Niosomes as Novel Drug Delivery System

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***Abstract*: Niosomes are non-ionic surfactant based unilamellar or multilamellar bilayer vesicles upon hydration of non-ionic surfactants with or without incorporation of cholesterol. Niosomes are biodegradable, biocompatible, non-immunogenic, and exhibit flexibility in their structural characterization. Niosomes are easy to be formulated. Niosomes as drug carriers improve the bioavailability of a poorly absorbed drug. In some cases, the chances of breaking vesicles into gastric pH to overcome this problem polymer coating are the best way in recent years. This review article focused on developing an effective delivery system to achieve maximum effective concentration, the structure of Niosomes, advantages, and disadvantages, components of niosomes, different methods of formulation, purification, and evaluations of Niosomes.**

***Keywords*: Niosomes, Vesicles, Cholesterol, Non-ionic surfactant, Encapsulated efficiency, dialysis.**

I. INTRODUCTION:

Niosomes are novel drug delivery systems in which the drug is encapsulated into vesicles[1]. It is also called a vesicular drug delivery system. The first vesicular drug delivery system is liposomes. But liposomes have some disadvantages like stability issues, expensive, and toxicity[2]. To overcome these problems scientists shifted towards Niosomes. Niosomes are made up of non-ionic surfactants, and they have no toxicity just because of surfactant[3]. In addition to non-ionic surfactants, they are cholesterol, a hydration medium, and some charged molecules. Niosomes are non-ionic surfactant based unilamellar or multilamellar bilayer vesicles upon hydration of non-ionic surfactants with or without incorporation of cholesterol. Niosomes are biodegradable, biocompatible, non-immunogenic, and exhibit flexibility in their structural characterization. Niosomes are less toxic and active at the site[4]. Oral polymers like Carbopol 974, and Carbopol 971 are used for coating purpose[5]. In a few cases, chances for breaking vesicles into gastric media to overcome this problem polymer coating is the best way[6,7]. Because polymer show rigid and stable bilayer[8,9]. Niosomes as drug carriers improve the bioavailability of poorly absorbed drug[10]. Niosomes are proved to be a promising drug carrier because they can encapsulate different types of drugs within their multi-environmental structure.

II. ADVANTAGES AND DISADVANTAGES:

Table 1 : Advantages and disadvantages of Niosomes

Advantages	Disadvantages
Niosomes are less toxic and more compatible	Drug leakage from the entrapment
They can be used to encapsulate both hydrophilic as well as hydrophobic drugs	Hydrolysis of encapsulated drug which limiting the shelf life of the dispersion
They are osmotically active and stable	Aggregate formation of Niosomes
They can enhance the skin penetration of drug	Fusion
Easy to be formulated	Physical instability

III. STRUCTURE OF NIOSOMES

Niosomes are bilayer structures of non-ionic surfactants[11]. The bilayer structure shows a hollow space in centre[12]. As shown in Figure 1.

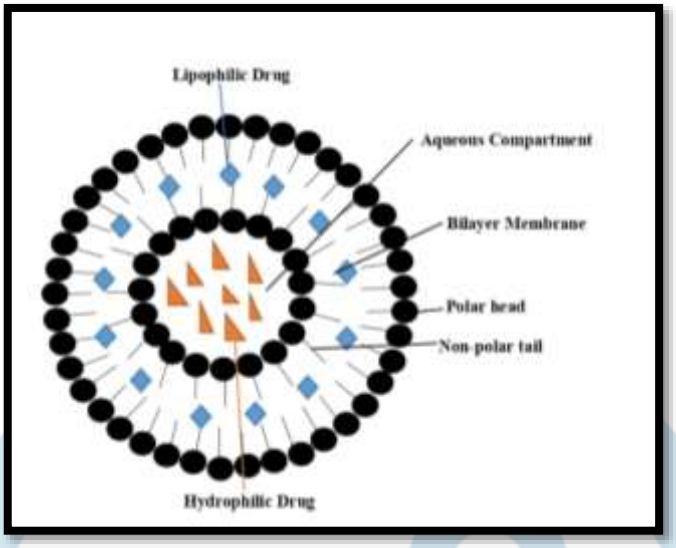

Figure 1 : Structure of Niosomes

IV. COMPOSITION OF NIOSOMES

Formulation components of Niosomes are cholesterol, non-ionic surfactant, charge inducers, and hydration medium.

