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Review Article

NIOSOMES: A NOVEL DRUG DELIVERY SYSTEM

Madhav NVS* and Saini A

DIT Faculty of Pharmacy, Mussoorie Diversion Road, Bhagwantpura, Dehradun, Uttarakhand, India.

*Corresponding Author: satheesh_madhav@yahoo.com

ABSTRACT

Niosomes are formations of vesicles by hydrating mixture of cholesterol and nonionic surfactants. Different novel approaches used for delivering these drugs include liposomes, microspheres, nanotechnology, micro emulsions, antibody-loaded drug delivery, magnetic microcapsules, implantable pumps and niosomes. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy. The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells. This article focuses on the recent advances in niosomal drug delivery, potential advantages over other delivery systems, formulation methods, methods of characterization and the current research in the field of niosomes. Niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, antiinfective agents. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes, discomes and aspasome. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Thus these areas need further exploration and research so as to bring out commercially available niosomal preparation.

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 niosomes.

Niosomes 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].

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs.

INTRODUCTION

Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that

would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc[4].

In niosomes, the vesicles forming amphiphile 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 [5].

Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy[6].

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[7-10].

Advantages of Niosomes

1. The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages
2. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
3. Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery
4. rate of drug and administer normal vesicle in external non-aqueous phase.
5. They are osmotically active and stable, as well as they increase the stability of entrapped drug.
6. Handling and storage of surfactants requires no special conditions.
7. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
8. They can be made to reach the site of action by oral, parenteral as well as topical routes.
9. They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.
10. The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
11. The vesicles may act as a depot, releasing the drug in a controlled manner.

METHODS OF PREPARATION

A. Hand shaking method (Thin film hydration technique) [11]

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, 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. This process forms typical multilamellar niosomes. (Fig 2)

B. Micro fluidization[12]

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 she*et al*ong 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**.** (Fig.3)**.**

C. Reverse Phase Evaporation Technique (REV) [13] Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition

of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes. Raja Naresh *et al* [13] have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

D. Ether injection method[14,15] This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm. (fig.4).

E. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading)[16]Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes.

F. The "Bubble" Method[17] It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

G.Sonication[15] A 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.(Fig 5).

h. Formation of niosomes from proniosomes
[18]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". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation. T=Temperature. Tm = mean phase transition temperature.
Blazek-Walsh A.I. *et al* [18] have reported the formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water. (Fig 6)

SEPARATION OF UNENTRAPPED DRUG

The removal of unentrapped solute from the vesicles can be accomplished by various techniques, which include: -

1. DIALYSIS[33]

The aqueous niosomal dispersion is dialyzed in a dialysis tubing against phosphate buffer or normal saline or glucose solution.

2. GEL FILTRATION[34,35]

The unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.

3. CENTRIFUGATION[36,37]

The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug.

COMPARISON OF NIOSOMES AND LIPOSOMES

Niosomes are now widely studied as an alternative to liposomes, which exhibit certain disadvantages such as –they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable.

Niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from double-chain phospholipids (neutral or charged).

Niosomes behave *in-vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability[46]. Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug[46]. They can be expected to target the drug to its desired site of action and / or to control its release [15].

CHARACTERIZATION AND FACTORS AFFECTING FORMATION OF NIOSOMES

Nature of surfactants

A surfactant used for preparation of niosomes must have a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal group[19].

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 former is less toxic than the latter due to ester-linked surfactant degraded by esterases to triglycerides and fatty acid in vivo[20].

The surfactants with alkyl chain length from C12-C18 are suitable for preparation of noisome [21,22]

Structure of surfactants

The geometry of vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameters. On the basis of critical packing parameters of surfactants can predicate geometry of vesicle to be formed. Critical packing parameters can be defined using following equation,

CPP (Critical Packing Parameters) =v / lc* a0

where v = hydrophobic group volume,

lc = the critical hydrophobic group length,

a0 = the area of hydrophilic head group.

