



Non-ionic surfactant carrier/vesicle drug delivery system

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Abstract

Niosomes are one of the prominent Novel Drug Delivery systems. Niosomes are made up of non-ionic surfactants with or without cholesterol. Primarily niosomes are similar to liposomes in terms of physical properties but differ in chemical nature. Due to their higher chemical stability of surfactants than lipids these are unsurpassed when compared with liposomes. As niosomes are amphiphilic they can be utilized as a carrier for both lipophilic, and hydrophilic drugs. The application of niosomes is widely varied and can be used to treat several diseases like cancer, leishmaniasis, Parkinson, Psoriasis disease, etc. This review focuses on all aspects of niosomes including their historical development, structural components, types, formulation techniques, factors affecting their formation, controlling the size, separation of untrapped materials, characterization, therapeutic potentials, and stability.

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Introduction

Niosomes are microscopic, non-ionic surfactant vesicles that are either unilamellar or multilamellar. These are obtained by hydration of synthetic non-ionic surfactants with or without the addition of cholesterol. Niosomes are similar to that liposomes but the only difference is niosomes are formed by a bilayer made up of non-ionic surfactants whereas the bilayer of liposomes is made up of phospholipids. The size of the niosomes ranges from 10-1000nm. This contains both a hydrophobic tail and a hydrophilic head. So these are amphiphilic. The arrangement of surfactants in niosomes is in such a way that the hydrophilic heads are exposed towards the outside and the hydrophobic tails face each other thus forming a bilayer.

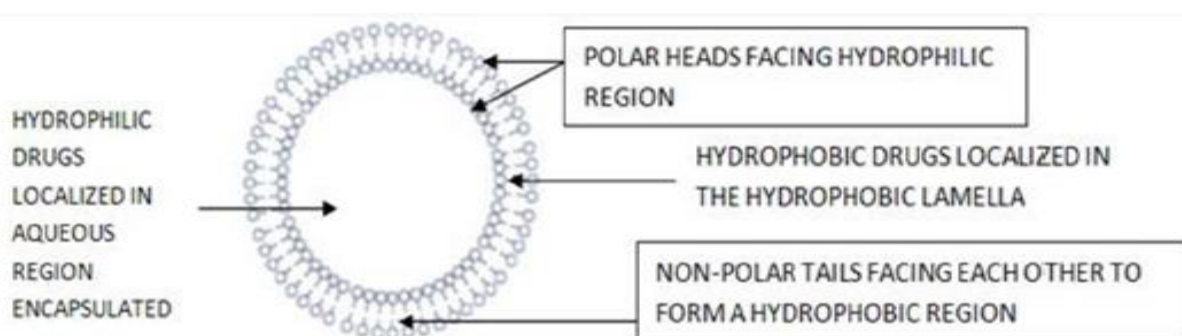


Fig 1: Basic Structure of Niosome

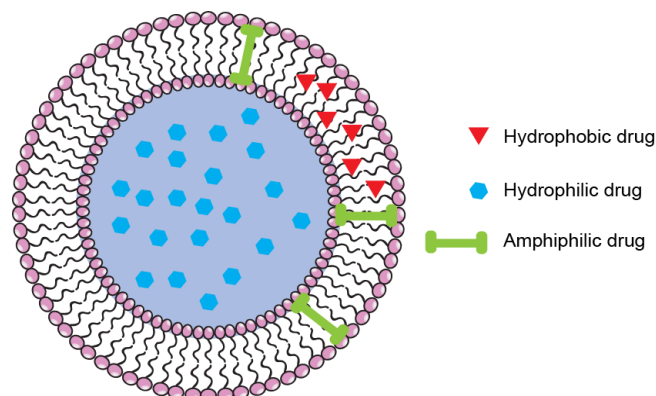


Fig 2: Drugs entrapped in Niosomal vesicles

Therefore, this system help in the entrapment of hydrophilic drug in the inner aqueous medium and the hydrophobic drugs are entrapped into the hydrophobic tails bilayer portion. The incorporated surfactants in this system are bio-degradable, bio-compatible, and non-immunogenic. Therefore, the bioavailability of a few drugs like – Diclofenac, Ciprofloxacin, Acetazolamide, Acyclovir, Metformin, Chlorpheniramine, etc. can be enhanced by this niosomal system of drug delivery system when compared to that of in other free states.