1. Cholesterol:

Cholesterol is a steroid derivative present in the cell membrane and an important additive in the formation of Niosomes[13]. Cholesterol can affect the rigidity of the membrane, fluidity, permeability, entrapment efficiency, ease of rehydration of freeze-dried Niosomes, storage time, and their toxicity. Cholesterol is used in the formulation of Niosomes but in very less quantity because a large quantity of cholesterol affects the penetration of niosomal vesicles[14]. If the cholesterol is used with low HLB surfactants, it can be increasing the stability of vesicles, if the HLB value is more than 6, it helps in the formation of bilayer vesicles. In the formation of Niosomes generally, a 1:1 M ratio used cholesterol: Surfactant. Cholesterol makes a hydrogen bond with an alkyl chain of non-ionic surfactants which provide better stability.

2. Non-ionic surfactants:

The selection of non-ionic surfactants in the preparation of Niosomes depends on the HLB value of the surfactant. For proper vesicle formation of Niosomes, the HLB value must range between 4 to 8[15]. Non-ionic surfactant contains a polar head and non-polar tail[16]. As shown in Table 2.

Table 2 : Non-ionic surfactants used for prepration of Niosomes

Non-ionic surfactant		Examples	Properties
Alkyl esters	Sorbitan fatty acids esters (Spans)	Span 20, Span 40, Span 60, Span 65, Span 80, Span 85	Usually referred to as Span. Generally used in water-based cosmetic preparations to solubilize oils. With an increase in the carbon chain length transition temperature increases i.e., the gel transition temperature of span 60 is higher than span 20 and span 40. Vesicles prepared from a higher span are more stable and less leaky. Niosomes prepared from span 60 give the highest entrapment efficiency. Span 60 is capable of protecting the drug from degradation by proteolytic enzymes.
	Polyoxymethylene sorbitan fatty acid esters (Tweens)	Tween 20, Tween 40, Tween 60, Tween 65, Tween 80, Tween 85	These are derived from fatty acid esterified ethoxylated sorbitans. For niosome preparation usually, Tween 20,40, 60, and 80 are used.
Alkyl ethers	Alkyl glycerol ethers	Hexadecyl diglycerol ethers	-
	Polyoxyethylene glycol alkyl ethers (Brij)	Brij 30, Brij 52, Brij 72, Brij 76, Brij 78	Brij 30 HLB value is 9.7 and Phase transition temperature is below 10, Brij 58 has the capacity of forming inverse vesicles. HLB value 15.7, HLB value of Brij 72 is 4.9 and Brij 76 is 12.4. The entrapment efficiency of Brij 72 is higher than Brij 76.
Crown ethers	-	Bola	-
Alkyl amides	Glycosides	C-glycoside derivative surfactant	These are alkyl galactosides and glucosides which have incorporated amino acid spacers. The alkyl groups are fully or partially saturated in C12 to C22 hydrocarbons

	Alkyl polyglucosides	Octyl-decyl polyglucoside	and some novel amide compounds have fluorocarbon chains.
Fatty alcohols and fatty acids	Fatty alcohols	Stearyl alcohol, acetyl alcohol, myristyl alcohol	These are amino acids that are made amphiphilic by the addition of hydrophobic alkyl side chains and long-chain fatty acids which form "Ufasomes" vesicles formed from fatty acid bilayers.
	Fatty acids	Stearic acid, Palmitic acid, myristic acid	
Block copolymer	Pluronic	Pluronic L64, Pluronic 105	Pluronic L64 and 105 are copolymers made up of polyethylene (EO) oxide and polypropylene oxide (PO). Arranged as EO-PO-EO. Pluronic's interact with multidrug-resistant cancer tumors

3. Charge inducers:

This molecule's induction of charge on the surface increases the stability of the niosomes by electrostatic repulsion. Two types of charged inducers are positive charge and negative charge inducers. Some examples of positive charge inducers are sterylamine and cetyl pyridinium chloride and negative charge inducers are dicetyl phosphate (DCP), dihexadecyl phosphate, and lipoamine acid[17].

4. Hydration medium:

Phosphate buffer is used as a hydration medium and the pH of phosphate buffer depends on the encapsulated drug solubility[15]. Sunil Kamboj prepared Niosomes of losartan potassium by conventional thin-film hydration technique in phosphate buffer saline (PBS) of pH 7.4 they observe stable Niosomes[18].

V. TYPES OF NIOSOMES:

Various types of niosome are based on vesicle size. As shown in table 3.

