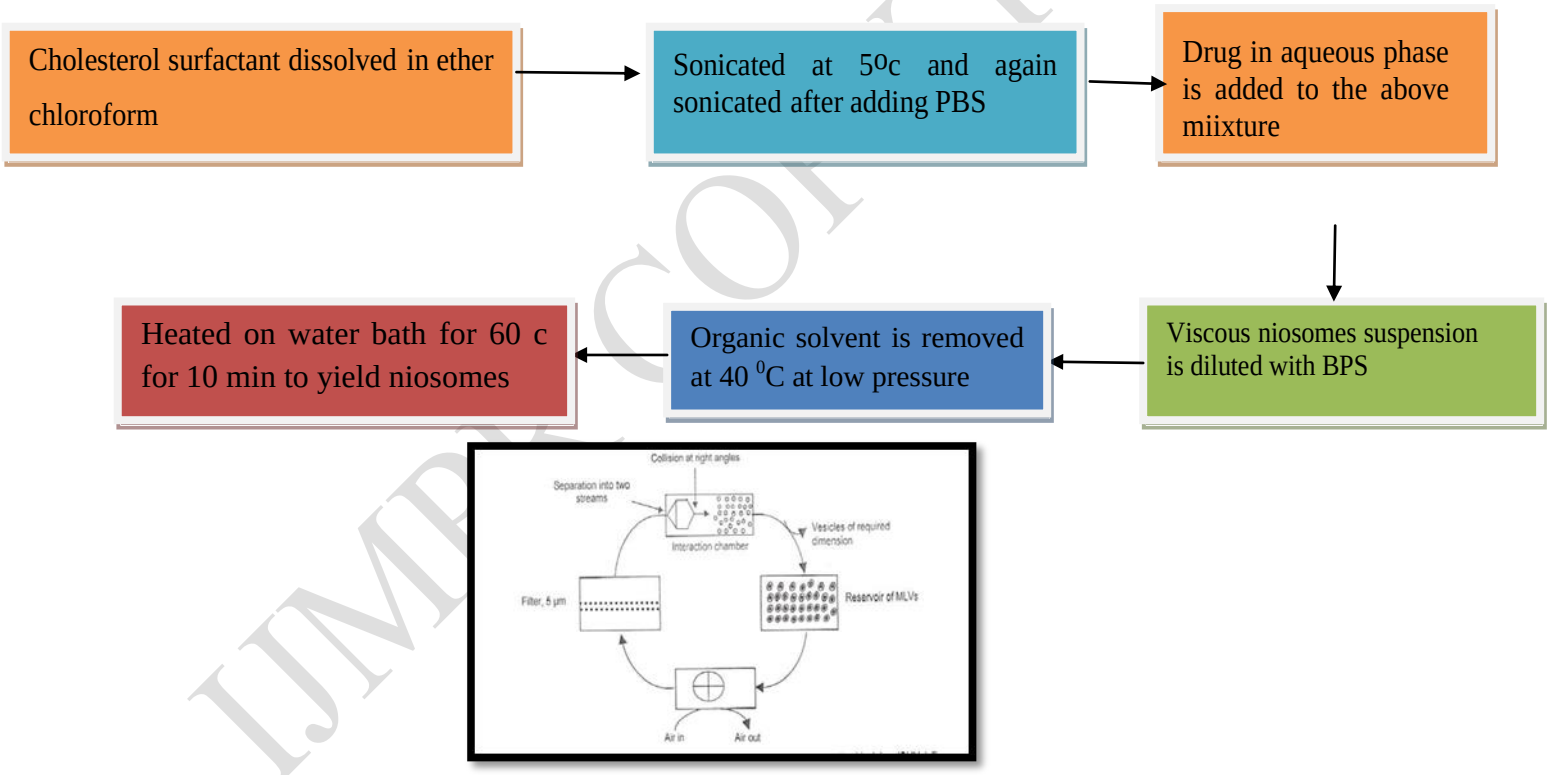
(A) Ether Injection Method

In this method, a solution of the surfactant is made by dissolving it in diethyl ether. This solution is then introduced using an injection (14 gauge needle) into warm water or aqueous media containing the drug maintained at 60°C. Vaporization of the ether leads to the formation of single layered vesicles. The particle size of the niosomes formed depend on the conditions used, and can range anywhere between 50-1000 μm.[22-23]



