

## NIOSOMES: A thorough evaluation of advancement in targeted medication delivery system

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### ABSTRACT

The sciences of nanomedicine and related subfields, including pharmaceutical nanocarriers, have emerged as new divisions of medical research due to the rapid and substantial advancements in the use of nanotechnology in the treatment and detection of illnesses. Polymers, metals, metal oxides, nano gel, lipid-based carriers (liposomes), and surfactant-based carriers (niosomes) are just a few materials that may be used to create nanostructures. Drug carriers can be made smaller to the nanoscale, which has many advantages including (1) better pharmacokinetics and biodistribution of therapeutic agents, (2) lessened toxicity due to drug accumulation in the target site, (3) Easier drug transport between cells, and (4) longer retention times in biological systems that boost drug effectiveness. The development of new medicine delivery technologies is important. With the use of this technology, medication absorption, distribution, and excretion may all be improved. Two criteria need to be taken into account while developing a novel medication delivery system: The medicine should first be released at a predetermined rate. When compared to dosages of conventional forms, it should release an effective quantity of the active component at the target location. Due to its chemical stability, biodegradability, biocompatibility, cheap production costs, minimal toxicity, and ease of handling and storage, niosomes are chosen over alternative bilayer structures. Different delivery techniques, including oral, intramuscular, intravenous, transdermal, and others, have been used to study niosomes. These vesicles also speed up the pace at which some medications are taken up by cell membranes. The evolution of drug-

delivery methods over the past ten years has made producing niosomes an effective technique for drug delivery. This review focuses on the highly effective drug delivery system which shows the rapid growth in the pharmaceutical sectors in the past decade and helps to achieve the therapeutic response in the patient with severity and critical care with improved bioavailability and effectiveness.

**Keywords:** Liposomes, Targeted Delivery, Drug Carrier, Targeting Moieties, Microfluidisation

### I. INTRODUCTION

There is currently no medication delivery method that combines controlled drug release kinetics with site-specific delivery. When Paul Ehrlich envisioned a medicine delivery system that would target specifically damaged cells, he launched the period of development for targeted delivery in 1909. Since then, a variety of carriers have been used to deliver drugs to the target organ or tissue, including immunoglobulins, serum proteins, artificial polymers, liposomes, microspheres, erythrocytes, and niosomes, among others. Niosomes are bilayer vesicles with an external lipophilic core and an interior hydrophilic core, comparable to liposomes [Figure 1]. They can be utilized for precise, prolonged, and regulated medication administration [1-2]. Despite being employed for vesicular medication administration, liposomes have a number of serious flaws that make them impractical for everyday use. Some drawbacks include in-vivo toxicity, complex surfactant derivatization, low pH stability, and expensive manufacturing costs. Due to these drawbacks, research has switched to niosomes, which provide much greater control over the

aforementioned problems [3]. Nonionic surfactants, sterol and its derivatives, and/or charged molecules make up niosomes. Niosomes are made by adding cholesterol as a lipid, and it also gives the bilayer membrane stiffness. The addition of charged molecules stabilizes the polar charges and maintains the stability of the niosomes. In contrast to traditional liposomes, niosomes use nonionic surfactants. [4]. Non-ionic surfactants that are not

ionic like spans and tweens give the vesicles amphiphilicity while also giving them neutrality, which increases their stability and potential for drug administration [5]. The highly lipophilic and polar cores of niosomes can be used to entrap pharmaceuticals more readily than liposomes due to better control over charge distribution characteristics.

