A COMPREHENSIVE REVIEW ON NIOSOMES;TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

Niosomes are targeted drug delivery system. In this system, drug directly act on the targeted or desired site while reducing the concentration of medication in the remaining tissue. Targeted drugdelivery system also known as “magic bullets”. Drug is encapsulated in vesicle and vesicle is composed of bilayer of non-ionic surface-active agents and hence it is called niosomes. Niosomes are classified into 3 types: SUV (Small Uni-lamellar Vesicle), LUV (Large Uni-lamellar Vesicle)and MLV (Multi-Lamellar Vesicle). Niosomes are prepared by different method of preparation. Niosomes are more advantageous than liposomes. It shows their action against various diseases.

KEYWORDS: Niosomes, Targeted drug deliver, Vesicular, Lamellar.

1. INTRODUCTION

Research in recent years has been directed towards developing different drug delivery systems with the goal of overcoming the drawbacks of traditional dosage forms and, in turn, guaranteeing enhanced bioavailability, decreased adverse effects, regulated drug release, and targeted drug administration. In this regard, the vesicular system has been used in clinical practise as a useful technological method to meet requested demand.[1] Niosomes are a vesicular, novel drug delivery system that can be used for long term, controlled and targeted drug delivery with high stability.[2]

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissue of interest or system act directly on desired or targeted site while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. Loss of drug does not happendue to localization of drug, leading to get maximum efficacy of the medication.[3] Paul Ehrlich introduced this idea in1909 and he called this strategy "Magic bullets".[4] Different carriers have been used for targeting of drug such as liposomes immunoglobulin, serum proteins, microsphere, and niosomes.[3] Among these various carriers, niosomes are highly efficient drug delivery systems.[2]

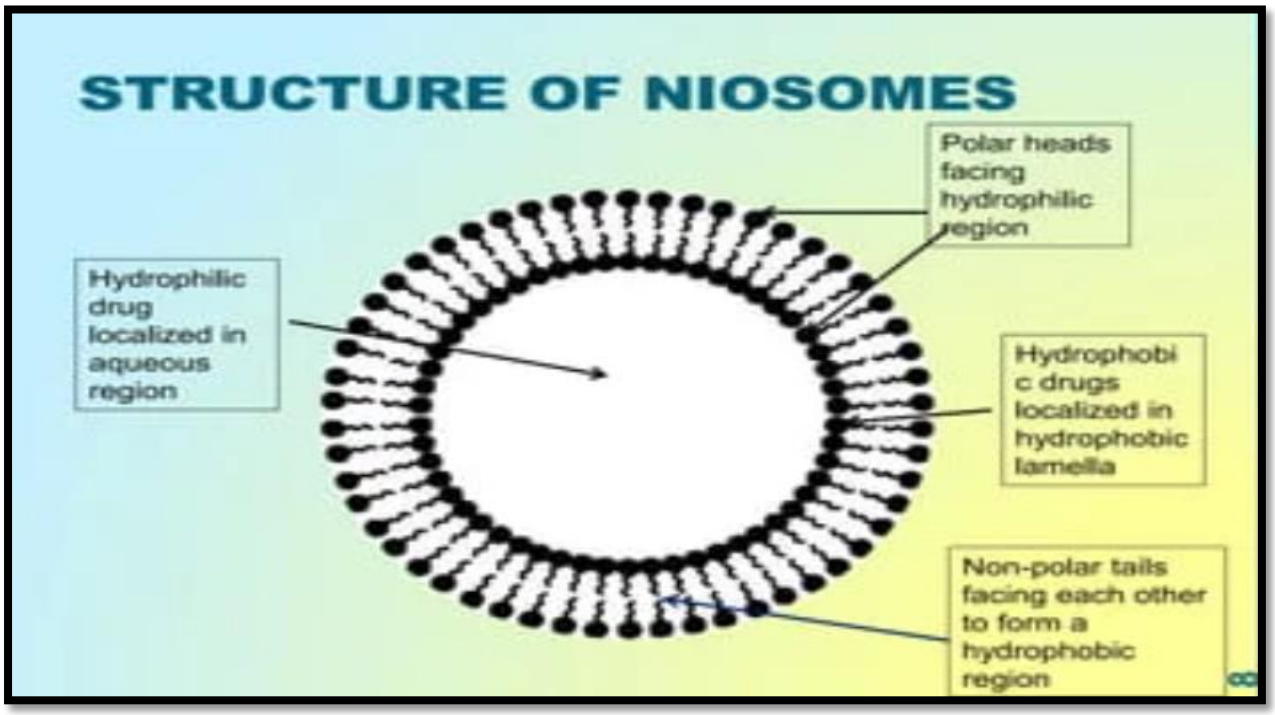
Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface-active agents and hence the name is called niosomes.[5] Niosomes are microscopic lamellar structures with sizes ranging from 10 to 1000nm. Because niosomes are amphiphilic in nature, hydrophilic drugs can be entrapped in the core cavity and hydrophobic drugs can be entrapped in the non-polar region present within the bilayer, allowing both hydrophilic and hydrophobic drugs to be incorporated into niosomes.[6] L'Oréal was the first firm to develop a skincare product incorporating niosomes in the 1970s as oilin water antiaging emulsion.[7,8,9] Chemical stability, biodegradability, low toxicity are the primary reasons for developing a niosomal system. Niosomes can be administered via a variety of routes including oral, parenteral, topical and ocular administration. [10,11,12]