Niosomes as drug carriers

Niosomes are very promising carriers for the delivery of numerous pharmacological and diagnostic agents. Several publications have reported the preparation, characterization, and use of niosomes as drug carriers. Because of their nonionic nature, they offer excellent biocompatibility and low toxicity. The unique structure of niosomes allows the development of effective novel drug delivery systems with the ability to load both hydrophilic and lipophilic drugs. Hydrophilic drugs and lipophilic drugs are entrapped into the aqueous core and membrane bilayer of the Niosome respectively.

Classification of Niosomes

Based on the vesicle size niosomes are classified into three types. They are:

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

Small Unilamellar Vesicles (SUV): The size range of these vesicles is 10-100nm. These are the ones that are prepared from the multilamellar vesicles with the help of the sonication method, French Press Extrusion Electrostatic Stabilization in which the inclusion of diacetyl phosphate in 5(6)-carboxyfluorescein (CF) is loaded with span 60 is done.

Large Unilamellar Vesicles (LUV): The size ranges from 100-3000nm. The niosomes which come under this type have a high lipid or aqueous compartment ratio, therefore the large volumes of bioactive materials can be entrapped with the help of membrane lipids which are very economical.

Multilamellar Vesicles (MLV): The size range of these vesicles is greater than 5 μ m. The aqueous lipid compartment is surrounded by numerous bilayers separately. These are used most widely. Multilamellar vesicles are used as drug carriers for lipophilic compounds.

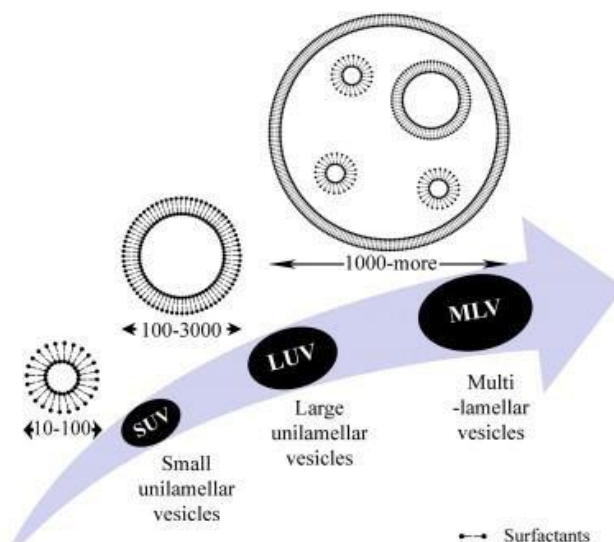


Fig 3: Types of Niosomal Vesicles

Advantages

- Niosomes are administered through various routes like oral, transdermal, intravenous and intramuscular, etc.
- The surfactants are bio-compatible, bio-degradable, non-immunogenic, and less toxic.
- The oral bioavailability of hydrophilic drugs can be enhanced and skin penetration of drugs can also be improved.
- Niosomes can be used in formulating sustained and controlled release drug delivery systems as it helps in releasing the medicament in a steady, organized manner.
- Incorporation of hydrophilic, lipophilic as well as amphiphilic drugs is possible.
- Handling and storage of these niosomes are easy.
- They are osmotically active and stable.
- They also improve the entrapped drug's stability.

Disadvantages

The main problems which arise in this system are

- The leakage of entrapped drugs.
- They cause aggregation and fusion of entrapped drugs. They may also cause hydrolysis of encapsulated drugs as they are aqueous suspensions.
- On the other hand extrusion, and sonication methods are time-consuming in the preparation of multilamellar vesicles.
- It is relatively expensive as it requires specialized equipment and processing.
- Less shelf life, and physical and chemical instability.

Applications

1. Anti-Cancer Treatment

- As we know that in the case of cancer, the cell undergoes proliferation.
- So, these niosomes decrease the rate of proliferation by increasing the drug plasma levels and causing slower elimination of drugs.
- The side effects of the drugs can be decreased as they alter the metabolism, and prolong the circulation and half-life of the drug.
- Examples of drugs that can be incorporated into niosomes are Adriamycin, Doxorubicin, Vincristine sulphate, Bleomycin, Cytarabine hydrochloride, Daunorubicin hydrochloride, etc.