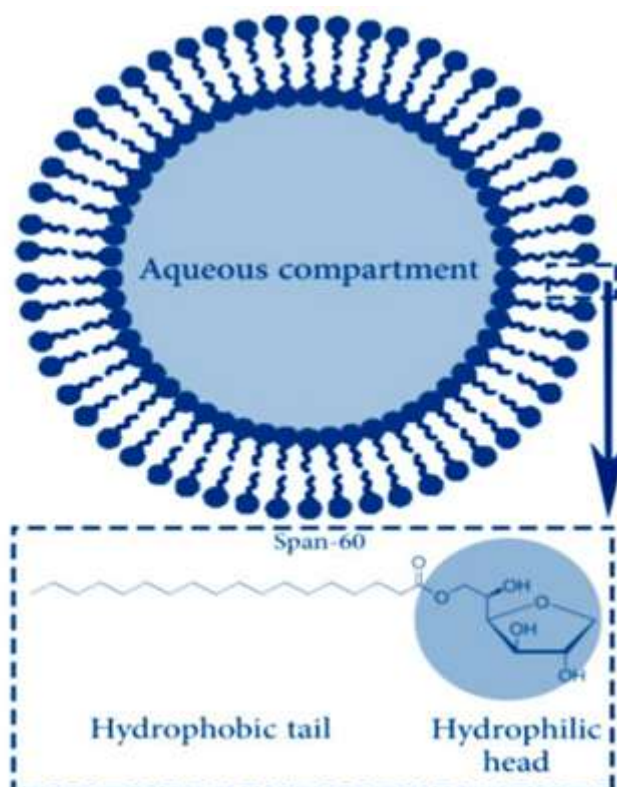


FIG:1 Representation of Niosomes (cross-sectional view)

## II. TYPES OF LIPOSOMES

These three categories of niosomes exist:

**1) Small Unilamellar Vesicles (SUVs):** French press and sonication techniques are used to create Small Unilamellar Vesicles (SUVs). The procedures for preparing them include solvent dilution and ultrasonic electrocapillary emulsification. These vesicles are around 0.025–0.05  $\mu\text{m}$  in size. [6]

**2) Multi-Lamellar Vesicles (MLVs):** These are composed of many bilayers that surround the aqueous lipid compartment individually. They display equilibrium solute distribution and

increased-trapped volume. Their lipid profiles are different. By shaking hands, they are made ready. These vesicles range in size from 0.5 to 10 microns.

**3) Large Unilamellar Vesicles (LUVs):** Lipids that have been solubilized in an organic solvent are injected into an aqueous buffer to create Large Unilamellar Vesicles (LUVs). However, the most common procedures for preparing them are the reverse process of evaporation or detergent solubilization. These vesicles' dimensions are about 0.10  $\mu\text{m}$ . [6-7]