TABLE 1: DRUGS USED IN NIOSOMES VIA DIFFERENT ROUTES [13,14]

S.No.	ROUTES OF DRUG ADMINISTRATION	EXAMPLES OF DRUGS
1	Intravenous route	Methotrexate, Vincristine, Diclofenac sodium, Rifampicin, Zidovudine, Amphotericin B
2	Peroral route	DNA Vaccine, Proteins, Peptides, Ergot alkaloids, Ciprofloxacin, Norfloxacin
3	Transdermal route	Levonorgestrel, Nimesulide,Ketoconazole
4	Ocular route	Cyclopentolate, Timolol maleate
5	Nasal route	Influenza viral vaccine
6	Inhalation	All trans retinoic acids

2. STRUCTURE AND COMPOSITION OF NIOSOMES

Niosome is a bilayered spherical structure composed of non-ionic surfactant and cholesterol. Thenon-ionic surfactant is present in such a way that hydrophobic end faces inward (toward the lipophilic phase) and hydrophilic end faces outward (toward aqueous phase), resulting in the closed lipid bilayer that surrounds solutes in the aqueous phase, which appear like the outer and inner surface of the hydrophilic area, that sandwiched lipophilic area in between them. [15,16]



The main components of niosomes are non-ionic surfactants, hydration medium and lipids such ascholesterol.[18]

TABLE 2: THE MATERIALS USED IN NIOSOME PREPAEATION

S.NO	NON-IONIC SURFACTANTS	EXAMPLES	REFERENCE
1	Alkyl ethers Alkyl glycerol ethers Polyoxyethylene glycol alkyl ether	 Hexadecyl diglycerol ether Brij 30, Brij 52, Brij 72, Brij 76, Brij 78	 19 20,21
2	Crown ethers	Bola	22,23
3	Alkyl esters Sorbitan fatty acid esters (spans) Polyoxyethylene Sorbitan fatty acid esters (tween)	 Span 20, Span 40, span 60, span 80, Span 65, Span 85 Tween 20, Tween 40, Tween 60, Tween 80, Tween 65, Tween 85	 24,25 26,27,28
4	Alkyl amides		

	Glycosides Alkyl polyglycoside	C-Glycoside derivative surfactant Octyl-decyl polyglycoside, decyl polyglycoside	29 30
5	Fatty alcohols or fatty acids Fatty alcohols Fatty acids	Stearyl alcohol, cetyl alcohol, myristyl alcohol Stearic acid, palmitic acid, myristic acid	31 31
6	Block Copolymer Pluronic	Pluronic L64, Pluronic 105	32,33

S.NO	LIPIDIC COMPONENTS	EXAMPLES	REFERENCE
1	Cholesterol	-	34
2	1-alpha Soya phosphatidyl choline	-	35

S.NO.	CHARGED MOLECUES	EXAMPLES	REFERENCE
1	Negative charge	Diacetyl phosphate, Lipoamino acid, Di hexadecyl phosphate	36,37
2	Positive charge	Stearyl amine, stearyl pyridinium chloride, Cetylpyridinium chloride	37

NON-IONIC SURFACTANTS

Non-ionic surfactants are a class of surfactants, which have no charged groups in their hydrophilic heads. They are more stable, biocompatible and less toxic as compared to their anionic, amphotericor cationic counterparts.[18] Therefore, they are preferred for formation of stable Niosome for in vitro and in vivo applications. Non-ionic surfactants are amphiphilic molecules that comprises two different regions: one of them is hydrophilic (water-soluble) and the other one is hydrophobic (organic-soluble). Alkyl ethers, alkyl esters, alkyl amides, fatty acids are the main non-ionic surfactant classes used for niosome production. The Hydrophilic-Lipophilic Balance (HLB) and Critical Package Parameter (CPP) values play a critical role in the selection of surfactant moleculesfor niosome preparation.[38]

HYDROPHILIC-LIPOPHILIC BALANCE (HLB):

The HLB value of non-ionic surfactants describes the degree to which a given molecule is hydrophilic or lipophilic and is an important parameter often used as an indicator for niosome forming capability.[39] HLB is a dimensionless parameter, which is the indication of the solubility of the surfactant molecule. The HLB value describe the balance between the hydrophilic portion to the lipophilic portion of the non-ionic surfactant. The HLB range is from 0-20 for non-ionic surfactants. The lower HLB referto more lipophilic surfactant and the higher HLB to more hydrophilic surfactant. Surfactants witha HLB between 4 and 8 can be used for preparation of vesicle.[38] Hydrophilic surfactant with a HLB value ranging from 14-17 are not suitable to form a bilayer membrane due to their high aqueous solubility.[40] With the addition of an optimum level of cholesterol, niosomes are intended formed from polysorbate 80 (HLB value= 15) and tween 20 (HLB value = 16.7). [41,42] Tween 20 forms stable niosome in the presence of equimolar cholesterol concentration.[43]

CRITICAL PACKAGE PARAMETER (CPP):

During the niosomal preparation the geometry of vesicle depends upon the critical packing parameter. Critical packing parameter depends on the symmetry of the surfactant. [44,45] It is expressed as the ratio between the volume ofhydrophobic group (V), divided by the product of critical hydrophobic group length(lc), and the area of polar head group (a0). [46]

