

# Recent Advances and Scopes In Niosomes

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## Abstract

Nanotechnology has recently become a significant force in contemporary medicine, with therapeutic uses ranging from contrast agents for imaging to medication transporters. It has been difficult in creating payloads that are both safe and effectively delivered. Modern approaches that focus on the drug delivery system, such as Niosomes, can accomplish this. Scientists working on drug delivery systems have become more interested in the formation of non-ionic surfactant vesicles as a technique to enhance drug delivery over the past few decades. The development of Niosomes involves hydration of synthetic surfactants with the right proportions of cholesterol or other amphiphilic compounds to form self-assembled vesicular Nanocarriers. Niosomes also offer an easy manufacturing process, with low production costs, and have increased stability, thus eliminating the fundamental drawbacks of liposomes. Simple preparation techniques and commonly used surfactants in pharmaceutical technology can be employed to prepare Niosomes. This review covers composition, preparation, characterization/evaluation, benefits, limitations, applications, and recent developments of Niosomes.

**Keywords:** Niosomes, Nanocarrier, Non-ionic surfactant, Composition, Targeted drug delivery, Advancements.

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## INTRODUCTION

The ability to construct materials, devices, and systems with atomic accuracy is known as nanotechnology. The United States National Science and Technology Council's statement, which reads in part, "The essence of nanotechnology is the ability to work at the molecular level, atom by atom, to create large structures with fundamentally new molecular organization," a concise and general definition of nanotechnology. Gaining control over atomic, molecular, and supramolecular structures and devices as well as how to produce and use them effectively will allow one to take advantage of their properties. "Paul Ehrlich in 1909, initiated the age of development for target drug delivery, when he projected the drug delivery mechanism that would target directly to diseased cells, in the same year he advocated the tactic known as "magic bullet".<sup>1</sup> The first non-ionic surfactant product was developed and marketed by the Loreal firm<sup>2</sup> and used for cosmetic purposes. Researchers studying drug delivery systems have become interested in the design of vesicles over the past ten years as a means of enhancing drug delivery. Liposomes, niosomes, transferosomes, pharmacosomes, ethosomes, immunoglobulin, serum proteins, microspheres, synthetic polymer, etc. are a few examples of vesicular systems that can be used to facilitate and improve medication administration. The highly effective medication delivery method Niosomes are one of these many carriers. The desired or targeted site is directly affected by the targeted drug delivery mechanism. The capacity of a therapeutic

substance to act directly on the chosen site with little to no interaction with other non-targeting locations is known as targeted medication delivery. The hydrophilic drug is confined in the inner cavity of Niosomes, which are a unique drug delivery method, whereas the hydrophobic drug is present in the bilayer of Niosomes in the non-polar region. As a result, medicines that are both hydrophilic and hydrophobic were integrated into Niosomes.<sup>3</sup> Hydrophilic medications can bind to the bilayer surface or the central aqueous domain of Niosomes for entrapment, whereas hydrophobic drugs partition within the bilayer structure. Amphiphiles like Spans and/or Tweens<sup>4</sup> and/or ethoxylated alcohols and/or sucrose esters are used in the production of Niosomes. These amphiphiles are stabilized by adding cholesterol and trace amounts of ionic substances like diacetyl phosphate or chitosan. The medication in this system is contained in a vesicle. Bilayer non-ionic surface-active substances like span 605 make up the vesicles, which can be stabilised by adding cholesterol and a little amount of an anionic surfactant like diacetyl phosphate.<sup>6</sup> Because surfactants are added to niosomes, drugs like Flurbiprofen, Bleomycin, and others are more efficacious and have a higher bioavailability than free drugs<sup>6</sup>. Drug molecules having a wide variety of solubilities can be accommodated by the structure's hydrophilic, amphiphilic, and lipophilic moieties. They might serve as a depot, delivering the medication gradually. By delaying clearance from the circulation, shielding the drug from its biological environment, and limiting its effects to target cells, drug

molecules can also work therapeutically better.<sup>5</sup> Because surfactant was incorporated and stabilized the Niosome structure, these types of Niosomes are biodegradable, immunogenic, and biocompatible in nature. The structure is made hard by the cholesterol, and the preparation is kept stable by the charged cholesterol molecule.<sup>5</sup>

#### Structure and Composition of Niosomes-

The basic components of Niosomes includes – non ionic surfactant, cholesterol hydration medium and charge inducer molecules.