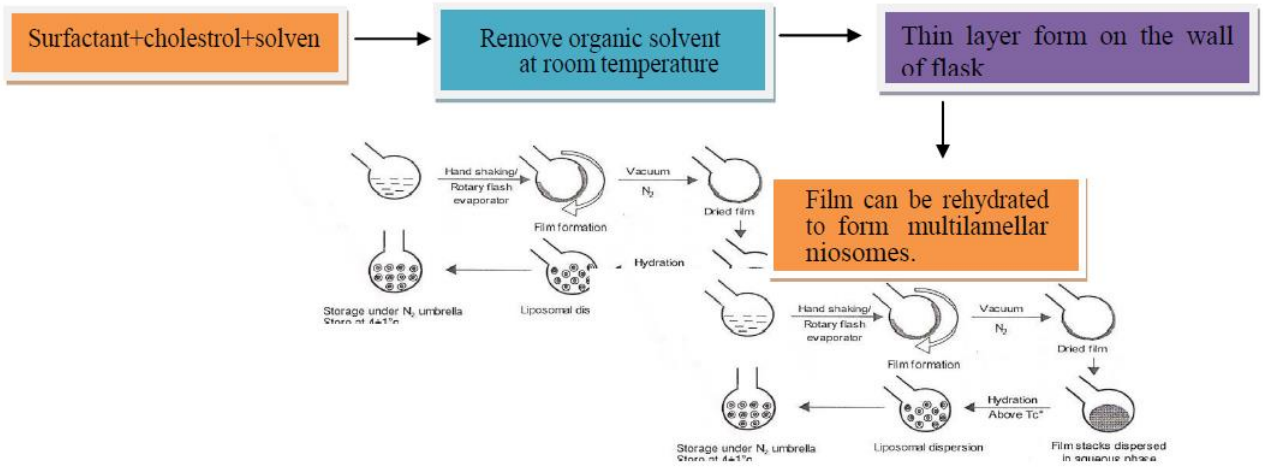
(B)**Reverse phase evaporation method**

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 niosomes suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes have reported by this method.



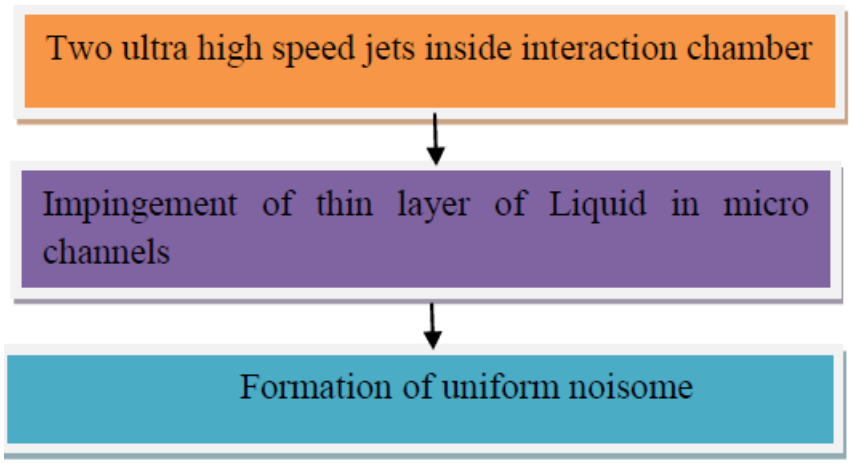
(C))**Hand shaking method**

In this method the surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl either, chloroform or methanol in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation to yield multilamellar niosomes.