CPP=V/lc * a0

Where, V= hydrophobic group volume Lc=critical hydrophobic group length a0=area of polar head group

If CPP < 3, spherical micelles may form

If CPP > 3 and <1/2, non-spherical micelles may form

If CPP > ½ and < 1, bilayer vesicle may formIf CPP > 1, inverted micelles form [47]

CPP could be considered as a tool for realizing, rationalizing and predicting the self-assembledstructure and its morphological transition in amphiphilic solution. [48]

CHOLESTEROL

Cholesterol is the most frequently used lipid for improving the mechanical strength and rigidity ofniosomal membrane as well as for reducing water permeability. [1] Cholesterol is steroid and present in cell membrane and this is very important component for rigidity, fluidity and permeability. Cholesterol is added in niosome but in very less quantity because in large quantity of cholesterol affects the penetration or permeability, rigidity and encapsulation efficacy. [49]

CHARGED MOLECULES

Charged molecule increase the stability of the vesicles by the addition of charged groups to the bilayer of vesicles. They increase surface charge density and thereby prevent vesicles aggregation.

[50] Charge molecule is added in niosomal formulation to avoid aggregation of niosome. If same charge present in formulation, then repulsion of particle takes place and aggregation not take place.

[51] Diacetyl phosphate and phosphatic acid are most used negatively charged molecules for niosome preparation and stearyl amine and stearyl pyridinium chloride are positively charged molecules used in niosomal preparation.[50] The charge molecule is also required in optimum concentration, if charge molecule added in more concentration, then formulation of niosome doesnot take place. About 2.5-5 mole percentage concentration of charge molecule required for preparation of niosome. [52]

3. ADVANTAGES OF NIOSOME [53,54,55,56,57]

- Niosomes are able to encapsulate a large amount of material in a small vesicular volume.
- Niosome can accommodate a variety of drug moieties such as hydrophilic, lipophilic as well as amphiphilic drugs.
- The drug can release in the sustained / controlled manner.

- Surfactants used to prepare niosomes are biodegradable, biocompatible and non-immunogenic.

DISADVANTAGES OF NIOSOME [56,57,58]

- The niosome formulation are physically unstable.
- Niosome shows aggregation if standard method of preparations not followed.
- Hydrolysis of entrapped drug take place sometimes.

TABLE 3: DIFFERENCE BETWEEN LIPOSOMES AND NIOSOMES [59.60]

	LIPOSOMES	NIOSOMES
Definition	Liposomes are delivery vesicles made up of bilayer of phospholipids.	**Niosomes are delivery vesicles made up of surfactants with or without the incorporation of cholesterol.**
Size ranges	10-3000nm	**10-100nm**
Comparative toxicity	Comparatively more toxic.	**Comparatively less toxic.**
Stability of materials	Phospholipids in liposomes are unstable.	**Non ionic surfactants in niosomes are stable.**
Special storage conditions	Special storage conditions are needed.	**Special storage conditions are not needed.**
Efficiency of Drug Entrapment	**Lesser.**	**Greater.**

3. TYPE OF NIOSOMES

Niosomes are classified based on their size or number of bilayers: Small Uni-lamellar Vesicles(SUV), Large Uni-lamellar Vesicles (LUV) and Multi Lamellar Vesicles (MLV). [61]

5.1. SMALL UNI-LAMELLAR VESICLES (SUV): The small Uni-lamellar vesicles are obtained from large Uni-lamellar vesicle (LUV) by sonication method, French press extrusion, electrostatic stabilization. Small Uni-lamellar vesicle having size range about 10-100nm are 0.01-0.1µm. [62]

5.2 LARGE UNI-LAMELLAR VESICLE (LUV): The LUV are having Uni-lamellar vesicle. It contains single bilayer membrane but it is having large diameter. Aqueous and lipidic content of this vesicle is more so that it has more size. [62] The entrapment quantity of drug in this vesicle is more as compared to other types. Average size of large Uni-lamellar vesicle is 100-3000nm or 0.1-0.3µm. [63] These vesicles generally prepared by ether injection method and reverse phase evaporation method. LUV are having more advantage than MLV such as high encapsulation of water-soluble drug, reproducible drug release rate and economy of lipid. [64,65]

5.3. MULTI-LAMELLAR VESICLE (MLV): The formulation of SUV, MLV and LUV are depending on which method used for preparation of niosome. MLV contain number of bilayers surrounding to aqueous lipid compartment separately. The average size of MLV is about 50nm or0.05µm in diameter. [65] The MLV is very simple for preparation and It is more stable for long period of time. This vesicle is more suitable for lipidic drug compound. This type of niosome mainly prepared by thin film hydration method. [62]

