Niosome: Novel drug delivery system: A review

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Abstract- Niosome is a novel medication delivery system, in which the solution is enclosed in vesicle which is made by Non-ionic surfactant. The niosomes provides several important advantages over conventional drug therapy. Structurally, niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in case of liposomes. Niosomes tackled the issue of insolubility, instability, low bioavailability and fast debasement of medications. This paper overviews the method of preparation of Niosomes along with applications in pharmaceutical areas.

Keywords: Niosome, Drug delievery, "Methods of preparation", "surfactant and Non surfactant"

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Introduction-

Niosomes are an unique drug delivery method that entraps hydrophilic pharmaceuticals in the core cavity and hydrophobic medications in the non-polar region located inside the bilayer, allowing for the absorption of both hydrophilic and hydrophobic drugs [1]. Niosomes are ampiphillic in nature; the word niosome comes from the fact that the drug is enclosed in a vesicle made of a non-ionic surfactant. The size of niosomes is extremely tiny and microscopic [2]. L'Oreal created and received a patent for the initial niosome formulations in 1975. when the thermodynamically stable vesicles' charge-inducing compounds and surfactants are properly blended. Since niosomes mitigate the drawbacks of liposomes, they are mostly studied as alternatives to them. [3]. **Table No- 1** Niosomes are an enhancement over liposomes in areas like chemical instability. Because of their susceptibility to oxidative degradation and the varying purity of their phospholipids, liposomes are chemically unstable. Chemical stability, biodegradability, biocompatibility, low production costs, simple storage and handling, and low toxicity are the primary goals of niosomal system development [4,5]. There are several ways to administer niosomes, including orally, parenterally, and topically. Niosomes are utilised as a vehicle to deliver a variety of medicines, including synthetic and natural ones, antigens, hormones, and other bioactive substances [6,7,8]. This article outlines the key characteristics of niosomes, as well as their current uses for encapsulating and delivering bioactive substances. It also provides an overview of their manufacturing methods.

Table No- 1 Advantage & Disadvantage

Advantage of Niosomes	**Disadvantage of Niosomes**
The characteristics such as size, lamellarity etc. of the vesicle can be varied depending on the requirement	Fusion
The vesicle can act as depot to release the drug slowly and offer a controlled release	Aggregation

Since the structure of the niosome offer place to accommodate hydrophilic, lipophilic, as well as ampicillin drug moieties, they can be used for a variety of drug	Leaking of entrapped drug
The vesicle suspension being water based offer greater patient complication over oil based system	Physical instability
They are osmotically active and stable	Hydrolysis of encapsulated drug which limiting the self life of the dispersion
They increase the stability of the entrapped drug	
Can enhance the skin penetration of drug	

2:Niosomes-

Niosomes are vesicles made primarily of hydrated non-ionic surfactants, along with cholesterol (CHOL) or its derivatives in many circumstances. Niosomes' distinctive architecture enable them to encapsulate both hydrophilic and lipophilic molecules. This can be done by attaching hydrophilic compounds in the aqueous core of vesicles or adsorbed on the surfaces of bilayers, while encasing lipophilic substances by partitioning them into the lipophilic domain of the bilayers. Liquid crystalline bilayer stacks that are thin lipid films or cakes are hydrated, becoming fluid, swelling, and forming liposomes. Agitation causes the hydrated lipid sheets to separate and self-assemble into vesicles, which prevents water from interacting with the bilayer's hydrocarbon core at the borders.Niosome production first developed in the cosmetics business, and later possible uses for niosomes in medicine administration were investigated [9]. In recent years, niosomes have received a lot of attention as prospective drug delivery methods for various routes of administration. They are one of the prominent vesicles in all vesicular systems. This is because niosomes are a very valuable drug delivery system with many uses and do not have the many drawbacks that

other drug delivery systems do. Niosomes have the capacity to entrap many kinds of chemicals, DNA, proteins, and vaccines. **Figure No: 1**

2.1 Structure of Niosomes-

Span-60, a non-ionic surfactant that forms vesicles, is typically stabilised by the addition of cholesterol, and a little quantity of dicetyl phosphate, an anionic surfactant that also aids in stabilising the vesicle, make up a normal niosome vesicle.