1) Non-ionic surfactant:- Amphiphilic molecules with a polar head and a non-polar tail make up non-ionic surface active molecules.<sup>7</sup> Surfactants are more stable, compatible, and less hazardous than anionic, cationic, and amphoteric surfactants since they don't carry any charge. These surface-active substances lessen cellular surface irritation and hemolysis. Non-ionic surfactants have the important property of inhibiting p-glycoprotein, which can improve the absorption and targeting of anticancer medications (for example, Doxorubicin, Daunorubicin, Curcumin, and Morusin), Steroids (for instance, hydrocortisone), HIV protease inhibitors (for instance, Ritonavir) and cardiovascular medications (for instance The effectiveness of Niosome entrapment is influenced by the HLB of the surfactant. The size of the vesicle and the length of the alkyl chain both increase with an increase in HLB value. Surfactants with HLB in the range of 14–17 are not acceptable for the formation of Niosomes.<sup>8</sup>

Examples: Type of Non-Ionic Surfactant <sup>9</sup>

- a. Twseens- (20, 40, 60, 80)
- b. Spans- (Span 60, 40, 20, 85, 80)
- c. Brijs -(Brij 30, 35, 52, 58, 72, 76) Decyl glucoside, Lauryl glucoside, Octyl glucoside,
- d. Fatty alcohol- Cetyl alcohol, stearyl alcohol, cetostearylalcohol, oleyl alcohol
- e. Ethers- Decyl glucoside, Lauryl glucoside, Octyl glucoside, Triton X-100, Nonoxynol-9
- f. Esters-Glyceryl laurate, Polysorbates, Spans
- g. Block copolymers- Poloxamer

2) Cholesterol:- The HLB value of the surfactants determines how much CHOL needs to be added. To counteract the impact of the bigger head groups on the critical packing parameter (CPP), the CHOL concentration must be increased as the HLB value rises over 10 s. In the absence of CHOL, the water-soluble detergent Tween20 (HLB value = 16.7) would be well hydrated and be present in solution as free monomers (CMC = 60 mg/l, in water at 20 °C). As a result, it forms persistent non-ionic surfactant vesicles in the presence of equimolar CHOL concentration. It lowers the membrane's flexibility and the drug's ability to pass through it.<sup>10</sup>

3) Charge inducer molecules:- The addition of a charged molecule to the bilayer is one of the techniques utilized to stabilize Niosomes. Niosomes are created using some charge-inducing chemicals. These molecules provide the

surface a charge, stabilize the Niosomes through electrostatic repulsion, and help avoid coalescence by doing so. A larger concentration of charged molecules may hinder the formation of Niosomes, thus they are often included to Niosomal formulations in amounts ranging from 2.5 to 5 mol% .Dicetyl phosphate (negatively charged), phosphotidic acid (negatively charged), Stearyamine (positively charged), etc. are a few examples of compounds that induce charges.<sup>11</sup>

4) Hydration method:- Another essential element required for the production of Niosomes is the hydration medium. Typically, phosphate buffer is used as a hydration medium. The pH of the buffer is impacted by the medication's solubility, though. It has been discovered that raising the hydration medium's content increases drug leakage, but increasing the hydration time from 20 to 45 minutes increases the efficiency of entrapment.<sup>12</sup>