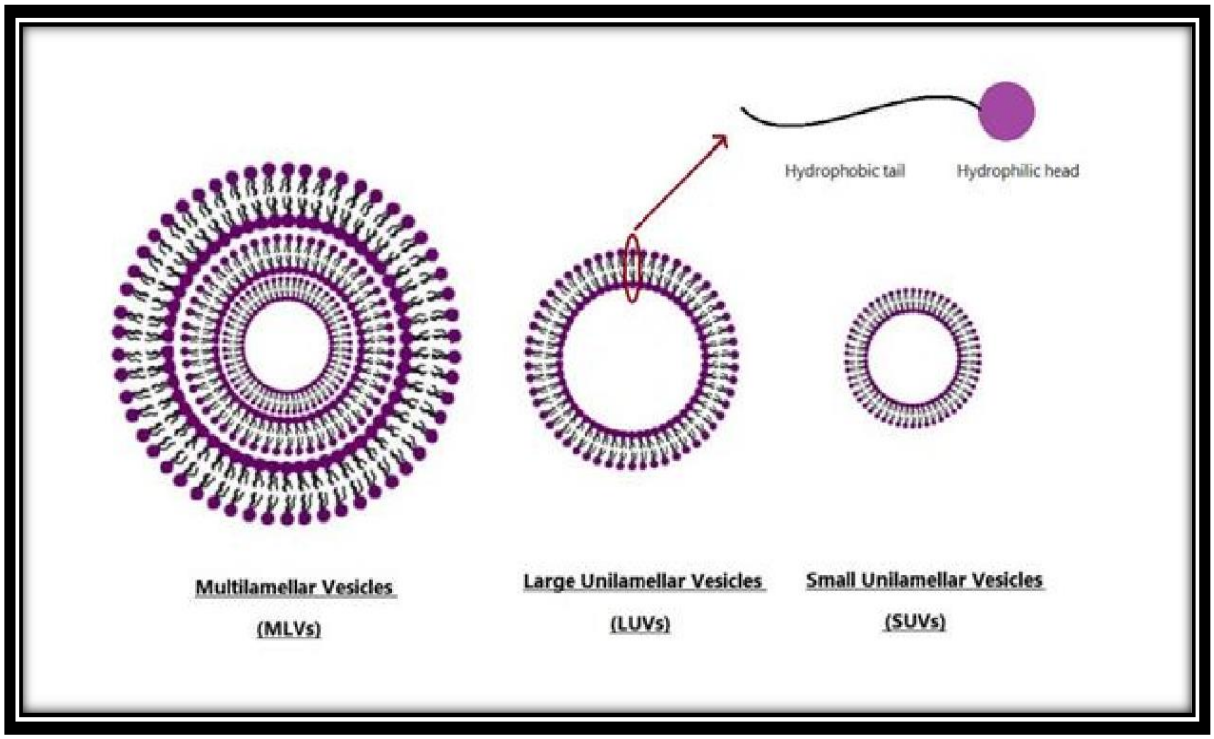


FIGURE 2: TYPES OF NIOSOMES [66,67]

4. METHOD OF PREPARATION OF NIOSOMES

Preparation methods will affect the number of bilayers, size distribution, dimensions and entrapment efficiency. [68,69]

PREPARATION OF UNILAMELLAR VESICLES

- SONICATION METHOD: It is the conventional method to produce small uniform size niosomes. This process includes mixture of drug solution in the buffer, surfactant and cholesterol and subjected to sonication by using titanium probe at a temperature of 60°C for 3min to get niosomes. [70,71]

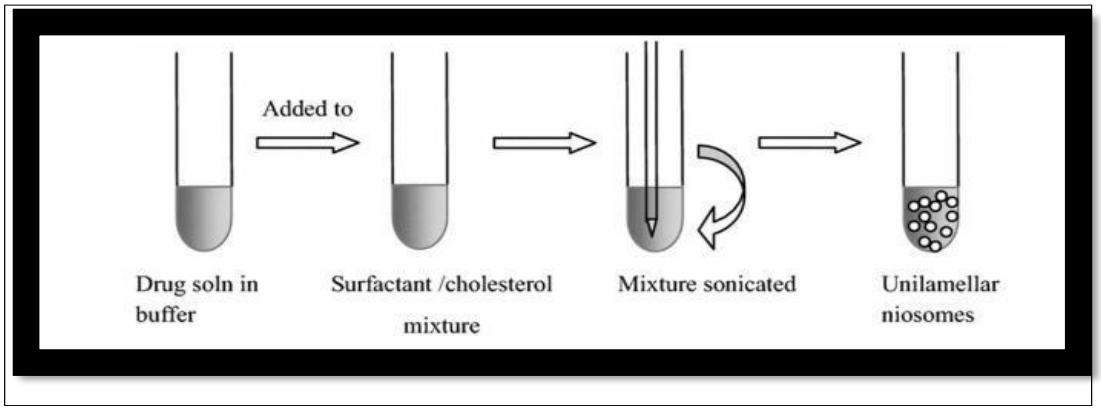


FIGURE 3: PREPARATION OF NIOSOMES VIA SONICATION METHOD [72]

PREPARATION OF LARGE UNILAMELLAR VESICLES

- ETHER INJECTION METHOD: The initial step in this preparation is to dissolve surfactant in diethyl ether and inject it into an aqueous phase containing a drug, which was at 60°C through 14-gauge needles. Subsequently ether was vaporized and resulted in single layer vesicles with a diameter ranging from 50-1000nm.