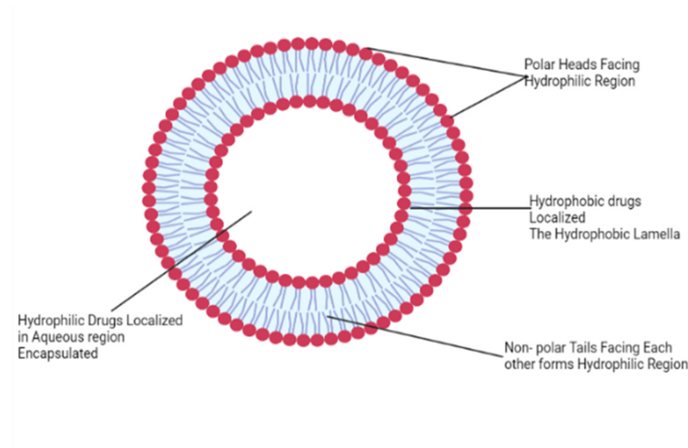


Figure No- 1 Niosome

2.2 Composition of Niosomes-

The two major components used for the preparation of niosomes are,

1. Cholesterol

2. Nonionic surfactants

[1]Cholesterol

Cholesterol is a steroid derivative, which is used to provide rigidity and proper shape, conformation to the niosomes preparations.

[2]Non- ionic surfactant-

Among chemical substances, surfactants belong to a distinct class. Surfactants are amphiphilic molecules with two distinct regions that have very different solubilities, a hydrophilic (water-soluble) end and a lipophilic (organic-soluble) end that is highly hydrophobic, for example, phospholipids (phosphatidyl choline) which are the building blocks of biological cell membranes. Alkane, fluorocarbon, aromatic, or other non-polar group chains make up the lipophilic portion of molecules. Sulfonates, carboxylates, phosphonates, and ammonium derivatives are a few examples of highly solvated hydrophilic functionalities found in the head group. The hydrophilic functionality head group of surfactants, which are sulfonate, quaternary ammonium salts, zwitterionic butanes, and fatty acids, can be classed as anionic, cationic, amphoteric, and non-ionic [10]. Non-ionic surfactants have a significant role in regulated, prolonged, targeted, and continuous drug administration, making them one of the best polymeric nanocarriers available. Surfactants are frequently grouped into polar head groups for classification purposes. There are no charge groups in the head of a non-ionic surfactant. An anionic surfactant is the term given to the head of an ionic surfactant, which possesses a net charge. These surfactants include phosphate esters, sulphates, ether sulphates, and fatty acid salts (often known as "soaps"). It is referred to be a cationic surfactant if the head charge is positive. Zwitterionic (amphoteric) surfactants are defined as having a head with two oppositely charged groups.Since cationic surfactants are typically irritating and occasionally even poisonous, their use in medication administration is less widespread than that of the other three groups of surfactants. Table 1 [11,12] includes examples of each group. Non-ionic surfactants are a subset of surfactants that lack charge groups in their hydrophilic heads. Therefore, in solutions, nonionic surfactants can form structures with hydrophilic heads opposing aqueous solutions and hydrophilic tails opposite organic solutions. Niosomes are created by the self-assembly of non-ionic surfactants in aqueous dispersions due to this characteristic of non-ionic surfactants. Alkyl esters, alkyl amides, alkyl ethers, and esters of fatty acids are the four subcategories of non-ionic amphiphiles utilized in niosomes [13].
Eg- Span (60,40, 20,80) Tween (20,40,80,60)

2.3 Type of Niosome-

The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation (e.g.REV, DRV). The various types of niosomes are described below:

i) **Multi lamellar vesicles (MLV)(MLV, Size=>0.05 μm)**

ii) **ii) Large unilamellar vesicles (LUV),(LUV, Size=>0.10 μm).**

iii) **iii) Small unilamellar vesicles (SUV).(SUV, Size=0.025-0.05 μm)**

[1]Multilamellar vesicles (mlv):

It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. Multilamellar vesicles are the most widely used niosomes.These vesicles are highly suited as drug carrier for lipophilic compounds.

[2]Large unilamellar vesicles (luv): These niosomes contain a high aqueous to lipid compartment ratio, allowing for the very efficient usage of membrane lipids while encasing higher amounts of bioactive compounds.

[3]Small unilamellar vesicles (suv):

These tiny unilamellar vesicles are primarily made from multilamellar vesicles using the sonication process, French press extrusion, and electrostatic stabilisation by adding dicetyl phosphate to 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes. [14].