Advantages:-

- (i) As compared to Liposomes Niosomes offer more chemical stability, osmotic activity and longer shelf life.<sup>13</sup>
- (ii) Because of the presence of a functional group on the hydrophilic head, the surface of Niosomes can be easily formed and modified.
- (iii) Niosomes are less toxic and more compatible since they do not carry any charge.
- (iv) Niosomes are degradable by the biological systems and do not initiate immunogenic reactions.
- (v) Niosomes can be used to encapsulate both hydrophilic as well as hydrophobic drugs.
- (vi) Niosomes can enhance the bioavailability of the active pharmaceutical ingredient by increasing the physical as well as biological stability.
- (vii) Patient compliance is better since given as aqueous suspension.
- (viii) Niosomes can be given by almost all the routes of delivery, for example, oral, parenteral, transdermal, ocular and pulmonary.
- (ix) Their shape, size, and entrapment can be changed by modifying the various parameters like additives, their ratio or their use in combination.
- (x) Niosomes can be used for targeted, controlled as well as sustained delivery of a drug.
- (xi) The drug can release in the sustained/controlled manner.
- (xii) No special conditions required for handling and storage of surfactants.
- (xiii) Due to the depot formulation, it allows controlled release of the drug.
- (xiv) Poorly soluble drugs have increased oral bioavailability.<sup>14</sup>

Disadvantages:-

- (i) Aggregation
- (ii) Time consuming

- (iii) Physical instability
- (iv) Leaking of entrapped drug.<sup>9</sup>

#### Types of Niosomes:-

1) Proniosomes = Dehydrated forms of Niosomes, should be hydrated, advantageous over Niosomes, transportation and distribution become easy.<sup>13</sup> Mop - spray coating, co acervation phase separation and the slurry method.<sup>15</sup>

2) Surfactant ethosomes = Ethanol is utilized in surfactant Ethosomes at a rather high concentration. Ethosomes are primarily categorized into three kinds on the basis of their composition: classical ethosomes, binary ethosomes, and transethosomes. Ethosomes are generated from non-ionic surfactants, ethanol or isopropyl alcohol, and water. Ma et al.<sup>16</sup> synthesized ethosomes that were paeonol-loaded

3) Aspasomes = Ascorbic Acid Derivative- Loaded Modified Aspasomes: Formulation, In-vitro, Ex- Vivo and Clinical Evaluation for Melasma Treatment. Aspasomes can enhance transdermal permeation. There are multilayered vesicles formed by amphiphile molecules.

4) Discosomes = Large disc-like Niosomes (Discomes). The preparation was done at 60 °C, which is lower than the previously reported temperature requirements and could therefore prove advantageous for items that are heat-sensitive.<sup>17</sup>

5) Elastic Niosomes = These are made from ethyl alcohol, water, and a non-ionic surfactant. Because the pores in the stratum corneum are bigger than vesicle pores, they can pass through them.<sup>15</sup> They could be utilized to administer both low and high-molecular weight medications.

6) Polyhedral Niosomes = Spherical vesicles, but they are not uniformly round. Solulan C24 and hexadecyl diglycerol ether (C16G2) were combined to create the Niosomes. A tiny amount of cholesterol can also be added to this combination to create these.<sup>10</sup>

7) Polyethylene Glycalated = It have ability to avoid being taken up by the mononuclear phagocytic system (MPS), which allows the medicine to be encapsulated to stay in the bloodstream for a longer period of time.<sup>18</sup> Cholesterol, dicetyl phosphate and span 60 can be used to make these Niosomes.

#### Methods of preparation:-

1) The "Bubble" method:-

In this procedure, no organic solvent is used. In a flask with three necks, phosphate buffers and cholesterol surfactant are combined.

The temperature of the flask is maintained using a water bath.

Assembly: One neck contains a thermometer. Nitrogen is passed through the second neck, and the third neck is connected to the water-cooled reflux.

These ingredients are mixed and homogenized for 15 seconds at 70 °C before being promptly infused with nitrogen gas.<sup>19</sup>

The resulting vesicles are big and unilamellar.

2) Thin film hydration technique:-

Another name for it is the hand-shaking approach.

Non-ionic surfactant, cholesterol, and organic solvent are introduced in an RBF.

In a rotational vacuum evaporator, the organic solvent is allowed to evaporate.

As a result, the inner surface of RBF develops a thin layer.