  Here, the drawback is that it is difficult to remove the small amount of ether i.e., still presentin the vesicle. [73,74,75]

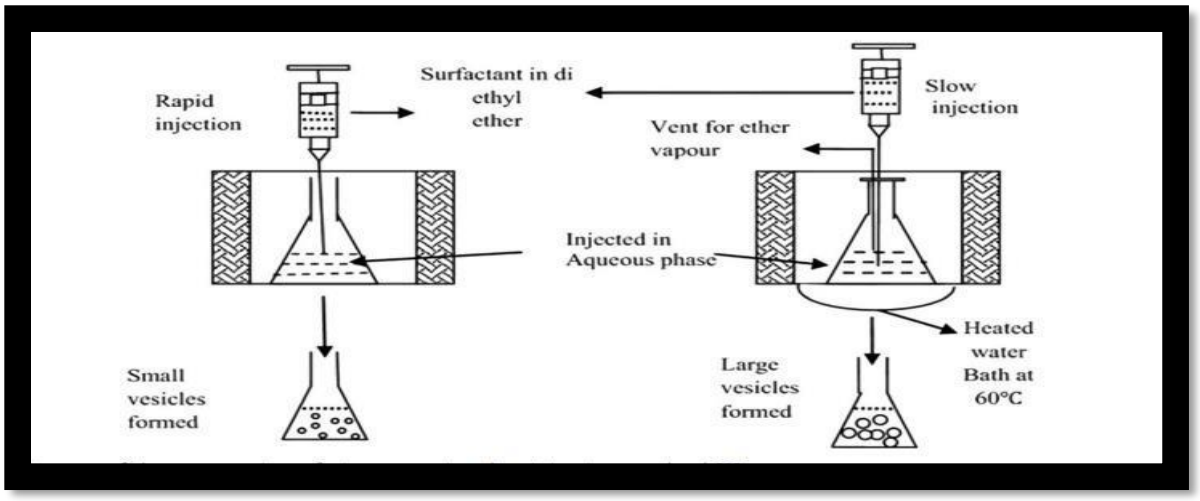


FIGURE 4: PREPARATION OF NIOSOME VIA ETHER INJECTION METHOD [76]

❖ REVERSED PHASE EVAPORATION METHOD: Weighed surfactant and cholesterol in a 1:1 ratio and dissolved in chloroform and ether mixture. To this mixture, aqueous phase containing drug was added and followed by sonication at a temperature of 4-5°C, a small quantity of phosphate buffer saline was added and continued to sonicate. Then the organic solvent was removed by applying it to low pressure at 40°C after that remaining suspension is diluted with phosphate buffer saline. The final product of the niosomes was obtained by heating the mixture at 60°C for 10min. [77,78]

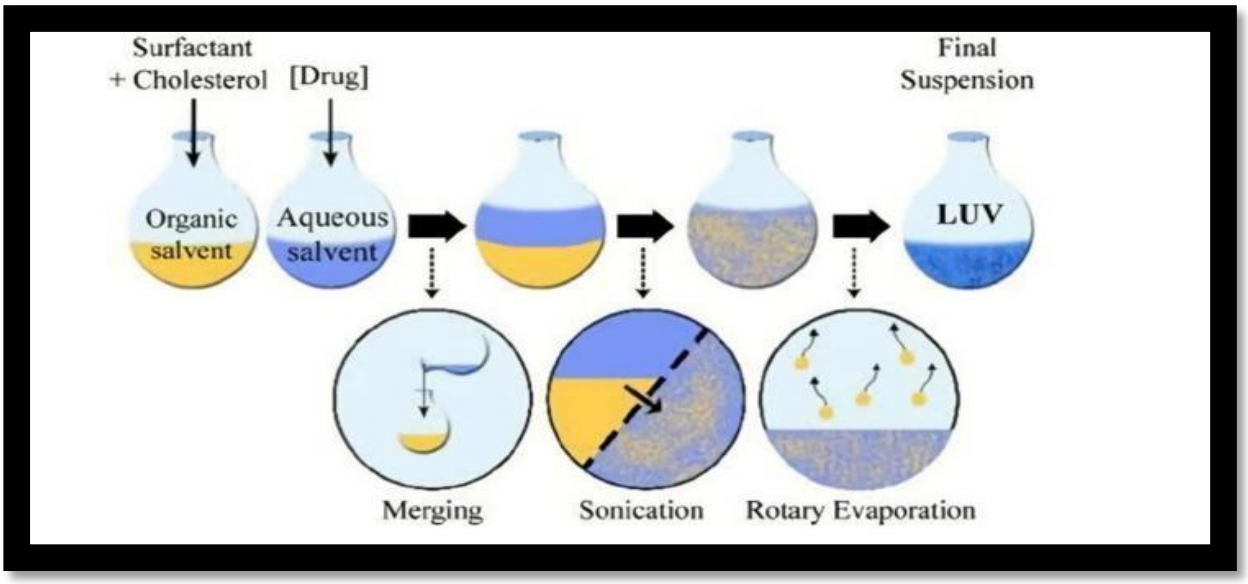


FIGURE 5: PREPARATION OF NIOSOME VIA REVERSE PHASE EVAORATION METHOD[79]

PREPARATION OF MULTILAMELLAR VESICLES

❖ THIN FILM HYDRATION TECHNIQUE (HAND SHAKING METHOD): Diethyl ether, chloroform, and methanol were the volatile organic solvents used to dissolve the mixture of surfactant and cholesterol in a round-bottom flask. Next, use a rotary evaporator set at room temperature (20°C) to evaporate the solvent, leaving behind a thin layer of solid mixture on the flask's walls. Niosomes are formed when this dry film is gently agitated at 0 to 60°C to rehydrate it with the aqueous phase. [80,81]