2. Delivery of peptide drugs

- Peptides are the one that activates the various receptors in the body such as to lower high blood pressure, improve immunity function, kills microbes, etc. but when it is taken through the oral route undergoes enzymatic degradation.
- Therefore, to avoid that and maintain its stability we are formulating in the form of niosomes.
- Examples: 9-desglycinamide, vasoactive peptide.

2. Protection from degradation

- Few drugs before reaching their site of action may undergo various types of degradation such as hydrolysis, oxidation, and enzymatic degradation which result in loss of pharmacological activity.
- So, by incorporating the drug into niosomes, the drug can be protected from degradation reactions.

3. Target Site

- Niosomes are used to deliver the drug to specifically targeted organs.

- Examples: Tumours, cancer, etc.

4. Anti-Leishmaniasis Treatment

- Leishmaniasis is caused by the genus leishmania (parasite) affecting the liver and spleen cells. But the drugs which are used for this treatment have shown several side effects.
- So, to minimize the side effects we are approaching a niosomal drug delivery system.
- Examples: Antimony, sodium stibogluconate.

5. Others

Anti-Diabetic: Glicazide, Insulin.

Anti-Inflammatory: Flurbiprofen, Piroxicam, Diclofenac, Indomethacin, Nimesulide, Flurbiprofen + Piroxicam, Aceclofenac, Rofecoxib.

Antibiotic: Cefuroxime axetil, Cefpodoxime proxetil, Gatifloxacin+Rifampicin.

Anti-Bacterial: Erythromycin, Ciprofloxacin + Norfloxacin, Enoxacin, Ofloxacin.

Formulation Technique

Handshaking Method: (Thin film hydration method)