1. Small unilamellar vesicles (SUV)
2. Large unilamellar vesicles (LUV)
3. Multilamellar Vesicles (MLV)

Table 3 : Types of Niosomes

Sr. No.	Types of Niosomes	Vesicle size	Description	Method of preparation
1.	Small unilamellar vesicles (SUV)	0.025 - 0.05 µm	SUV mostly prepared from multilamellar vesicles	Sonication method, Extrusion method, Solvent dilution technique
2.	Large unilamellar vesicles (LUV)	Greater than 0.10 µm	LUV has a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped	Reverse phase evaporation method
3.	Multilamellar vesicles (MLV)	Greater than 0.05 µm	MLV contains several bilayers. MLVs are mechanically stable upon storage for a longer period.	Hand shaking method, Ether injection method

VI. METHOD FOR PREPARATION NIOSOMES :

The methods of preparation of Niosomes involve evaporation of solvents to form a thin film by using a hydration medium. There are different methods described below in detail. As shown in Fig.2.

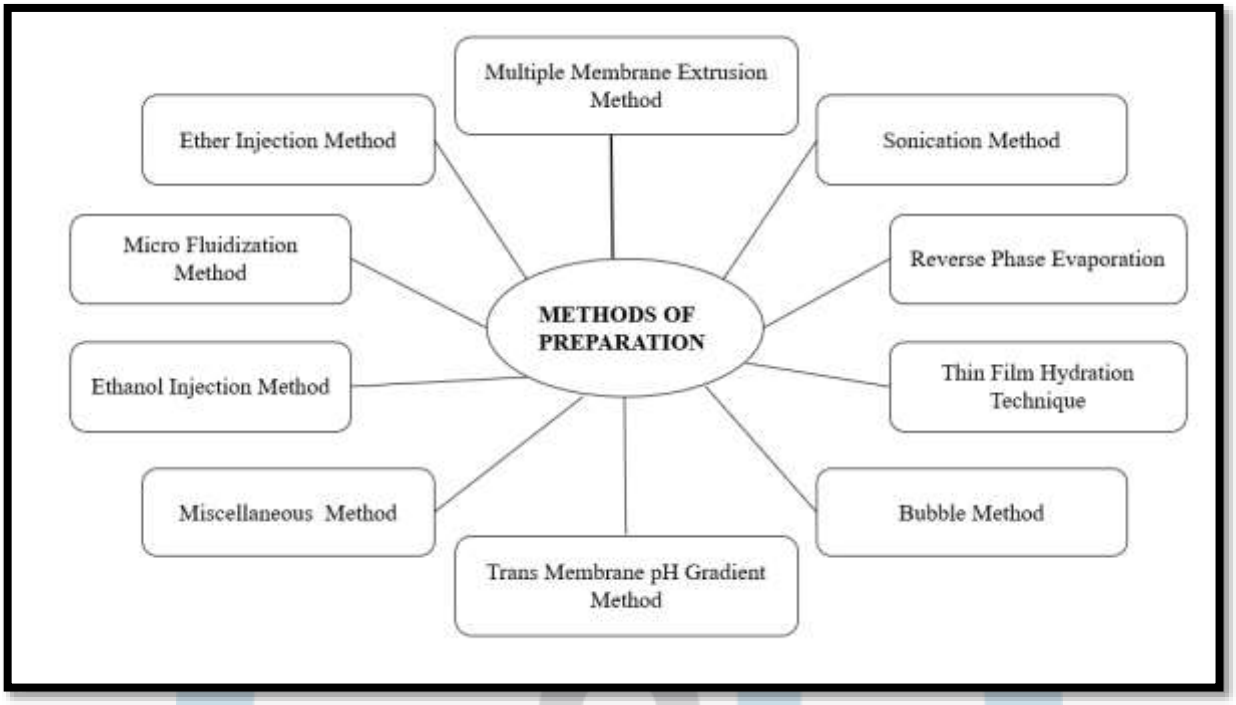

Figure 2 : Method of Prepration of Niosomes

1. Ether injection method:

The ether injection method was reported in 1976 by Deamer and Bangham. Niosomes are prepared by this technique using Non-ionic Surfactants and Cholesterol at different concentrations. Surfactants and cholesterol are dissolved in diethyl ether and mixed with methanol containing a drug. The resulting organic solution was slowly injected using a microsyringe into an aqueous solution (Phosphate buffer) with continuous stirring and maintained temperature of 60-65^0 C[19]. The organic solution was injected into the aqueous phase, the difference in temperature between the two phases cause rapid vaporization of ether and the formation of single-layered vesicles[20,21].