The formed thin layer is hydrated using either water or phosphate buffer at a temperature higher than the surfactant's transition temperature.

After rehydrating, a multilamellar vesicle containing the medication causes layer swelling.<sup>20</sup>

3) Method of injecting ether:-

Cholesterol and surfactant are combined using an organic solvent like diethyl ether in this process.

This mixture is added gradually to the warmed drug containing aqueous solution.

The temperature of this solution is kept at or above 60 °C.

The unilamellar vesicles of the pharmaceuticals that include surfactants are produced during solvent evaporation.

The sizes of the Niosomes that are formed might vary from 50 to 1000 m.<sup>8</sup>

Shreedevi et al.<sup>21</sup> produced Stavudine Niosomes by employing this approach.

4) Sonication procedure:-

The process of sonication was used to create Cefdinir's Niosomes.

The surfactant and cholesterol mixture was added to the medicine solution in the buffer.

To form multilamellar vesicles, the resultant mixture is probe-sonicated at 60 °C using a probe sonicator. Further ultrasonically processing it could result in the formation of unilamellar vesicles.<sup>22</sup>

5) Reverse phase evaporation method:-

In this procedure, cholesterol and surfactant are

combined with an organic solvent.

- A drug's water-based delivery method is manufactured separately.
- The organic phase is supplemented with the aqueous phase. Two-phase system manifests upon mixing.
- Under negative pressure, the organic phase is extracted from this system after it has been homogenized.
- During this stage, large unilamellar vesicles are formed.
- Niosomes of Isoniazid, Ellagic acid and Bovine serum albumin are prepared using this method.<sup>22</sup>

6) Method of "freeze and thaw":-

- Using this method, multilamellar vesicles can be produced, frozen, and thawed.
- Niosomes produced by using a thin-film hydration technique were frozen and thawed.<sup>23</sup>
- Eight millilitres of Niosomal solution were utilized, and it was placed through five cycles of freezing in liquid nitrogen for one minute and then defrosting in a water bath at 60 °C for an additional minute.

7) Rehydration after dehydration:-

- The thin-film hydration technique was used to make these vesicles, which were subsequently frozen in liquid nitrogen and freeze-dried for an extended period of time.
- Powder Niosomes were hydrated with phosphate buffered saline (pH 7.4) and heated to 60 °C
- The scientists compared the degree to which different approaches for entrapping Niosomes were developed.<sup>24</sup>
- They learned about the efficiency of entrapment. Reverse-phase evaporation of Niosomes has demonstrated the highest entrapment efficiency compared to newly formed Niosomes utilizing the thin-film hydration method.

8) Microfluidization method:-

- In this procedure, a reservoir of dissolved drug and surfactant is pumped under pressure into an interaction chamber that is filled with ice.
- The solution is circulated through a cooling loop in order to eliminate the heat produced during the process. Smaller, more homogeneous Niosomes are produced by this mechanism.<sup>24</sup>

9) Transmembrane pH gradient:-

- Using these proportions, surfactant and cholesterol are ingested simultaneously.
- After that, these are dissolved in an organic solvent, like chloroform. The organic solvent is extracted under reduced pressure.
- As a result, a thin layer of lipid forms on the flask's circular bottom's inner surface.

- Typically, a vortex mixing solution containing citric acid or another mildly acidic solution is used to moisten the lipid layer's thinness.
- An aqueous solution of the drug is then added and blended with this vortexing after the resulting mixture has gone through a freeze-thaw cycle.
- The final pH solution of phosphate can be altered using disodium hydrogen.<sup>25</sup>

10) Single-pass method:-

- In certain investigations, it has also been referred to as multiple ejection membrane.
- In this method, a suspension of a lipid-containing drug is passed through a nozzle after exiting a porous device.
- It produces homogeneously sized Niosomes, usually between 50 and 500 nm.<sup>26</sup>

11) The Handjani:Vila approach:-

- In this process, an aqueous solution of the drug is mixed with cholesterol and a surfactant.
- The finished mixture is homogenized.
- Agitation or ultracentrifugation are used to keep the process's temperature under control.<sup>2</sup>