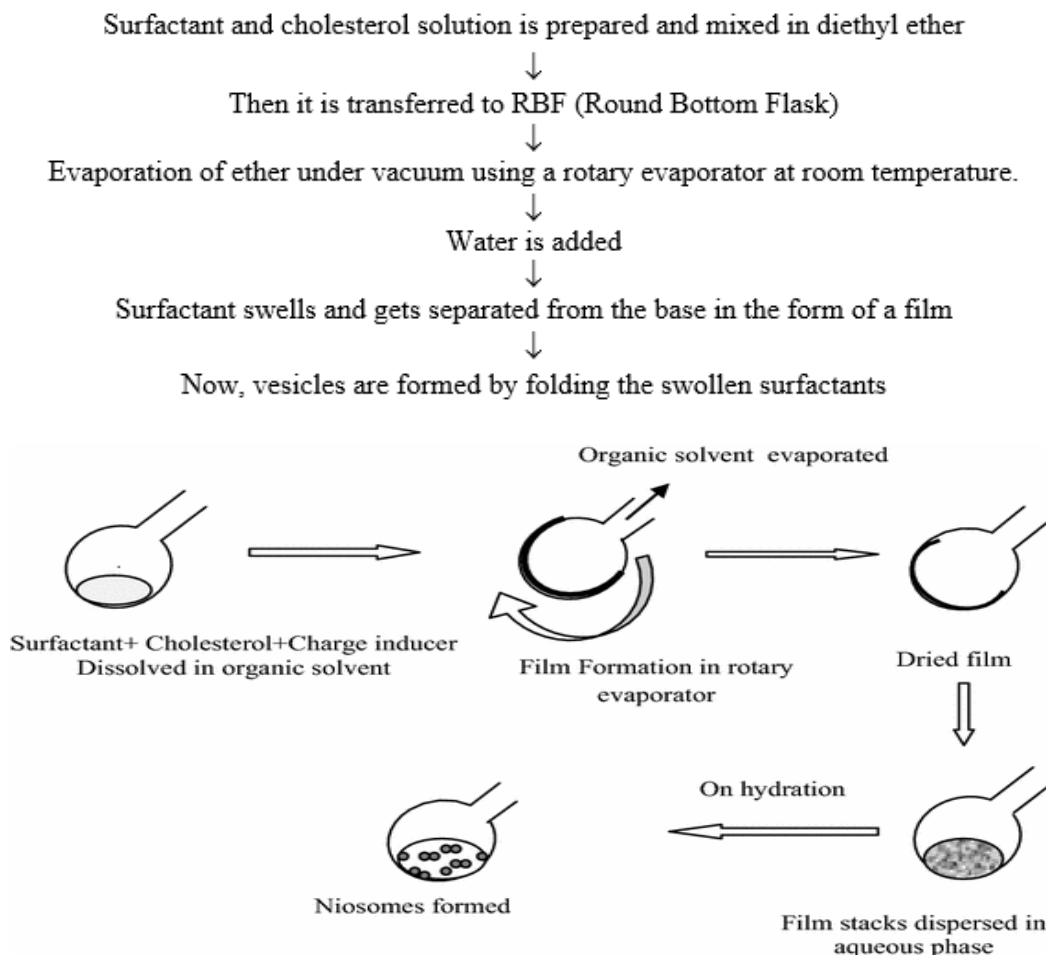


Fig 4: Hand-Shanking method

2. Sonication Method

The required amount of surfactant and cholesterol are taken individually and then mixed to form a uniform mixture.
 ↓
 The above mixture is dispersed in an aqueous phase in the vial
 ↓
 Probe sonication is done for 3min, at 60°C
 ↓
 Results in multilamellar vesicles formation
 ↓
 Upon subjection to ultrasonic vibrations, unilamellar vesicles are produced.

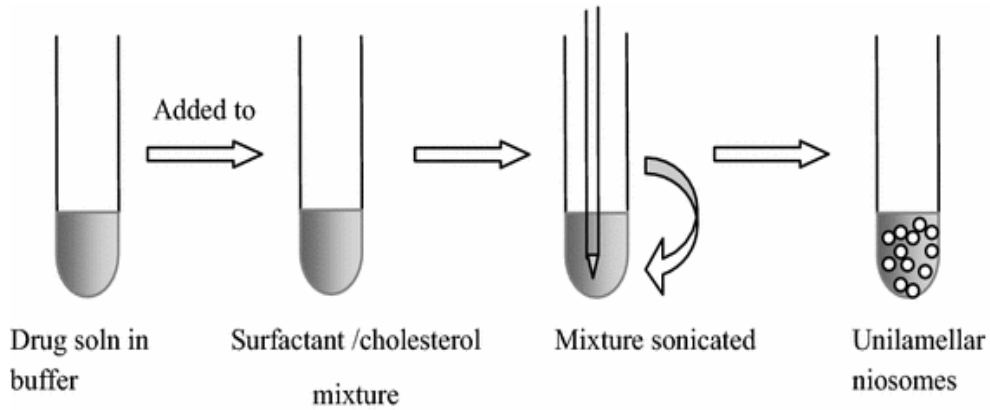


Fig 5: Sonication method

3. Ether injection method

The surfactant–cholesterol solution in ether is introduced into the aqueous medium which is maintained at 60°C with the help of an injection with a rate of 0.25/min, through a 14/16 gauge needle.

↓
 The solvent is vaporized (evaporated)
 ↓
 Leads to unilamellar vesicle formation.