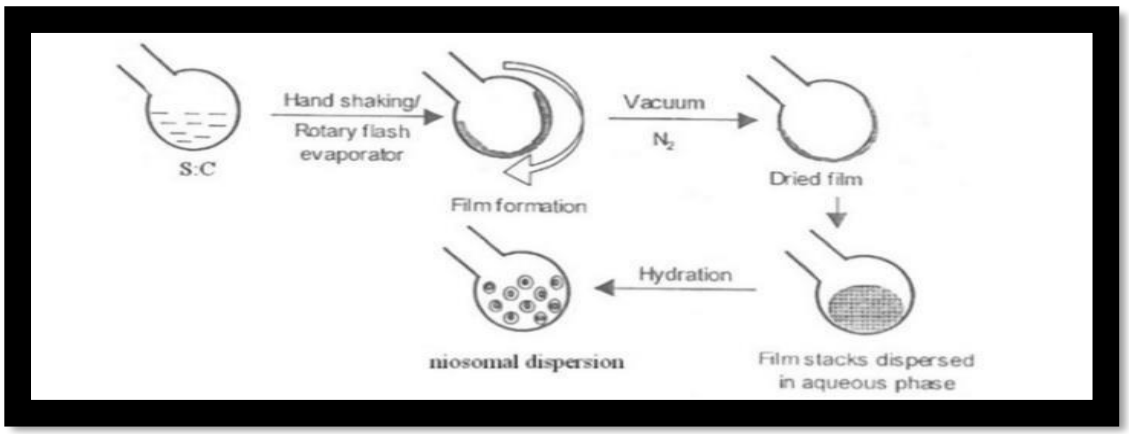
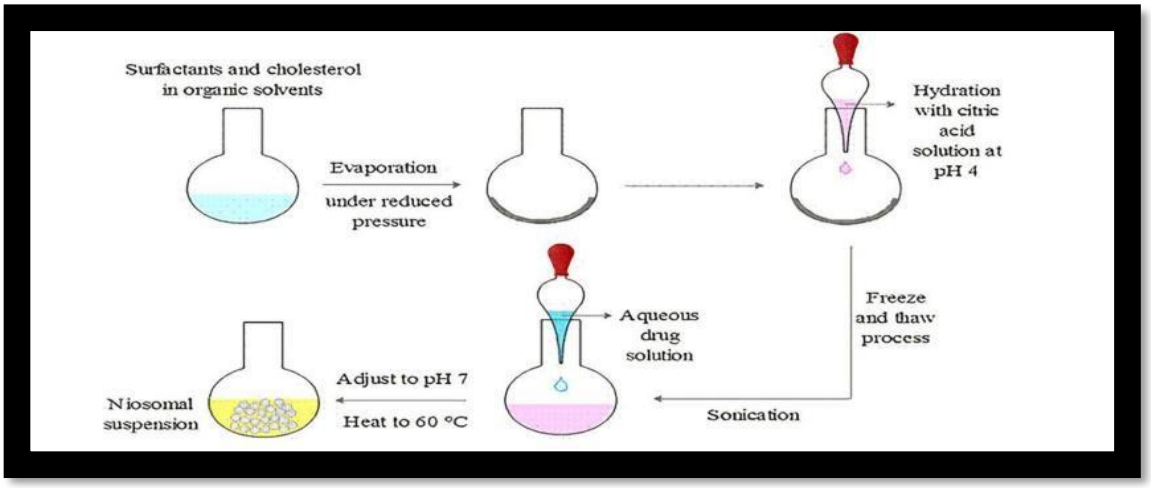


FIGURE 6: PREPARATION OF NIOSOME VIA THIN FILM HYDRATION TECHNIQUE [76]

❖ TRANSMEMBRANE PH GRADIENT (INSIDE ACIDIC) CYCLE OF DRUG ABSORPTION (REMOTE CHARGE): In a round bottom flask, the mixture of cholesteroland surfactant was dissolved in chloroform. Then remove the organic solvent by using a rotary evaporator at a room temperature (20°C) that left a thin film of the solid mixture onthe walls of the flask, which rehydrates with 300mM citric acid (pH 4.0). Further subjected to 3 successive freeze – thaw cycles and sonicated. To this, adding the aqueous drug solution and vortexes increased the pH 7.0-7.2 by adding disodium phosphate (1M) and subjected to eating for 10min at 60°C to obtain niosome. [82,83]

FIGURE 7: PREPARATION OF NIOSOME VIA TRANSMEMBRANE PH GRADIENT [84]



MISCELLANEOUS METHOD

❖ MULTIPLE MEMBRANE EXTRUSION METHOD: It is a good method to produce smallsize niosomes. In this, the mixture of surfactant, cholesterol, diacetyl phosphate and chloroform is evaporated, leaving a thin film and rehydrated with the aqueous drug solution. The resultant dispersion extruded through a polycarbonate membrane, then placed in a series of up to 8 passage to obtain niosomes.[85]