12) Microfluidic hydrodynamic focusing:-

- Microfluidic hydrodynamic focusing by diffusive mixing with the two miscible liquids.
- The miscible liquids are swiftly and precisely combined in micro channels.
- When compared to Niosomes made using a conventional method, those made using this technology have better size and size distribution.
- Various factors, such as the microfluidic mixing settings, surfactant's chemical composition, and the device material used to fabricate the micro channels, can influence how Niosomes are put together.
- They discovered that a higher flow rate ratio results in smaller Niosomes and a shorter diffusive mixing period.
- Using a bigger microchannel will lengthen the time required for diffusive mixing and, as a result, produce large Niosomes.<sup>2</sup>

13) Supercritical carbon dioxide fluid:-

- In this method, volatile, non-toxic, non-flammable solvents are used.
- This method creates Niosomes that are between 100 and 440 nm in size.<sup>22</sup>

14) Heating method:-

- A heating method has been patented by Mozafari et al.<sup>27</sup>

- In this method, cholesterol and surfactant are hydrated separately in a buffer solution.
- To dissolve cholesterol, it is heated for an hour at roughly 120 °C after hydration.
- By reducing the solution's temperature, it is possible to continually stir the buffer solution while also adding surfactant and other ingredients.
- Niosomes are created during this stage. These are kept at room temperature for 30 minutes.
- Finally, Niosomes are maintained at 4-5 °C in a nitrogen atmosphere.

#### Methods of purification of Niosomes:-

##### 1) Gel filtration:-

- Gel filtration technique is used obtain the purified dispersion of Niosomes.<sup>8</sup>
- The untrapped drug is removed by gel filtration of Niosomal dispersion through a Sephadex G-50 column and elution with phosphate buffered saline or normal saline.

##### 2) Centrifugation:-

- It is the most popular technique for Niosome purification because cited in the most current scholarly publications.
- This exact approach was employed by Niosomes to release the untrapped genetic material centrifugation of gradient densities.
- Several writers combined these method employing Sephadex-based gel filtration chromatography.
- To remove the untrapped drug, spin the sample for one hour in a refrigerator.
- The preparation was centrifuged at 4 °C and 4000 rpm for 15 minutes are required for the release of the free medication.
- The preparation was centrifuged for 30 min. at 8000 rpm, for at least three cycles, according to Agarwal et al.<sup>28</sup>

##### 3) Dialysis:-

- It is an osmosis and diffusion-based process that depends on the passage of a semi-permeable membrane for the passage of a solvent and a solute.
- Niosomes are administered in a dialysis bag while the free medication is dialyzed using phosphate buffer.
- The Niosomal suspension in a dialysis bag with a molecular weight cutoff of 12,000 that was 3 cm by 8 cm in size.
- The process was carried out for 24 hours by keeping this in the beaker containing phosphate buffer, which was replaced with fresh buffer every three hours.

#### Factors influencing technique of preparation:-

- 1) Cholesterol:- The incorporation increases Niosome hydrodynamic diameter and entrapment efficiency.

Cholesterol has two effects: increases the liquid state bilayer's chain order. Reduces the gel state bilayer's chain order. The stiffness of the bilayers increases with a rise in cholesterol concentration, and the pace at which encapsulated material is released decreases.

- 2) Nature of the medication:- Properties of a drug, such as its molecular weight, structural characteristics, hydrophilic or lipophilic nature, and the proportion of each effect to the other the trapping of drugs. The vesicle's size could expand as a result of Interaction between drugs and surfactants.<sup>29</sup> In some pieces from earlier, According to some reports, a hydrophilic drug's Niosome entrapment efficiency could be as high as 10–20% combination between adverse positive charge of Gallidermin and Niosome charge trapping of an ionic Niosomes contains a hydrophilic medication (Gallidermin, positive charge) could reach 45%.