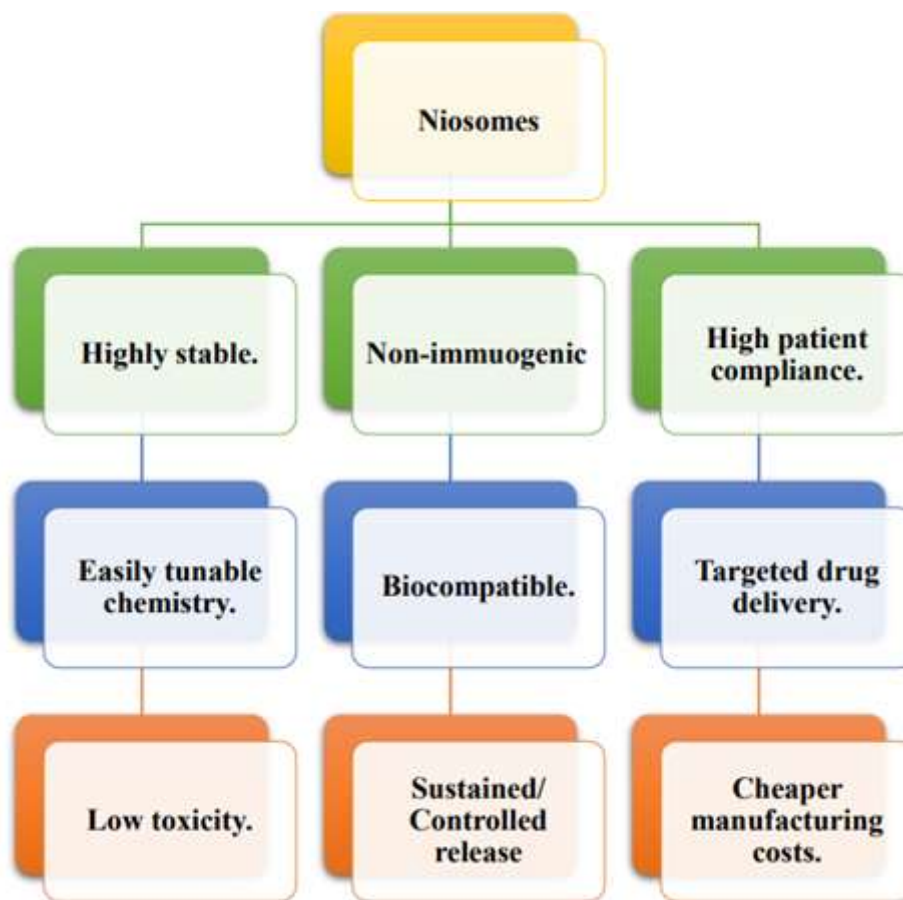


FIG:2 Advantages of Niosomes in (targeted drug delivery system)

### III. NIOSOME COMPOSITIONAL ASPECTS

The factors that influence how niosomal vesicles develop are included in the elements of niosomes' formulation. Excipients such as non-ionic surfactants, polar lipids, and charge inducers are included in niosomes in various amounts. Critical packing parameters (CPP), Transition temperature ( $T_c$ ), and Hydrophilic-lipophilic balance (HLB) are other crucial factors in niosomal vesicle production. [8] Surfactants often have two separate hydrophilic and hydrophobic areas that are amphiphiles. Alkanes, fluorocarbons, aromatic, and other non-polar groups are made up of the lipophilic area in the form of chains. The hydrophilic functions (highly solvated) found in the head group include phosphonates, ammonium, sulfonates, carboxylates, and derivatives. The hydrophilic functionality head group of surfactants, which is made up of quaternary ammonium salts, sulfonate, zwitterionic butanes, and fatty acids, may be used to categorize them as cationic,

anionic, amphoteric, or non-ionic. The polar head group is used to categorize surfactants; however, a surfactant that is not ionic has no charged groups in its head. Ionic surfactant heads are known as anionic surfactants because they have a net charge. fatty acid (soap) salts, phosphate esters, sulfates, and ether sulfates, as examples. Similar to this, cationic surfactants are defined as having a net charge that is favorable for the head group. It is referred to be an amphoteric (zwitterionic) surfactant if the head group is comprised of two oppositely charged moieties. Since cationic surfactants are generally seen to be irritating and occasionally even harmful, their usage is restricted in comparison to other surfactant types. [9]

Non-ionized surfactants are the kind of surfactants whose head groups don't carry any charge. These surfactants create structures with hydrophilic heads opposing water-based solutions and tails that are hydrophobic opposite to organic solutions when they are distributed in liquids. Thus,

niosomes are easily generated by the non-ionic surfactants self-assembling in aqueous dispersions. Four kinds of non-ionic amphiphiles are distinguished for niosome use: Fatty acid esters, alkyl esters, amides, and ethers.[10]

#### IV. PREPARATION METHODS

Niosomes are self-assembling nanocarriers made in a variety of ways. They are coated with a variety of different chemicals, such as PEG, HA, charged inducers, stabilizers, etc. for targeting reasons to achieve particular targeting, longer durations of circulation, and prolonged releasing impact. The following list of niosome preparation techniques includes:

##### 1. Thin- Film hydration method (TFH)

A straightforward process called "thin film hydration" involves creating a thin film of niosomal

components, namely lipid and non-ionic surfactant, then hydrating it with an aqueous solution that contains a medication. [11] This approach involves dissolving a lipid, often cholesterol, and a non-ionic surfactant in a chemical solvent before transferring the mixture to a flask with a flat bottom [Figure 3]. After being subjected to the evaporation of the solvent in a rotary vacuum evaporator, a thin film is created, which is subsequently hydrated with a buffer or water at a temperature of 50–60 °C to dissolve the film in the aqueous solution. In this stage, multilamellar vesicles are often generated, which are then transformed into unilamellar shapes either by high-speed homogenization or probing sonication under ice cold temperatures to homogenise the niosomes fully. Drugs including minoxidil, nimesulide, glucocorticoids, methotrexate, etc. have been captured using TFH.