2. Multiple membrane extrusion methods:

The mixture of dicetyl phosphate, surfactant, and cholesterol dissolved in chloroform. The resulting mixture was vaporized in a rotary evaporator to form a thin film. This film is hydrated with a hydration medium to form a suspension. The resulted suspension was extruded through polycarbonate membranes and placed in series to create 8 passages[11].

3. Sonication method:

The mixture of surfactant, cholesterol, and an aqueous phase containing the drug, this mixture maintained at 60^0 C and placed in a bath sonicator or probe sonicator to yield Niosomes[22].

4. Reverse phase evaporation technique:

The mixture of surfactant and cholesterol is dissolved in diethyl ether or chloroform or a mixture of surfactant and cholesterol and the drug is added in the aqueous phase[23]. The aqueous phase is added to the organic phase. The resulting two-phase mixture is homogenized using a homogenizer. The organic phase is evaporated under negative pressure to yield Niosomes[24].

5. Thin-film hydration technique:

The hand shaking method was reported in 1985 by Azmin *et al.* and Baillie *et al.* In a round bottom flask take a mixture of surfactant and cholesterol were dissolved in chloroform and ethanol or methanol[20]. The organic solvents were evaporated by using a rotary flash evaporator under reduced pressure at a temperature 60±2^{0}C[25]. The resulting smooth thin film on the wall of a flask, this thin lipid film was hydrated with phosphate buffer saline (PBS) with gentle shaking to yield multilamellar Niosomes[1,18].

6. Bubble method:

The bubble method is used to preparation of Niosomes in one step without using organic solvents. The bubble machine contains a round bottom flask with three necks placed in a water bath. Water-cooled reflux was placed in the first neck, a thermometer placed in the second neck, and nitrogen gas supply through the third neck[23]. The surfactant and cholesterol were mixed with phosphate buffer saline (PBS) pH 7.4, this dispersion was mixed with a high shear homogenizer at 70^{0}C for 15 seconds and instantly bubbled at 70^{0}C by using nitrogen gas[26].

7. Trans membrane pH gradient Method:

In this method surfactant and cholesterol are dissolved in an organic solvent such as chloroform in a round bottom flask. The organic solvents evaporated under low pressure to get a thin film on the wall of the round bottom flask[26]. This film is hydrated with citric acid by vortex mixing[27]. Multilamellar vesicles are formed which are freeze-thawed three times and sonicated. For niosomal suspension drug added in an aqueous phase, vortexed and pH raised to 7.0-7.2 with 1 M disodium phosphate[28]. The mixture is heated at 60^{0}C to yield Niosomes[29].

8. Ethanol injection method:

The ethanol injection method is just similar to the ether injection method, only instead of with ether ethanol is used in the ethanol injection method to yield Niosomes.

9. Micro fluidization method:

The micro fluidization method is used in the preparation of unilamellar vesicles. In this method interaction chamber, two ultra-high-speed jets are present, impingement of thin layer of liquid in microchannels to yield uniform Niosomes[27].

10. Miscellaneous methods:

Miscellaneous methods contain the emulsion method, lipid injection method, heating method, and formation of Niosomes from proniosomes.

Table 4 : Different method of prepration of Niosomes and advantages and disadvantages

Sr no.	Method	Advantages	Disadvantages
1.	Ether injection method	This method does not cause oxidative degradation	i. A small amount of ether is present in vesicle suspension and is difficult to remove the complete organic solvent i. Ether is free from chances of oxidative degradation i. Slow vaporization of solvent, ether gradients extending towards the interface of an aqueous-non aqueous interface then they form bilayer vesicles
2.	Multiple membrane extrusion methods	i. A good method for controlling vesicle size i. Reducing polydispersity	i. High product loss i. Time-consuming
3.	Sonication method	High-frequency sound waves reduce the size of large vesicles	Tip of probe sonicator may contaminate niosomal dispersion
4.	Thin-film hydration technique	A simple and reproducible method	Time-consuming method
5.	Bubble method	Preparation of Niosomes without organic solvents	-
6.	Micro fluidization method	Greater uniformity, small size, and better reproducibility	In a chamber high-pressure present that can cause degradation of lipid
7.	Reverse phase evaporation method	Used to encapsulate molecules of a very wide range of size	The materials to be encapsulated are made to come in contact with organic solvents

VII. METHODS FOR PURIFICATION OF NIOSOMES

The removal of unentrapped drugs from the vesicles can be done by various techniques, such as centrifugation, dialysis, and gel filtration.