- 3) Quantity of lipid and surfactant:- Typically, the maximum amount of lipid and surfactant utilized for Niosome preparation is 1-2.5% w/w. The amount of medication entrapped and the viscosity of the solution fluctuate with variations in the surfactant: cholesterol ratio. The system itself alters. A shift in the aforementioned ratio during the hydration phase might have an impact on Niosome characteristics. The Niosomes of Bovine Serum Albumin were produced and used the varying percentages to examine the impact of cholesterol % (0%, 20%, 40%, and 80%) of cholesterol. In the outcomes, they have noticed that 60% cholesterol Niosomes have displayed the best entrapment efficiency. However, as the concentration rises above 60%, less medication is entrapped.<sup>30</sup>

- 4) PH of the hydration medium:- Another element that may have an impact on hydration is the pH of the medium the drug's capacity for trapping. For instance, Flurbiprofen exhibits greater entrapment (maximum 94.6% at pH 5.5) at acidic pH values. Flurbiprofen's entrapment effectiveness increases when the pH drops from 8 to 5.5, and it considerably drops at pH 6.8.<sup>31</sup>

- 5) Hydration time:- Using the thin-film hydration approach, <sup>32</sup>Niosomes containing methylene blue and probe-sonicated the vesicles to check for size uniformity. They looked at how entrapment effectiveness and vesicle size were affected by hydration time and volume. They discovered that a brief period of hydration results in vesicles with greater diameters and reduced drug entrapment. For the entire hydration of span 60 and creation of vesicular size, they recommended a hydration duration of 60 minutes and a volume of 5 ml. Smaller vesicles are produced by prolonged hydration.

- 6) Method Of Preparation:- Niosome size and

entrapment effectiveness may vary depending on how they are made.<sup>33</sup> Niosomes of Naltrexone were created by scientists using the freeze-thaw, dehydration-rehydration, and reverse-phase evaporation methods as well as thin-film hydration techniques. According to the findings, the preparation technique had a substantial impact on the entrapment efficiency.

7) Resistance to osmotic stress:- The size of the Niosome decreases when a hypertonic solution is added to a Niosomal suspension. When Niosomes are maintained in hypotonic salt solution, the drug is first released slowly, causing the swelling. This slow release may be caused by the inhibition of fluid eluting from vesicles. Later, a faster release phase was observed. This faster release phase may be caused by the disruption of the Niosome's mechanical structure as a result of mechanical stress.<sup>34</sup>

8) Co surfactant:- In comparison to non-ionic water-soluble surfactant mixing a non-ionic water-insoluble surfactant with span 60 led to larger vesicles and less effective methylene blue entrapment. This might be due to competition between the lipophilic co surfactant and cholesterol in the bilayer structure, which leads to a weak membrane structure and drug leakage.<sup>8</sup>

Characterization:-

1) Niosome size, morphology, and size distribution :- The size of Niosomes and their morphology can be determined using a variety of methods, including light microscopy, coulter counter, photon correlation spectroscopy, electron microscopic analysis, SEM (scanning electron microscope), TEM (transmission electron microscope), freeze-fracture replicator, light scattering, zeta sizer and metasizer.<sup>9</sup> Because the two methods apply different measurement philosophies, the transmission electron microscopy (TEM) approach yields smaller particle sizes than the dynamic light scattering (DLS) method.

2) Bilayer rigidity and homogeneity:- The stiffness of the bilayer affects the biodistribution and biodegradation of Niosomes. Homogeneity can be detected using Differential Scanning Calorimetry (DSC), and Fourier Transform Infrared Spectroscopy (FT-IR) techniques. It can occur both within Niosome structures and between Niosomes in dispersion.