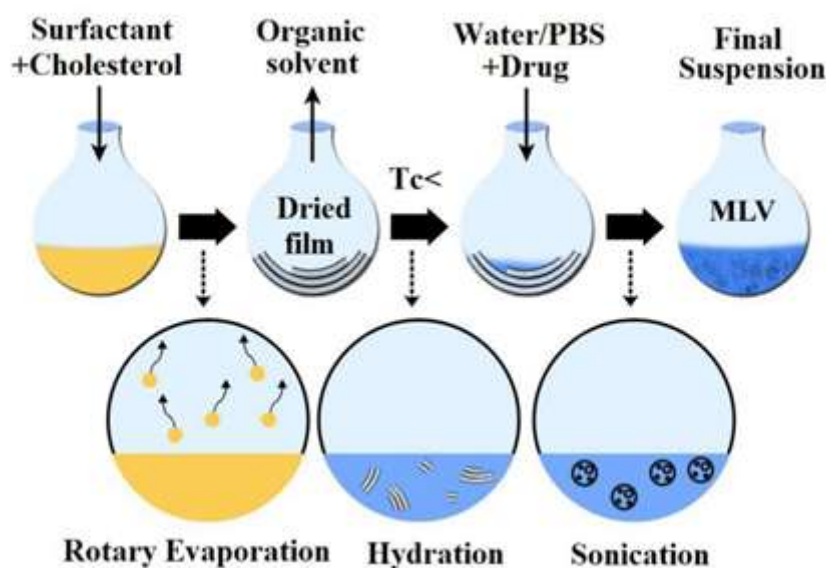


FIG:3 An illustration of the thin-film hydration process for making niosomes.

##### 2. Solvent Injection Method (SIM)

In SIM, a syringe is used to slowly inject both surfactants and lipids into the drug-containing aqueous phase after they have been dissolved in an organic solvent such as methanol, ethanol, acetone, diethyl ether, or acetone. [Figure 4] [13].

While mixing the phases, the assembly is kept at 60 °C. After that, the organic solvent is vaporized at 60°C using a rotary evaporator or magnetic stirring. This approach results in the formation of single-layered vesicles, and it has a greater drug entrapment efficiency than the others.

This method of making niosomes enables the development of dual drug-loaded niosomes by allowing the entrapment of a lipophilic substance into the outer layer. While creating niosomes, a specific amount of the lipophilic medication may be added to the organic phase that already contains cholesterol and a non-ionic surfactant. In comparison to previous approaches, these niosomes exhibit greater stability. Their particle sizes might be anywhere between 50 and 1000 nm depending on the circumstances. Doxorubicin, methotrexate,



and salt have all been drug-entrapped using SIM. [14]