From the critical packing parameter value type of miceller structure formed can be ascertained as given below,

If CPP < ½ then formation of spherical micelles,

If ½ < CPP < 1 formation of bilayer micelles,

If CPP > 1 formation inverted micelles[23].

Membrane composition

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral niosome remains unaffected by adding low amount of solulan C24 (cholesteryl poly-24-oxyethylene ether), which prevents aggregation due to development of steric hindrance[24].

Nature of encapsulated drug

The physico-chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers and hence increases vesicle size[25].

Temperature of hydration

Hydration temperature influences the shape and size of the noisome. For ideal condition it

should be above the gel to liquid phase transition temperature of system. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation[26].

Bilayer formation

Assembly of non-ionic surfactants to form bilayer vesicle is characterized by X-cross formation under light polarization microscopy[27].

Number of lamellae

It is determined by using NMR spectroscopy, small angle X-ray scattering and electron microscopy[28].

Membrane rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as function of temperature[27].

Entrapment efficiency (EE)

The entrapment efficiency (EE) is expressed as **EE** = amount entrapped / total amount added ´ 100 It is determined after separation of unentrapped drug, on complete vesicle disruption by using about 1ml of 2.5% sodium lauryl sulfate, briefly homogenized and centrifuged and supernatant assayed for drug after suitable dilution[29]. Entrapment efficiency is affected by following factors.

a. **Surfactants**

The chain length and hydrophilic head of non-ionic surfactants affect entrapment efficiency, such as stearyl chain C18 non-ionic surfactant vesicles show higher entrapment efficiency than lauryl chain C12 non-ionic surfactant vesicles . The tween series surfactants bearing a long alkyl chain and a large hydrophilic moiety in the combination with cholesterol at1:1 ratio have highest entrapment efficiency for water soluble drugs[27]. HLB value of surfactants 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 HLB value from 8.6 to 1.7[30].

Cholesterol contents

The incorporation of cholesterol into bilayer composition of niosome induces membrane-stabilizing activity and decreases the leakiness of membrane.[31]Hence, incorporation of cholesterol into bilayer increases entrapment efficiency. The permeability of vesicle bilayer to 5, 6-carboxy flourescein (CF) is reduced by 10 times due to incorporation of cholesterol[32].

APPLICATIONS

Niosomes as Drug Carriers

A number of workers have reported the preparation, characterization and use of niosomes as drug carriers.

Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug. Doxorubicin niosomes possessing muramic acid and triglycerol surfaces were not taken up significantly by liver. The triglycerol niosomes accumulated in the tumor and muramic acid vesicles accumulated in the spleen. Those vesicles with polyoxyethylene surface were rapidly taken up by the liver and accumulated to a lesser extent in tumor. Baillie *et al*[38] investigated the encapsulation and retention of entrapped solute 5,6-carboxy fluorescence (CF) in niosomes. They observed that stable vesicles could not be formed in the absence of cholesterol but were more permeable to entrapped solute. The physical characteristics of the vesicles were found to be dependent on the method of production.

Chandraprakash *et al*[39] reported the formation and pharmacokinetic evaluation of Methotrexate niosomes in tumor bearing mice.

Cable *et al*[40] modified the surface of niosomes by incorporating polyethylene alkyl ether in the bilayered structure. They compared the release pattern and plasma level of Doxorubucin in niosomes and Doxorubucin mixed with empty niosomes and observed a sustained and higher plasma level of doxorubicin from niosomes in mice.

D' Souza *et al*[41] studied absorption of Ciprofloxacin and Norfloxacin when administered as niosome encapsulated inclusion complexes.

Raja Naresh *et al*[42] reported the anti-inflammatory activity of niosome encapsulated Diclofenac sodium in arthritic rats. It was found that the niosomal formulation prepared by employing a 1:1 combination of Tween 85 elicited a better consistent anti-inflammatory activity for more that 72 hrs after administration of single dose.