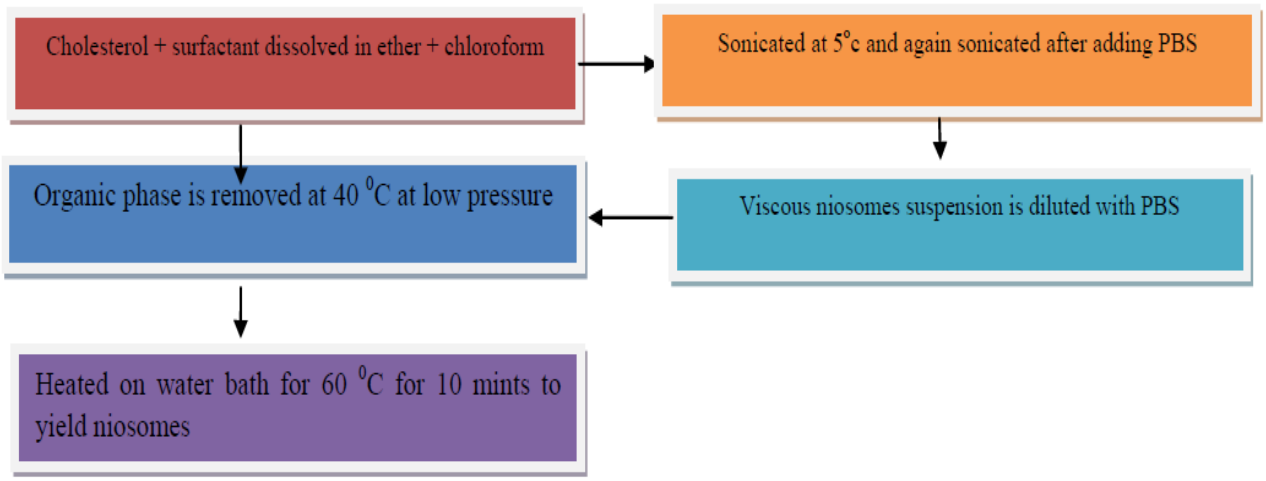
(D) Micro fluidization Method

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along 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 size and better reproducibility of niosomes formed.



(D) Multiple membrane extrusion method

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug.



(E) Sonication

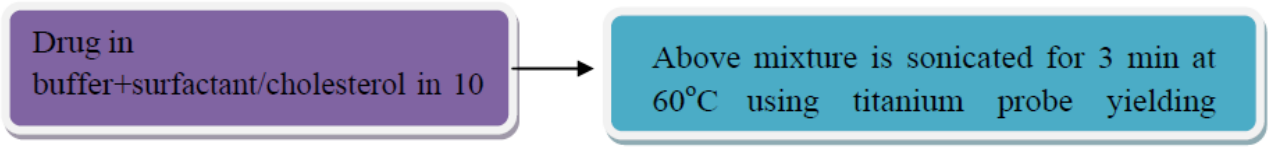
Typical method of production of the vesicles is by sonication of solution as described by Cable (32). In this method an aliquot of drug solution in buffer is added to the surfactant/choleste mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.[24]

(F)Tran's membrane P^H gradient drug uptake

A solution of 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. This film is hydrated with 300mm citric acid (PH 4.00) by vertex mixing. The resulting multilamellar vesicles are frozen and shared three times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexes. 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.[25]

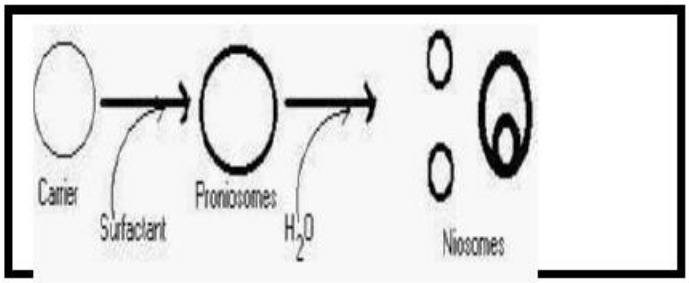
(G) The bubble method

The bubbling unit consists of round-bottomed flask with three necks, and this is positioned in a 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 to yield niosomes.[26]



(H) 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. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes".[27]



Size of Niosomes

The size ranges of niosomes have a great effect on their *in-vitro* and *in-vivo* evaluation. Thus, after the hydration stage of niosomes, sizes reduction stage is important.

Methods Implemented for Niosomal Size Reduction:

1-Probe sonication
2-Nucleophore filters extrusion
3-Laser diffraction

(1)Probe Sonication

Reverse phase evaporation and hand shaking method generally produces the niosomes of micron size ranging between 1.15 and 2.75 mm. by using probe sonication their size can be reduced to 100-140nm.

(2) Nucleopore Filter Extrusion

By the extrusion of niosomes through the nucleopore filters of pore size 100nm, niosomal size can be reducedto nano range.

(3) Laser Diffraction

It is used to reduce the size of niosomes up to nano range.

Apart from these methods, micro fluidization and high pressure homogenization are also used for the sizing of niosomes.