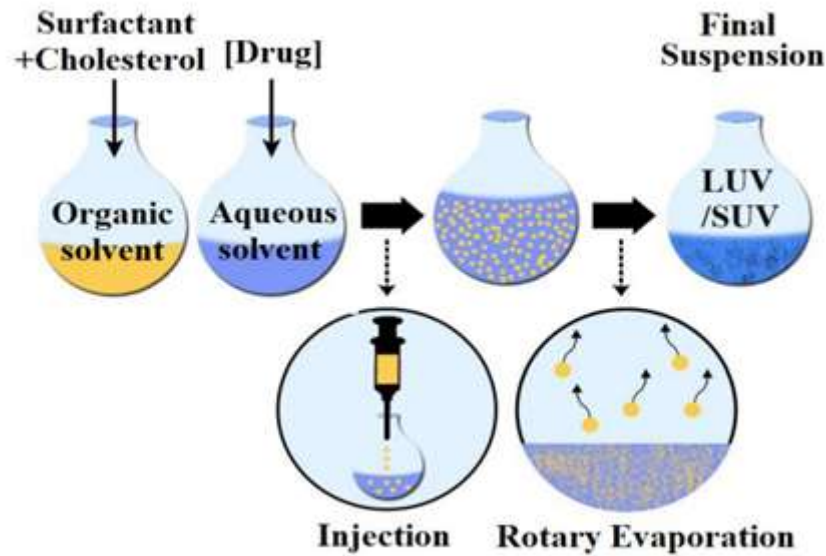


FIG:4 A schematic representation of the solvent injection technique for making niosomes.

### 3. Reverse Phase Evaporation Method (REV)

In REV, the drug-containing aqueous medium is introduced to the organic phase after the niosomal parts—surfactants and additives—have been dispersed into an organic solvent [Figure 5]. [15]. Sonication is used to turn the mixture into an emulsion, and then the solvent is gently evaporated

at 40–60°C in a rotating vacuum evaporator to finish the hydration process. The formation of LUVs occurs during this evaporation. This approach has been used to create niosomes that contain acetazolamide, naltrexone, and anti-HBsAg (HBsAg) [16].

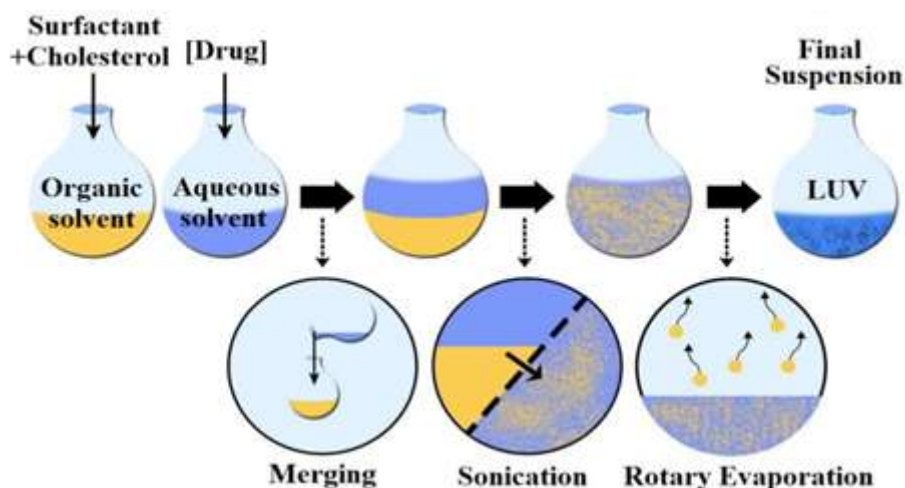


FIG:5 An illustration of the reverse phase evaporation process for making niosomes

#### 4. Heating Method (HM)

Surfactants and cholesterol from niosomal components were hydrated separately in PBS for an hour at room temperature under an environment of N<sub>2</sub> in HM [Figure 6]. [17]. The mixture is then heated to 120°C on an electromagnetic stirrer to dissolve cholesterol after 15 to 20 minutes. The temperature is then dropped to 60°C, other ingredients are added, and the buffer is then added

to the aforementioned combination. Stirring is then continued for an additional 15 minutes. The niosomes produced are stored in R.T. for 30 min., followed by a period of time at 4-5°C and N<sub>2</sub> atmosphere for further study. By using this technique, niosomes containing -tocopherol, Vitamin D<sub>3</sub>, and certain anthocyanins have been created [18].