3) Entrapment efficiency:- It can be computed by deducting the total amount of drug added from the quantity of drug unloaded. Techniques such thorough dialysis, filtering, gel chromatography, or centrifugation can be used to identify the unloaded drug.<sup>35</sup> You can determine the amount of loaded medicines by dissolving Niosome in 0.1% Triton X-100 or 50% n-Propanolol. and any particular technique can be used to test the final answer . The % entrapment efficiency can be calculated using the following equation- %Entrapment Efficiency = Quantity of drug-

loaded in the Niosome/Total quantity of drug in the suspension X 100

4) Charge on Niosome and zeta potential:- The charge on Niosomes causes them to repel one another. And by preventing their aggregation and fusion, electrostatic repulsion maintains their stability . Zeta potential is used to estimate the charge on niosomes. Microelectrophoresis, a mastersizer, a zeta potential analyzer, High-performance capillary electrophoresis, pH-sensitive fluorescent molecules, The zeta potential is calculated using a DLS instrument . The

$$\xi = \mu E \pi \eta / \Sigma$$

Where  $\xi$  = Zeta potential.

$\mu E$  = Electrophoretic mobility

$\eta$  = Viscosity of medium

$\Sigma$  = Dielectric constant

Dicetyl phosphate (DCP) was utilized by Bayindir and Yuksel<sup>36</sup> to produce Niosome surface charge and discovered that a negative zeta potential between 41.7 and 58.4 mV is sufficient to maintain the electrostatic attraction between the particles keeps the system steady.

5) Number of lamellae:- The number of lamellae can be determined using a variety of techniques including small-angle X-ray spectroscopy and electron microscopy. Small-angle X-ray scattering and in-situ energy-dispersive x-ray diffraction can be utilized to characterize the thickness of bilayers.<sup>37,38</sup>

6) Membrane rigidity:- A fluorescent probe's mobility can be used to measure membrane stiffness be applied as a temperature function. Fluorescence polarization can be used to determine the microviscosity of the Niosomal membrane in order to gain insight into its packing configuration.<sup>39</sup>

7) Tissue distribution/in-vivo study:- The method of distribution, drug concentration, action, and duration of drug presence in organs such the liver, lung, spleen, and bone marrow all affect in-vivo investigations for Niosomes .Animal models can be used to study how a medication is distributed throughout tissue. Animals are sacrificed, and various tissues such the liver, kidney, heart, lungs, and spleen should be taken, washed with buffer, homogenized, and centrifuged in order to investigate the distribution pattern. The amount of drugs in the supernatant is examined.<sup>39</sup>

8) Stability studies:- The method of distribution, drug concentration, action, and duration of drug presence in organs such the liver, lung, spleen, and bone marrow all affect in-vivo investigations for Niosomes.

9) In-vitro Release: In-vitro release rate study carried out by the various methods:-

1. Dialysis Tubing,
2. Reverse dialysis
3. Franz diffusion cell

Franz diffusion cell:- Franz diffusion cells can be used to carry out the in vitro diffusion research. Proniosomes are inserted into a Franz's donor chamber cellophane membrane-equipped diffusion cell . Then, proniosomes are dialyzed using an appropriate samples in a dissolving media at room temperature are periodically removed from the medium, and Utilizing appropriate techniques, such as HPLC, U.V. spectroscopy, and sink maintenance the importance of condition.<sup>2</sup>

10) Vesicle charge:- Niosome behavior can be significantly influenced by the vesicle surface charge both in vivo and in vitro. In comparison to unaltered vesicles, charged Niosomes are more resistant to aggregation and

fusion. The zeta potential of individual Niosomes can be evaluated by micro electrophoresis to provide an idea of the surface potential. Using pH-sensitive fluorophores is an alternate strategy. More recently, the zeta potential of Niosomes has been determined using dynamic light scattering.<sup>2</sup>

Recent advances in niosomes:-

The advances made by these changes aim to improve the aforementioned traits. The production and characterization of specialized. Niosomes are identical to those of normal Niosomes, with the inclusion of components that give rise to some of these specialized capabilities.