Separation of Unentrapped Drug

The removal of unentrapped drug from the niosomal vesicles can be accomplished by various techniques suchas

(a) Dialysis
(b) Gel filtration
(c) Centrifugation

(a) Dialysis
Dialysis of the aqueous niosomal dispersion is carried out in dialysis cellophane tubing against normal saline or phosphate buffer or glucose solution.[28, 29]

(b) Gel Filtration
The Unentrapped drug from the niosomal dispersion is removed by passing through sephadex G50 column and elution with phosphate buffered saline or normal saline. The vesicles percolate down the column whereas the free drug gets retained on column.[30.31]

(c) Centrifugation
The niosomal dispersion is centrifuged in water or saline. Niosomes get sedimented down as pellet which is washed and resuspended to obtain a niosomal suspended free from unentrapped drug. The supernatant containing the unentrapped drug is separated.[32]

Characterization of niosomes

1. Size, Shape and Morphology
Structure of surfactant based vesicles has been visualized and established using freeze fracture microscopy while photon correlation spectroscopy used to determine mean diameter of the vesicles. Electron microscopy used for morphological studies of vesicles while laser beam is generally used to determine size distribution, mean surface diameter and mass distribution of niosomes.

2. Entrapment efficiency
After preparing niosomal dispersion, Unentrapped drug is separated by dialysis, centrifugation, or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug. Where, % Entrapment efficiency (% EF) = (Amount of drug entrapped/ total amount of drug) x 100

3. Vesicle diameter
Niosomes diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing (keeping vesicles suspension at 20°C for 24 hrs and then heating to ambient temperature) of niosomes increases the vesicle diameter, which might be attributed to fusion of vesicles during the cycle.

4. In-vitro release
A method of in-vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipette into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method.

5. Vesicle charge
The vesicle surface charge can play an important role in the behaviour of niosomes in vivo and in vivo. In general, charged niosomes are more stable against aggregation and fusion than uncharged vesicles. In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes can be measured by micro electrophoresis. An alternative approach is the use of pH sensitive fluorophores. More recently, dynamic light scattering have been used to measure the zeta potential of niosomes.

6. Bilayers rigidity and homogeneity
The bio distribution and biodegradation of niosomes are influenced by rigidity of the bilayers. In homogeneity can occur both within niosomes structures themselves and between niosomes in dispersion and could be identified via. NMR, differential scanning calorimetry (DSC) and Fourier transform-infra red spectroscopy (FT-IR) techniques. Recently, fluorescence resonance energy transfer (FRET) was used to obtain deeper insight about the shape, size and structure of the niosomes.

7. Niosomal drug loading and encapsulation efficiency
To determine drug loading and encapsulation efficiency, the niosomal aqueous suspension was ultracentrifuge, supernatant was removed and sediment was washed twice with distilled water in order to remove the adsorbed drug.[33, 34]

Application of niosomes

Drug Targeting
One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticulo endothelial system. The reticulo-endothelial system (RES) preferentially takes up niosomes vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosomes for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infections of the liver. Niosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to niosomes (as immunoglobulin's bind readily to the lipid surface of the niosomes) to target them to specific organs.

Anti-neoplastic Treatment
Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Niosomes is decreased rate of proliferation of tumor and higher plasma levels accompanied by slower elimination.

Niosomes as Drug Carriers
Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for X-ray imaging. Topical

niosomes may serve as solubilisation matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

Delivery of Peptide Drugs

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in vitro study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.

Leishmaniasis

Leishmaniasis is a disease in which a parasite of the genus Leishmaniasis invades the cells of the liver and spleen. Use of niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment.

Use in Studying Immune Response

Due to their immunological selectivity, low toxicity and greater stability; niosomes are being used to study the nature of the immune response provoked by antigens. Non-ionic surfactant vesicles have clearly demonstrated their ability to function as adjuvant following parenteral administration with a number of different antigens and peptides.

Niosomes as Carriers for Haemoglobin

Niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anaemic patients.[35, 36, 37, 38, 39]

CONCLUSION

In niosomes provide as a drug carrier to achieve better bioavailability and targeting properties and as well as reducing the toxicity and side effects of the drugs From the past few decades, there is a great revolution in development of novel drug delivery system. The technology of utilizing niosomes as promising drug delivery system is still in its infancy. Niosomes have shown a profound influence in targeting the particular organ and tissue. Niosomes can serve as better diagnostic agents, vaccine delivery system, tumor targeting agents, ophthalmic, nasal and Tran's dermal delivery systems. Research has to be carried out extensively to have commercially available niosomal formulations. Niosomes have ability to encapsulate different type of drugs within their multi environmental structure like anti infective, anticancer drug. And various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, etc.

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