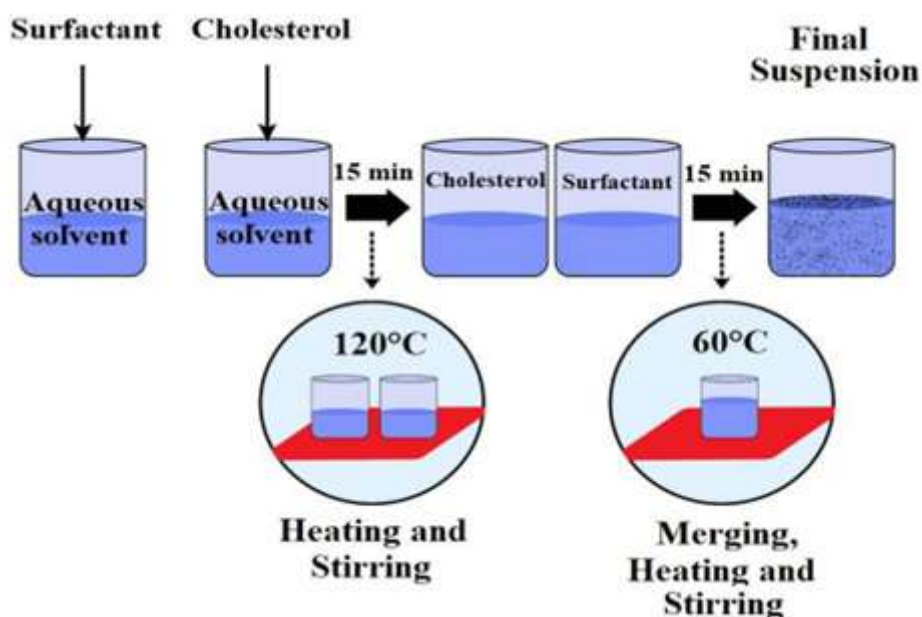


FIG:5 An illustration of the Heating Method process for making niosomes

#### V. COMPONENTS OF NIOSOMES

The numerous parts that makeup niosomes are as follows:

##### Surfactants without ions

- Non-ionic surfactants are found in niosomes' bilayer frameworks, where hydrophobic heads (hydrocarbon segments) are found in patterns that have fewer opportunities to interface with water and hydrophilic heads in patterns that face bulky media. Vesicles arise as a result of the bilayers of the membrane folding continually to achieve thermodynamic stability. [20]

The four main forms of non-ionic surfactants employed in the production of niosomes are as follows:

- ❖ **Alkyl Ether:** In the creation of niosomes, certain particular surfactants are utilized that comprising of pharmaceuticals or other

compounds, were characterised as follows by L'Oreal:

- ❖ Surfactant I is a C16 monoalkylglycerolether with a molecular weight of 473 g/mol and a mean value of three glycerol units.
- ❖ Surfactant II is a diglycerol ether with a molecular weight of 972 g/mol and a mean of seven glycerol units.
- ❖ Surfactant III is an ester compound-linked surfactant with a molecular weight of 393 g/mol.

Alkyl glycerol and alkyl ethers with head groups are also used in place of alkyl glycosides in the manufacture of niosomes. [24-26]

- ❖ **Alkyl Ester:** By using certain instances, such as the utilization of polyoxyethylene (polysorbate 60) for the encapsulation of sodium diclofenac, we may investigate this further.[27] Polyoxyethylene10-stearyl ether: glyceryl laurate: cholesterol (27:15: 57) has

been used for the transdermal administration of Cyclosporine-A. [28-29]