1. Centrifugation/ Ultracentrifugation:

The most preferred method for the purification of Niosomes in recent research work is the centrifugation method. In this technique separation of unentrapped genetic material from Niosomes by density gradient centrifugation. Some authors separated the unentrapped drug by ultracentrifugation[30].

2. Dialysis:

Dialysis is a technique based on osmosis and diffusion that depends upon the movement of solute and solvent across a semi-permeable membrane. The aqueous niosomal suspension is taken in a dialysis bag and the free drug is dialyzed using phosphate buffer or normal saline or glucose solution[31].

3. Gel Filtration:

The unentrapped drug can be removed by gel filtration technique using Sephadex G50, G25, and G75 column and elution with phosphate buffer saline or glucose solution or normal saline[32].

VIII. CHARACTERIZATION OF NIOSOMES

Evaluation parameters are shown in Table 5.

Table 5 : Evaluation parameters of Niosomes

Evaluation Parameter	Characterization method
Particle size	Dynamic light scattering particle size analysis (Zeta sizer)
Morphology	SEM, TEM
Entrapment efficiency	Gel chromatography. Dialysis method, Centrifugation
Turbidity	UV Spectrophotometer

Thermal analysis	DSC
Viscosity	Ostwald viscometer
Permeation study	Franz diffusion cell
In-vitro drug release	Dialysis membrane

1. *In-Vitro* drug release:

In-vitro drug release of niosomal suspension was determined by the dialysis bag method. *In-vitro* drug release studies were performed using different pH buffers for gastric stimulation and blood pH and to evaluate the effect of pH on drug release. The dialysis sac was soaked in distilled water before being used. One end was sealed with a closure clip and 5 ml of niosomal suspension was pipetted into a dialysis bag and sealed another end with a closure clip to prevent leakage[20,33]. The dialysis bag was placed into a beaker containing 100 ml PBS pH 7.4 and the beaker was placed over a magnetic stirrer at 100 rpm and maintained the temperature at 37±1^{0}C[28]. The dialysis membrane act as the donor compartment whereas the media act as the receptor compartment. The 5 ml samples were collected every hour from PBS and replaced with fresh PBS. After samples were diluted with PBS and checked absorbance by using a UV Spectrophotometer[34].

2. Entrapment efficiency:

The entrapment efficiency of drug-loaded Niosomes was determined by using Cooling Centrifugation. For separation of an unentrapped drug, take 1 ml niosomal dispersion was measured into a 1.5 ml capacity Eppendorf tube and placed in a centrifuge at 17000 rpm for 30 min at 4^{0}C. After centrifugation, the supernatant liquid was separated containing unentrapped drug and diluted with PBS, and analyzed by using a UV Spectrophotometer[18]. The Entrapment efficiency is calculated by:

$$\text{Entrapment efficiency} = \frac{\text{Total amount of drug} - \text{The amount of drug in supernatant liquid}}{\text{Total amount of drug}} \times 100$$

Equation 1 : % Entrapment efficiency

3. Particle Size and shape:

The shape of vesicles is spherical. Particle size is determined by the zeta sizer instrument. Particle size analysis was carried out for the 60s at 165^{0}C scattering angle of detection[19]. The sample was filled in cuvettes and then insert into an instrument by opening the lid of the zeta sizer and the sample was analysed[35].

4. Morphology analysis:

The surface morphology was determined by using a Confocal microscope and Scanning electron microscope[19]. In SEM the sample was fixed on an SEM stub using double-sided adhesive tape. Samples were coated with a thin layer of gold under a vacuum. Sample stub kept in SEM chamber and operate at 10 kV. Then run the sample and capture the images at different magnifications.

CONCLUSION:

Niosomes are easy to be formulated, non-toxic, non-immunogenic, biocompatible, stable, and biodegradable. A special requirement is not required for the storage of surfactants. The Niosomes as a vesicular delivery system has some advantages over the conventional delivery system. The concept of the encapsulated drug into vesicles is better targeting a drug into an appropriate site or tissue. The polymer-coated niosomes are more stable.

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