Carter *et al*[43] reported that multiple dosing with sodium stibogluconate loaded niosomes was found to be effective against parasites in the liver, spleen and bone marrow as compared to simple solution of sodium stibogluconate.

Namdeo *et al*[44] reported the formulation and evaluation of Indomethacin loaded niosomes and showed that therapeutic effectiveness increased and simultaneously toxic side effect reduced as compared with free Indomethacin in paw edema bearing rats.

Parthasarthi *et al*[45] prepared niosomes of vincristine sulfate which had lesser toxicity and improved anticancer activity. Jagtap and Inamdar[35] prepared niosomes of Pentoxifylline and studied the *in-vivo* bronchodilatory activity in guinea pigs. The entrapment efficiency was found to be 9.26 ± 1.93% giving a sustained release of drug over a period of 24 hrs.

Azmin *et al*[46] reported the preparation and oral as well as intravenous administration of Methotrexate loaded niosomes in mice. They observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution.

Diagnostic imaging with niosomes

Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglcemine with [N-palmitoyl-glucosamine (NPG)],

PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging[47].

Ophthalmic drug delivery

Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendency for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide) The chitosan-coated niosomal formulation timolol maleate (0.25%) exhibits more effect for reduction intraocular pressure as compared to a marketed formulation with less chance of cardiovascular side effects[48].

Targeting of bioactive agents

a) To reticulo-endothelial system (RES)

The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver[49].

b) To organs other than RES

It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies[50]. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier.Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

Delivery of peptide drugs

Yoshida *et al*[51] investigated oral delivery of 9-desglycinamide, 8-arginine vasopressin entrapped in niosomes in an in-vitro intestinal loop model and reported that stability of peptide increased significantly.

Neoplasia

Doxorubicin, the anthracyclic antibiotic with broad spectrum anti tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma[58]. Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination[39,59].

Immunological application of niosomes

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander[60] have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

Transdermal delivery of drugs by niosomes

Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Jayraman *et al*[61] has studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse. From the studies, and confocal microscopy, it was seen that non-ionic vesicles could be formulated to target pilosebaceous glands.

Niosome formulation as a brain targeted delivery system for the vasoactive intestinal peptide (VIP)

Radiolabelled (I125) VIP-loaded glucose-bearing niosomes were injected intravenously to mice. Encapsulated VIP within glucose-bearing niosomes exhibits higher VIP brain uptake as compared to control[62]

Niosomes as carriers for Hemoglobin.

Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum superimposable onto that of free hemoglobin. Vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin[63,64].

CONCLUSION

It is obvious that niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, antiinfective agents.Drug delivery potential of niosome can enhance by using novel concepts like proniosomes, discomes and aspasome.Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Thus these areas need further exploration and research so as to bring out commercially available niosomal preparation. The concept of incorporating the drug into liposomes or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes represent a promising drug delivery module. They presents a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. Niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parentral.

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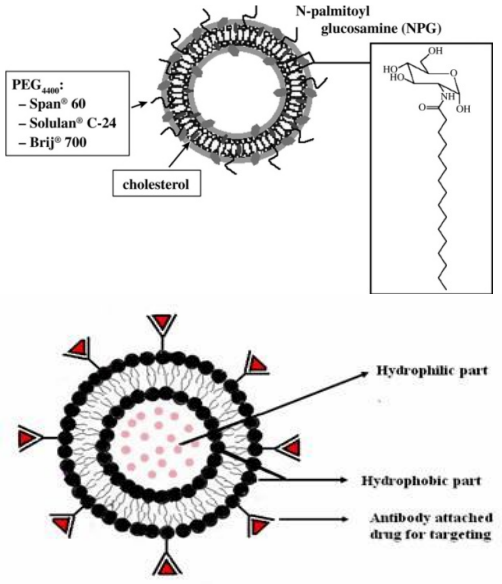
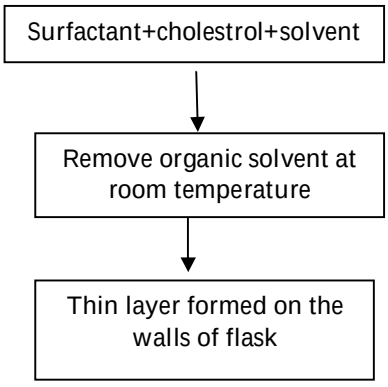
Fig 1: Structure of Niosomes