- ❖ **Fatty Acid and Ester** :The constituents of amino acid and various lengthy fatty acid chains are utilised in the construction of some specialised niosomes.
- ❖ **Cholesterol**: Steroid presence primarily impacts the cell membrane's multilayer permeability and bilayer fluidity. The Cholesterol, a steroid derivative, was employed in the creation of niosomes.As a result, it does not participate in the creation of the bilayer, but it does affect how the bilayers behave and is crucial for the development of niosomes. The features of niosomes, include their toxicity, stiffness of membrane, effectiveness of encapsulation, and freezing point The inclusion of cholesterol into the niosomes might have an impact on dried niosomes because of the straightforward rehydration process and susceptibility of the niosome membrane. Due to the cholesterol molecules' stability against the formation of aggregates with the aid of electrostatic forces, which results in the transformation of the gel into the liquid phase, the addition of specific cholesterol molecules to the niosome system inhibits the aggregation of the vesicles. This result reduces the likelihood that the medication will escape from the niosomes. [30-31]

#### Charged Molecule

Because some particular charged molecules were included into the niosomes to prevent the conjoining of the niosome particles, the long-term viability of the niosomes will be improved with the help of electrostatic repulsion. Negatively charged molecules were utilised, such as phosphatidic acid and diethyl phosphate. While positively charged compounds like stearyl pyridinium chloride and stearyl amine were used. The use of these charged molecules can help avoid the aggregation during the niosome preparation. [33] Due to the substantial amount of inhibition, there is a restriction on the percentage concentration of charged molecules utilised in the formation of the niosomes; thus, only 2.5 to 5-mole proportion concentration of particles with charge were used. [34-35].

## VI. FACTORS AFFECTING THE FORMATION OF NIOSOMES

The manufacture of niosomes and the accomplishment of their intended structure are based on sufficient knowledge and a detailed understanding of the biophysical characteristics of their components. Several factors are engaged in the formation of niosomes. These parameters can depend on the technique of preparation, route of therapy, and material consumption.

### • Types of Surfactants

Surfactants are niosomes' primary building blocks. These substances have a distinctive chemical structure that gives them two different characteristics. Since surfactants have two sections with distinct solubilities—a lipophilic tail and a portion of the hydrophilic head—they are called surfactants. Cationic, anionic, and amphoteric molecules that are readily dissolved in water make up the head group. Alkanes, fluorocarbons, fragrant, or other groups that are nonpolar may make up the lipophilic area. Cationic, anionic, amorphous, and nonionic surfactants are categorized according to the properties of the head group region. Given their stability, reliability, and low toxicity in comparison to other surface-active chemicals, nonionic surfactants are the most often used ones in the creation of niosomes. [19]

## VII. ADVANTAGES OF NIOSOMES

- The normal vesicles speed up the pace at which the medication is administered in the exterior, non-aqueous phase.
- The stability of the drug molecules that were entrapped was improved, and the niosomes are functional and osmotically stable.
- The niosomes can be administered by a variety of methods, including parenteral, topical, and oral, to speed up their delivery to the site of action.
- Surfactants can be handled and stored without the need for any particular conditions.
- Niosomes can be used to enhance the oral bioavailability of medications that are poorly soluble as well as the skin penetration of pharmaceuticals.
- The niosomal dissemination in an aqueous state can be homogenized to control the drug administration in a non-aqueous phase.
- By utilizing niosomes, the rate of bioavailability can be increased. The niosomes in the gastrointestinal tract retain the

medication and guard it against acidic and enzymatic vesicle breakdown, increasing the medication's bioavailability.

- The niosomes enhance the drug particles' ability to heal by delaying flexibility from dispersion and shielding the chemical from the environment, which has an impact on the targeted cells. [20-22]

### VIII. CONCLUSION

The niosomes drug delivery system is a successful strategy in this field when we talk about innovative drug delivery systems. To create niosomes, several kinds of non-ionic surfactants and cholesterol are often combined with a medication. Niosomes are produced using a variety of techniques, including reverse phase evaporation, handshaking, ether injection, and others. From this review article, we can infer that niosomes are a crucial drug delivery technique that is used to include or target drugs for a variety of therapeutic actions and offer a number of benefits over other drug delivery technologies. The niosomes will show to be a wonderful payoff for the foreseeable future.

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### Conflict of Interest

No Conflicts of interest were raised by any of the authors in reference to the publication/investigation.

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