Category	Compound /surfactant	Result
PH responsive Niosome <sup>40,41</sup>	Cholesteryl hemisuccinate and paclitaxel	<ul style="list-style-type: none"> <li>• Due to its inherent lipophilicity and membrane stabilizing function, the cholesterol derivative cholesteryl hemisuccinate (CHEMS) is one of the most often utilised pH-sensitive substances. In alkaline condition, it can self-assemble into a bimolecular layer.<sup>20</sup></li> <li>• Barani et al used CHEMS to create pH-responsive niosomes loaded with paclitaxel and research their anti-cancer effects in vivo and in vitro.</li> <li>• The study discovered parallels between findings from earlier investigations regarding particle size distribution, in vitro drug release patterns, and cell culture experiments observed for pH-sensitive substances than those of free medication. Niosomes.</li> <li>• The research also shown stability for up to three months after cooled to 4 °C.</li> </ul>
	Ibuprofen	<ul style="list-style-type: none"> <li>• The previously described innovative Tween® 20-glycine surfactant was also used to create ibuprofen Niosomes, where the bilayer was unstable when exposed to an acidic pH, causing payload release.</li> <li>• We administered Niosomes significantly increased pain threshold was seen after subcutaneous (SC) injection at the sites of inflammation in male mice between the hours of 2 and 4 shown for only 1 hour, indicating their potential for tailored lipophilic drug delivery.</li> <li>• The study also confirmed the Niosomes stability for up to three months when stored at 4 °C.<sup>42</sup></li> </ul>
	Ammonium Glycyrrhizinate	<ul style="list-style-type: none"> <li>• (AGN) have been explored as a potential nanotherapeutic system for anti-inflammatory activity in murine models.</li> <li>• The study showed that pH-sensitive or neutral AGN are ideal nanotherapeutics for the treatment of inflammation and pain.</li> </ul>



#### Toxicity of Niosomes:-

- Niosome toxicity is dependent on the individual components; for example, nonionic surfactants are less toxic and more biocompatible than their cationic, anionic, and amphoteric counterparts.<sup>48</sup>
- These qualities sharply decline when the same surfactants are in vesicular systems.
- Human keratinocytes were used in the evaluation of the toxicity of several surfactant types used in Niosomal formulations.
- It was found that ester-type surfactants are less hazardous than ether-types due to the enzymatic breakdown of bonds in esters.
- Traditional methods for predicting the toxicity of a surfactant and in vesicular systems generated from them include hemolytic tests.
- Recent research has shown that the size of the colloidal aggregates in solution as well as the length of the alkyl chain in the surfactant affect the ability of Niosomes to disrupt erythrocytes.
- Since Niosomes interact more difficult with biological membranes, there is significant hemolysis.
- It is assumed that a shorter carbon chain intercalates better into the erythrocytes membranes, destroying their molecular order.
- When applied topically to healthy human volunteers, bola form Niosome formulations demonstrated good safety and acceptability evidence in vitro in human keratinocytes and in vivo in humans, where there was no skin erythema.
- Recently, the toxicity of Niosomes in ocular applications was examined by assessing the conjunctival and corneal irritation potential of Span® 60 Niosomes and surface-modified Span® 60 Niosomes using excised bovine corneal opacity and permeability models and hen's egg chorioallantoic membranes. Niosomes showed less ocular discomfort, which indicates high tolerance for the eyes.<sup>49</sup>

#### DISCUSSION:-

This review provides a thorough overview of the Niosomes chemical make-up, structural makeup, benefits, and applications. For the regulated percutaneous administration of both hydrophilic and lipophilic medicines, Niosomes have been shown to be promising. Utilizing new methods for Niosome preparation, loading, and customization can increase their potential. Due to the potential for their improvement by novel preparation techniques, modification methods to tailor delivery, and novel formulation components, which would enable them to achieve targeted delivery, better drug entrapment efficiency, and to develop specialized Niosomes with special structures, this adaptable technology has great potential in the fields of pharmaceutical, veterinary, and cosmetic sciences. They can be used to encapsulate virtually any type of medication, including pharmaceuticals with natural sources, enzymes,

peptides, DNA, vaccines<sup>50</sup>, and anti-cancer medications. They provide versatility in the mode of administration in addition to the medicine. They are better suited for medication delivery due to their non-toxic advantage over liposomes. Thus, it appears that Niosome research will continue to grow and may result in effective market formulation in the pharmaceutical business.

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