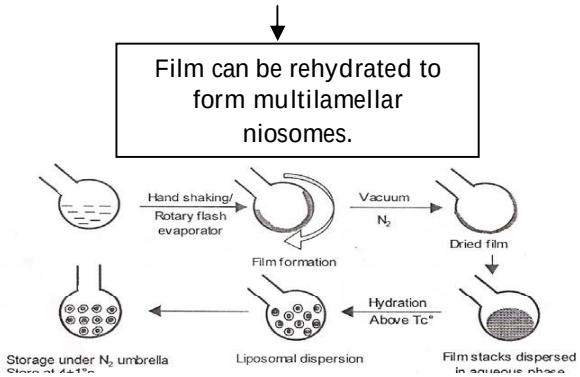
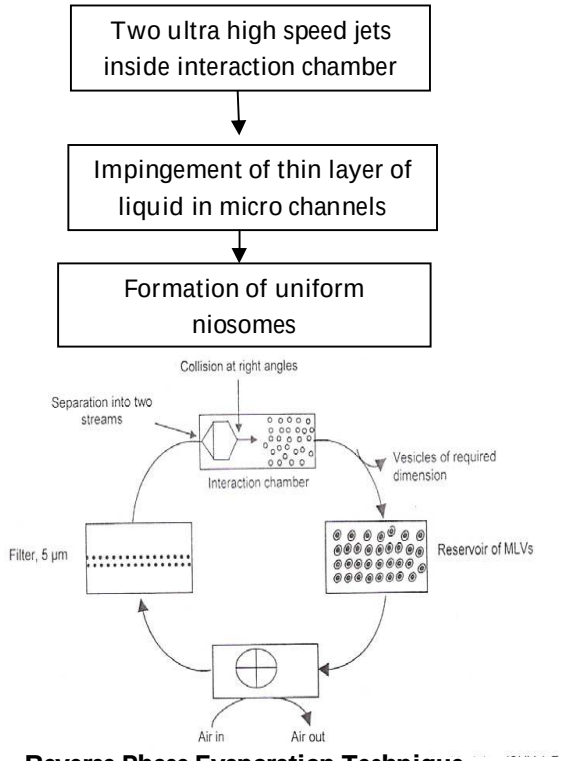
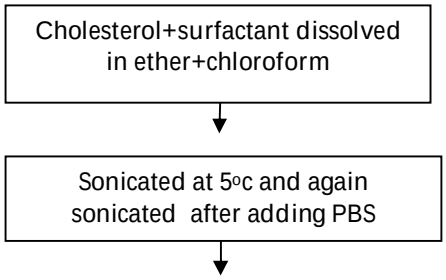


Fig 2: Hand Shaking Method of Niosomes Preparation

Fig 3: Microfludisation



Reverse Phase Evaporation Technique



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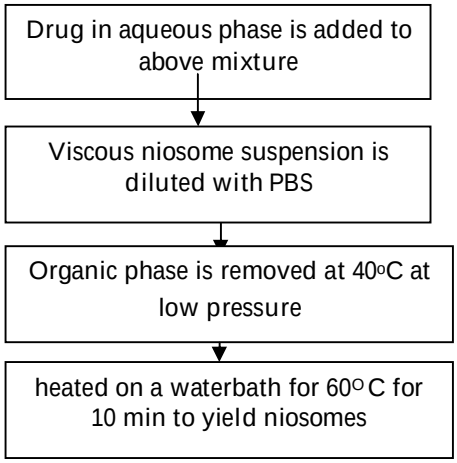