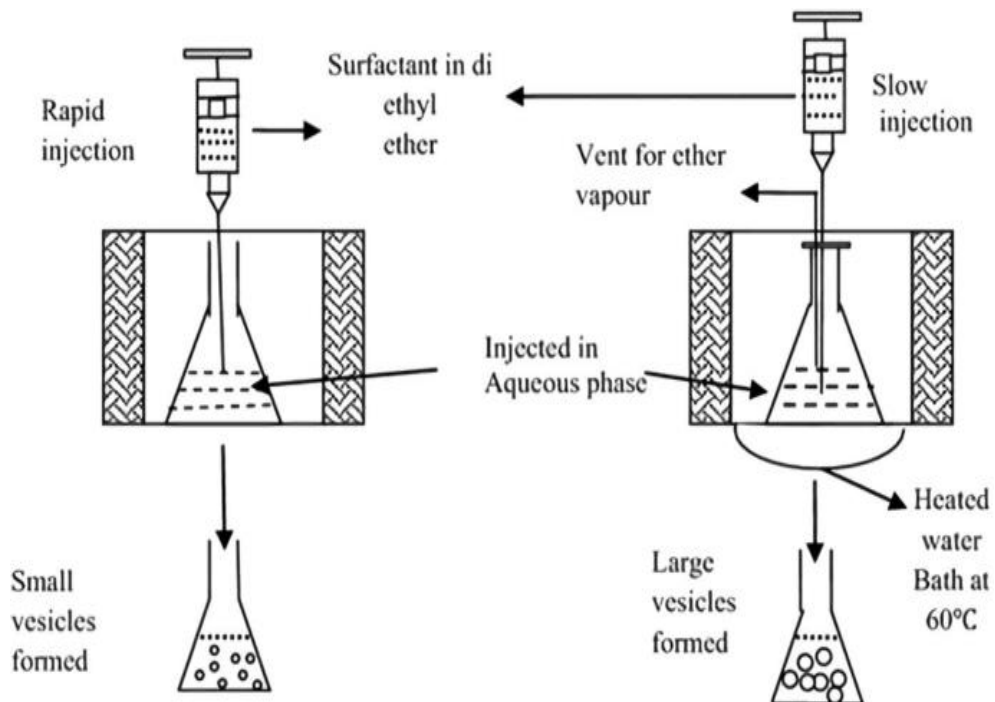


Fig 6: Ether injection method

4. Reverse Phase Evaporation

Firstly, W/O emulsion is prepared by dissolving surfactant in

chloroform and phosphate saline buffer

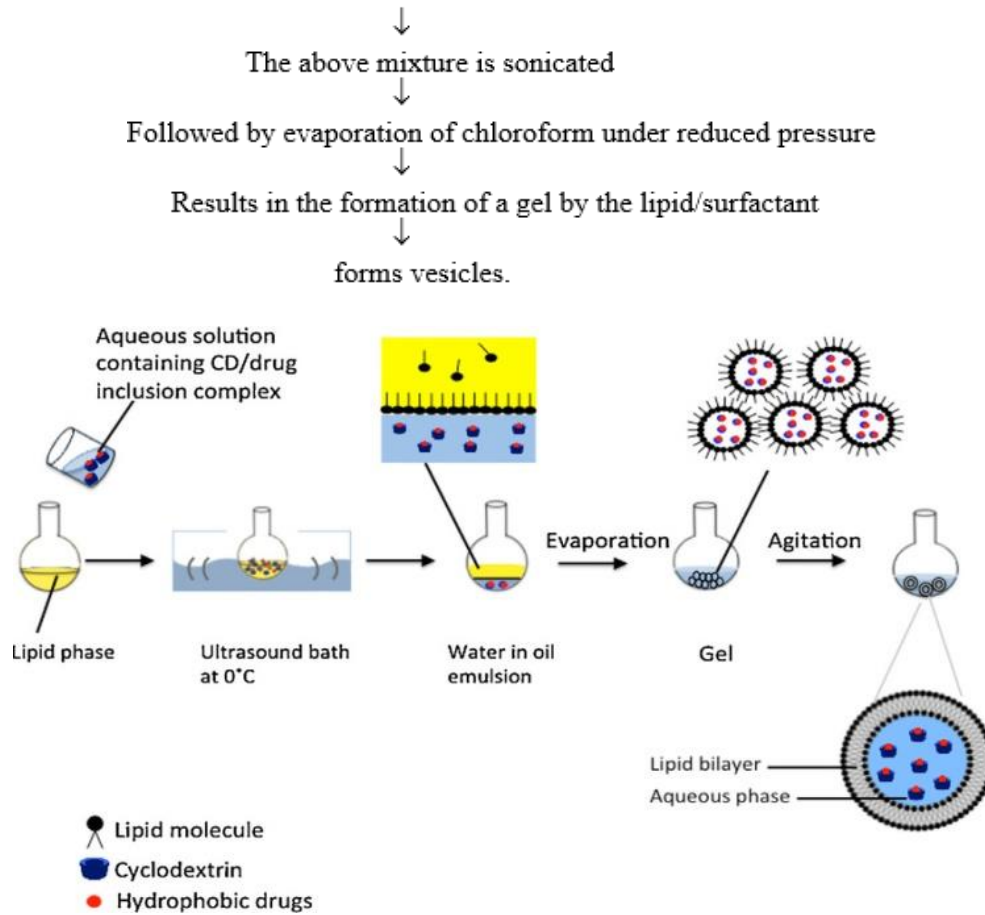
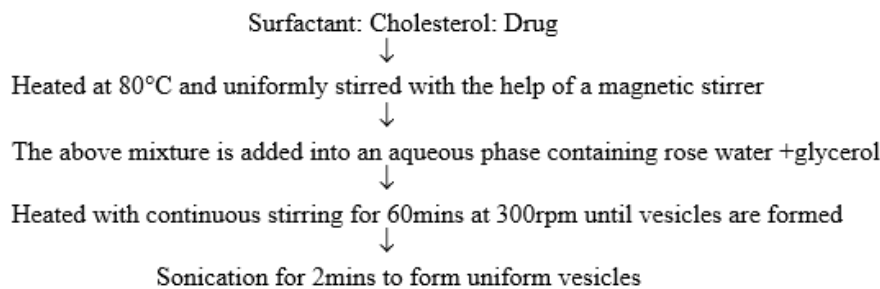


Fig 7: Reverse phase evaporation

Heating Method



Characterization

1. Size, shape, and morphology

- Freeze Fracture Electron Microscope is used to determine the structure of vesicles.
- Photon Correlation Spectroscopy is used to determine the vesicle mean diameter.
- The morphological studies of vesicles can be studied with the help of an electron microscope.