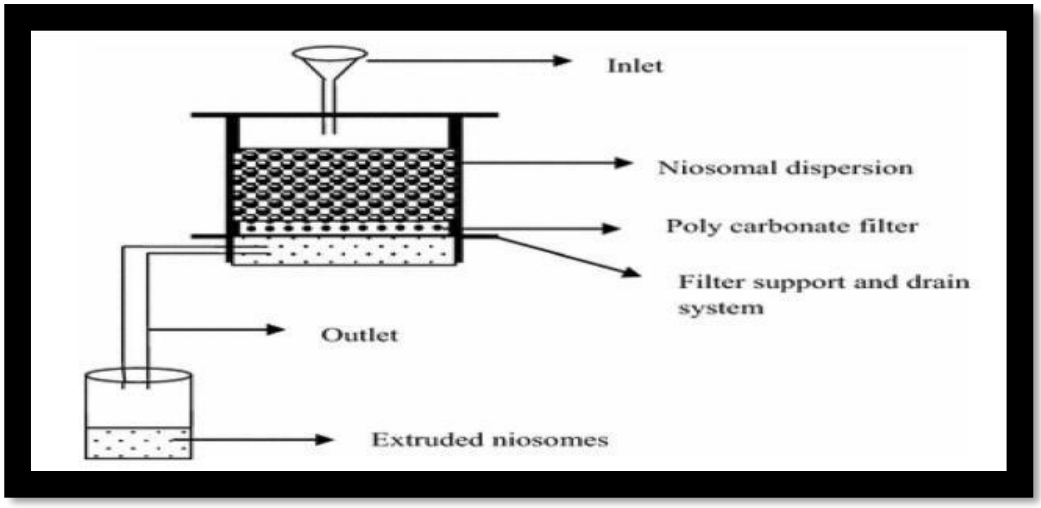


FIGURE 8: PREPARATION OF NIOSOME VIA MULTIPLE MEMBRANE EXTRUSIONMETHOD [86]

- EMULSION METHOD: This is a simple method to form niosome in which oil in water (o/w) emulsion is prepared from an organic solution of surfactant, cholesterol and an aqueous solution of the drug. Finally, the organic solvent is evaporated leaving niosomes dispersed in the aqueous phase. [87]

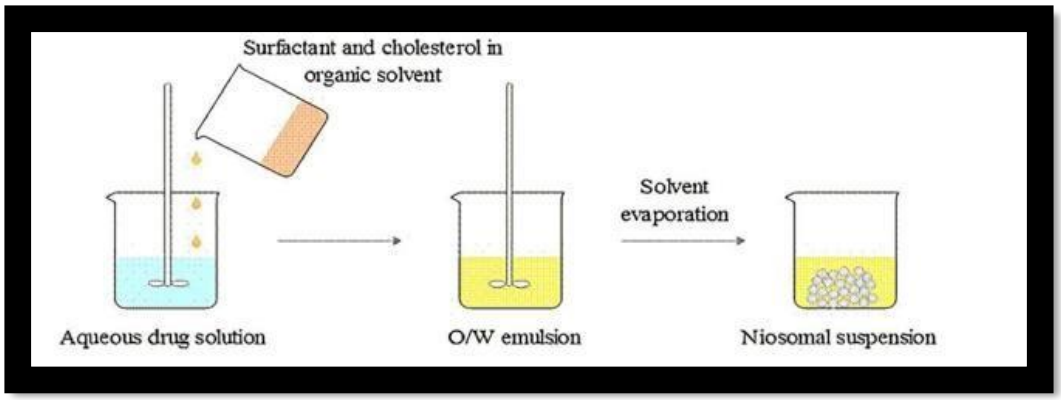


FIGURE 9: PREPARATION OF NIOSME VIA EMULSION METHOD [84]

- THE "BUBBLE" METHOD: It is a novel technology to get niosomes in one step without adding an organic solvent. This method contains a "bubbling unit" having round bottomed flask with three necks i.e., positioned in a water bath. Water cooled reflex, thermometer and nitrogen gas suppliers are positioned in first, second and third necks respectively. In this, surfactant and cholesterol are mixed in the buffer and then homogenized and "bubbled" at 70°C in a "bubbling unit" to obtain niosomes. [88]