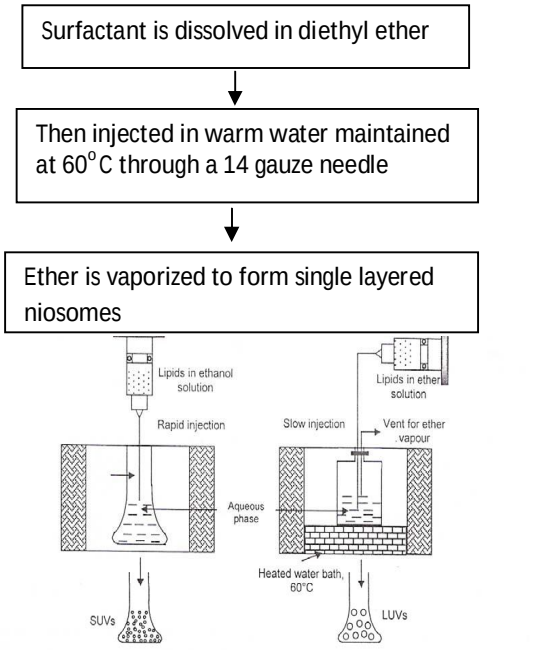
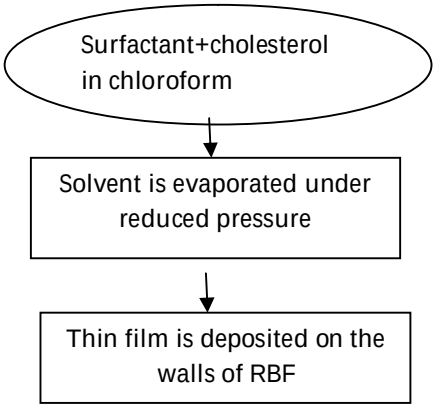


Fig.4: Ether injection method

Trans membrane pH gradient



Hydrated with citric acid by vortex mixing

3 cycles of freezing and thawing then sonication

Addition of aqueous drug solution and vortoxing

Ph raised to 7.0-7.2 by 1M disodium phosphate

RBF as bubbling unit with three necks in water bath

Reflux,thermometer and nitrogen supply by three necks

Cholesterol+surfactant dispersed in buffer pH 7.4 at 70°C

Above dispersion is homogenized for 15 sec and then bubbled with nitrogen gas at 70°C to get niosomes

Bubble Method

Drug in buffer +surfactant/cholesterol in 10 ml

Above mixture is sonicated for 3 min at 60°C using titanium probe yielding niosomes

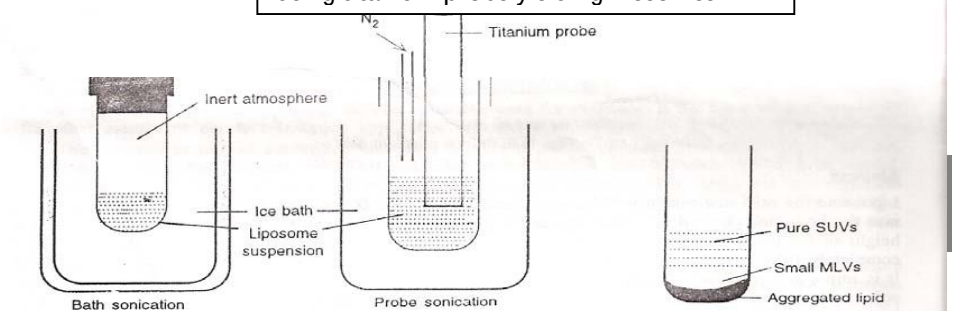


Fig. 5: Sonication method

Fig 5: Sonication method

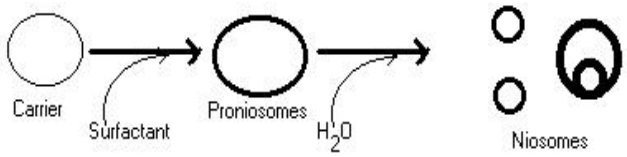


Fig 6: Proniosome Method