2. Zeta Potential

The surface zeta potential of niosomes can be determined using a zeta sizer and DLS instruments. The surface charge of niosome plays an important role in the behavior of niosomes. In general, charged niosomes are more stable against aggregation than uncharged vesicles. Bayindir and Yuksel prepared paclitaxel-loaded niosomes and investigated

the physicochemical properties such as the zeta potential of niosomes. They found that negative zeta potential values ranging between -41.7 and -58.4 mV are sufficiently high for the electrostatic stabilization of niosomes.

3. pH Measurement

pH is another parameter of niosomes to be evaluated. A digital pH meter is used to determine the pH of the niosomal formulations. One gram of the sample is dissolved in 100 ml of distilled water and stored for two hours. The pH of each formulation is measured three times and average values are calculated by using a pH meter.

4. Entrapment Efficiency: (Encapsulation Efficiency and Drug Loading)

We can determine the amount of drug entrapped in the

niosomal vesicles. This can be determined after separating the entrapped drug from the niosomal dispersion. This separation of untrapped drugs can be done by following the process of dialysis, centrifugation, gel filtration, etc.

- Calculation of niosomal recovery (%) can be done by using the following formula

$$\text{Niosomal Recovery (\%)} = \frac{\text{Amount of niosomes recovered}}{\text{Amount of polymer} + \text{Drug} + \text{Excipient}} \times 100$$

The amount of entrapped drug is determined by disrupting the vesicles completely by using 0.1 % triton X-100 or 10% n-propanol.

Then by using a suitable assay method the resultant solution is analyzed.

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount of drug in niosomes}}{\text{Amount of drugs used}} \times 100$$

Drug loading percentage can be calculated by

$$\text{Drug loading (\%)} = \frac{\text{Amount of drug in niosomes}}{\text{Amount of drug recovered}} \times 100$$

5. In-vitro Drug Release

Dialysis, Reverse dialysis, and Franz Diffusion Cell are the methods by which we can study the in-vitro drug release.

A) Dialysis

- It is the most widely used and simplest method for the determination of in-vitro release kinetics of the niosomal loaded drug.
- In this method, dialysis tubing is used.
- Firstly, the dialysis sac is washed and soaked in distilled water. Then the suspension of niosomal vesicles is placed in a dialysis sac and sealed. The process of dialysis is carried out by placing the sac in the buffer solution of 200 ml. Then it is constantly stirred at 25°C or 37°C. At regular time intervals, samples are withdrawn and analyzed for drug release by using UV / Visible Spectrophotometer.

B) Reverse dialysis

Several small dialysis tubes are taken, into which 1ml of dissolution medium and niosomes are added. The displacement of the niosomes takes place from the dissolution medium.

C) Franz Diffusion

In this method, a Franz diffusion cell is used in which the niosomes are dialyzed against a suitable dissolution medium at room temperature, with the help of a cellophane membrane. At regular time intervals, samples are withdrawn and analyzed for the determination of drug content.

5. Stability of niosomes:

The stability of niosomes is primarily determined by constant particle size and constant concentration of the entrapped drug. It also depends upon the concentration and type of surfactant, and cholesterol used.