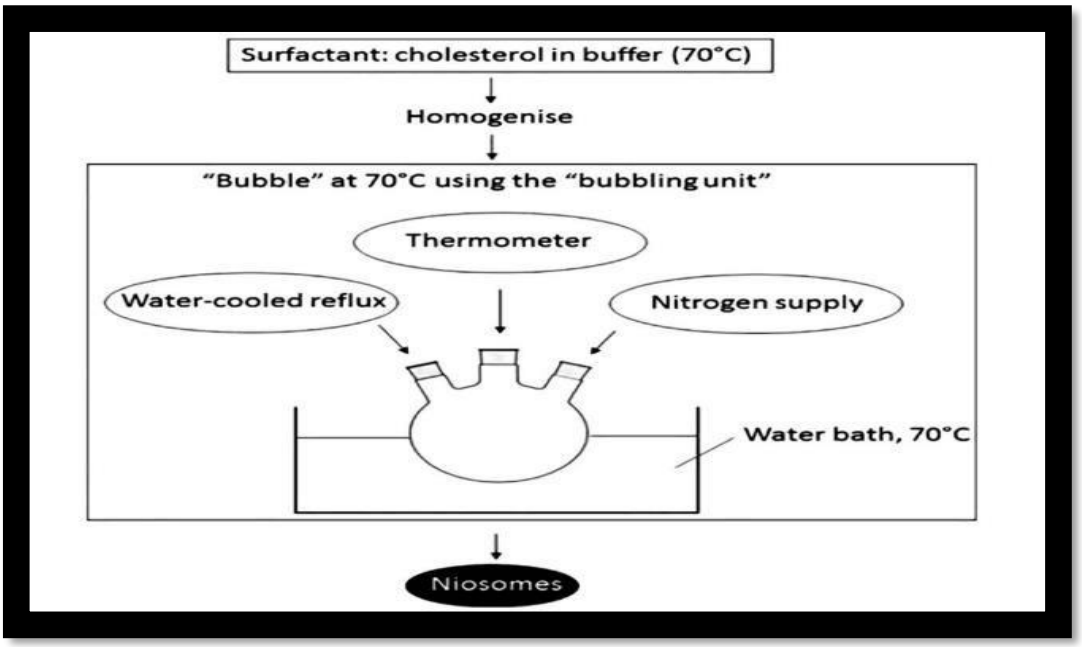


FIGURE 10: PREPARATION OF NIOSOME VIA THE BUBBLE METHOD [89]

FORMATION OF NIOSOMES FROM PRONIOSOMES: Another method of producing niosome is to coat a water-soluble carrier such as sorbitol with the surfactant. The result ofthe 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. [90]

T= temperature

Tm=mean phase transition temperature Carrier + Surfactant = Proniosomes Proniosomes + Water = niosomes [91]

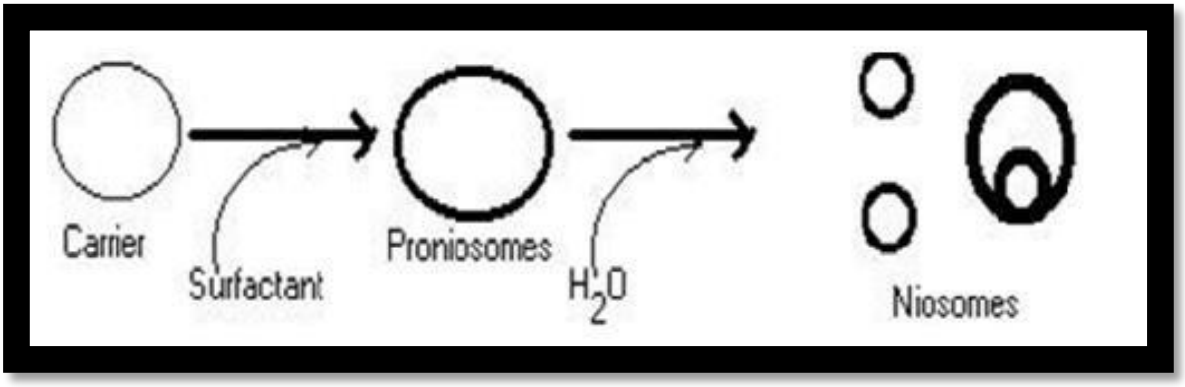


FIGURE 11: PREPARATION OF NIOSOME VIA PRONIOSOME [91]

5. APPLICATION OF NIOSOMES

These are potentially applicable to many pharmacological agents to show their action againstvarious diseases.

NIOSOMES AS DRUG CARRIERS:

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

- ANTI-NEOPLASTIC TREATMENT:

  Most anti-neoplastic drugs cause severe side effects. Niosomes can alter the metabolism prolong the circulation and half- life of the drug, decreasing the side effects of the drugs.

  Niosomes decrease the rate of proliferation of tumor and higher plasma levels by slower elimination.

- LEISHMANIASIS:

  Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells ofthe liver and spleen. Niosome use in tests, conduct and shows that it was possible to administer higher levels of the drug without the triggering of the side effects, allows greaterefficacy in the treatment.

- DELIVERY OF PEPTIDE DRUGS:

  Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown being investigated. In an in- vitro study conduct by oral delivery of a vasopressin entrap derivative in a niosomes show that entrapment of the drug increases thestability of the peptide.

- USE IN STUDYING IMMUNE RESPONSE:
  Due to their immune system selection, low toxicity, greater stability niosomes are used to study the nature of the immune response provoke by antigens. Non-ionic surfactants vesicles have clearly demonstrated their ability to function as adjuvants as a parenteral administration with a number of different antigens and peptides.
- COSMETICS:
  The first report of non- ionic surfactant vesicles came from the cosmetic applications devised by L'Oréal. Niosomes develop and patent by L'Oréal in the 1970s and 80s. The first product 'Niosome' introduce in 1987 by Lancôme. Niosome advantage in cosmetic and skin care an application include their ability to increase the stability of entrapped drugs and also improve bioavailability of poorly absorb ingredients and enhance skin penetration.

CONCLUSION

Niosomes are vesicular and novel drug delivery system whose structure consist of 2 layers of non- ionic surfactants. Because of their amphiphilic nature, hydrophobic and hydrophilic drugs can be loaded into niosomes. The niosome having similar structure like liposome but niosome is more advantageous than liposome. Niosomes increase the stability of entrapped drug, slow drug release,reduce the dose and reduce drug toxicity. Niosomes also increase the bioavailability of drug, sustained release, controlled release of drug and enable targeted delivery to a specific type of tissue without affecting the surrounding tissues. No special conditions are required for handling, preparation and storage of niosome. Niosome formulations can be administered via oral, topical/transdermal, parenteral and ocular routes. Niosomes are advantageous in encapsulate toxic anti-cancer drugs, anti-infective drugs, anti-AIDS drugs, anti-inflammatory drugs, anti-viral drugs etc. Hence, it improves the overall therapeutic performance of drugs.

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