Table 1: Niosomes Marketed drugs

S. No.	Applications	components	Method used	Drug used
1	As a drug delivery carrier	α, ω -Hexadecyl- β -D-glucopyranoside (1- α -D-glucopyranosyl)- β -D-glucopyranoside, span 80, cholesterol.	Thin layer evaporation technique.	5-Fluorouracil(5-FU)
2	To increase Bioavailability	Cholesterol, sorbitan monostearate (span 60), Dicyclic Phosphate (DCP), span20, span 40, span 60, cholesterol, DCP.	Film Hydration method	Acyclovir
3	In leishmaniasis	Span 40, cholesterol, DCP.	Solvent evaporation method.	14-deoxy-11-oxoandograpfolide.
4	To prolong the release time.	Sorbitan esters.	Reverse phase method.	Rifampicin.
5	For drug targeting.	Palmitic acid, N-Hydroxy succinimide, Glucosamine, Sorbitan monostearate (span 60), Cholesterol, Glycol chitosan, Sorbitan monostearate.	Sonication method.	Transferrin.
6	For stability improvement.	Span 60, cholesterol.	Reverse phase evaporation method.	Methotrexate.
7	To increase entrapment efficiency.	Span 60, cholesterol, DCP.	Ether injection method.	Fluconazole.
8	To reduce toxicity.	Span 20, Span 40, Span 60, cholesterol.	Thin film hydration method.	Ketoprofen., Cefpodoxime Proxetil.
9	For enhancement of Therapeutic Index.	Span and Tween (20 and/or 60), cholesterol.	Reverse phase evaporation method.	α -lipolytic acid.
10	For lung targeting.	Span 85, cholesterol.	Hand shanking method	Rifampicin.
11	For liver targeting.	Span 60, cholesterol, DCP.	Thin film Hydration Method.	Ribavirin.
12	In Diagnostic imaging.	N-Palmitoyl-glucosamine (NPG), polyethylene glycol (PEG)-4400.	Ether injection method.	Gadobenate.
13	In thromboembolic disease.	Hexadecyl poly(3) glycol, DCP, cholesterol.	Film method.	Urokinase.
14	In oral delivery of peptide drug.	Brij52, Brij 72, Brij 92, Brij 76, Brij 97, Brij 58, Brij 35, DCP, cholesterol.	Film hydration method.	Insulin.
15	To increase immune	Dimethyl di octa decyl is m onium (DDA) and \square, \square' -	Dehydration-	Ag85B-ESHT-6

	response and immunological selectivity.	trehalose 6,6'-dibehenate (TDB) 1- mono palmitoyl glycerol (MP), cholesterol.	rehydration method.	MSP1 or GLURP.
16	In anticancer therapy.	C16 monoalkyl glycerol ether, span60, cholesterol, DCP, span 20, span 60, span 40, tween 20, tween 60, Brij 76, Brij 78, Brij72, span 40, cholesterol.	Sonication method.	Doxorubicin.
			Lipid layer hydration method.	Bleomycin.
			Thin layer hydration method.	Paclitaxel.
17	For anti-inflammatory effect.	Cholesterol(CH), Di cetyl phosphate (DCP), and surfactants (Tween 85, Pluronic F 108).	Reverse phase evaporation method.	Diclofenac sodium.
18	In Transdermal drug delivery system.	α,ω -Hexadecyl-bis(1-aza) 18-crown-6 (bola), span 80, cholesterol, Brij 96, cholesterol.	Film hydration method.	Ammonium Glycyrrhizinate.
19	In the ophthalmic drug delivery system	Poly-oxyethylene 20, sorbitan monostearate (Tween 60), ploy-oxyethylene 20, sorbitan monostearate (Tween 80), polyoxyethylene 23, lauryl-ether, cholesterol, DCP, chitosan, Carbopol.	Sonication method.	Estradiol.
20	In localized psoriasis.	Chitosan, phosphotidyl choline, span 60, cremophor RH40, cholesterol, Butylated hydroxy toluene.	Lipid layer hydration method.	Methotrexate.

Conclusion

Niosomes are one of the most promising Novel Drug Delivery Systems. Niosomes are popularly known for their drug targeting of specific organs or tissue. When compared to other drug delivery systems such as liposomes, these have advantages in case of cost, and stability and are osmotically active and non-immunogenic. Another interesting fact is that they do not require any special conditions for handling, manufacturing, and storing. Niosomes also serve as better vaccine-delivering agents, diagnostic agents, and tumor-targeting agents. Also helps to deliver toxic drugs safely which are needed at high concentrations or doses. Niosomes all over improve drug bioavailability, and stability, reduce side effects or harmful effects of the drug, protects the drug from enzyme metabolism and enhance permeation of drugs through biological barriers, and finally can provide sustained or controlled drug delivery system by using appropriate excipients. The relevant studies demonstrated that niosomes improve the stability of the entrapped drug, reduce the dose, and enable targeted delivery to a specific type of tissue.

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