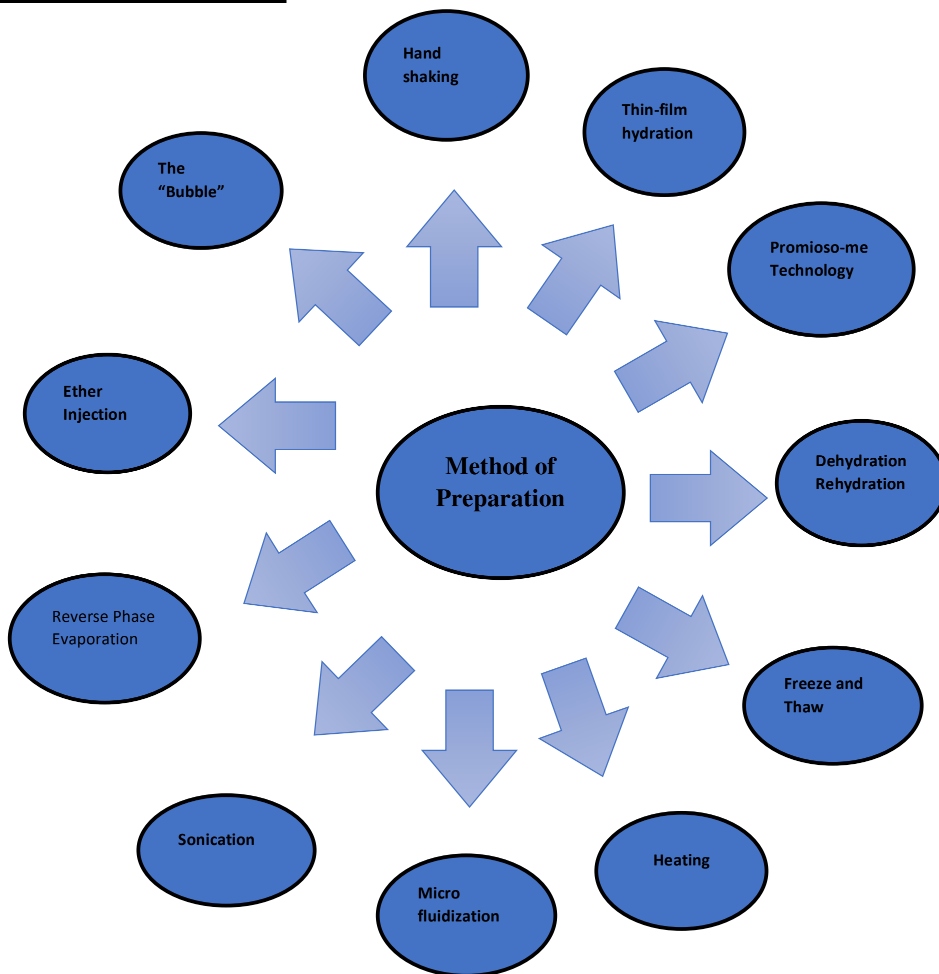
Table:3CLASSIFICATIONS OF SURFECTANT

Surfactant class	**Example**
Non- Ionic	Polyoxyethylene alchol Polyoxyethylene glycol alkyl ether Alkyl ethoxylate Alkyl phenol ethoxylate Fatty acid alkanolamide

Anionic	Stearate Soap Alkyl benzene sulfonate Alkyl sulfate Ether sulfate Alkyl ether sulfate Laurylamine
Cationic	Laurylamine Trimethyl dodecylammounium Cetyl trimethylammonium Alkyl diamine salt
Zwitterionic	Dodecyl betaine Lauramidopropyl betaine Alkyl imidazoline

A typical niosome vesicle would consist of a vesicle forming amphiphilic i.e. a non-ionic surfactant such as Span-60, which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle.

3:Method of Preparation-



3.1 Hand shaking method-

The hand shaking method (HSM), which is comparable to the TFH method and is one way to synthesize (Multi lamellar vesicles) MLVs, has occasionally been used with TFH method [15]. In this procedure, an organic solvent is used to dissolve the surfactants and some additives, including cholesterol, in a round-bottom flask. Using a rotary evaporator, the organic solvent was evaporated, leaving a thin layer on the flask's interior wall.The fully dried film was directly hydrated with an aqueous solution [containing the drug] for about an hour while being gently mechanically shaken to create a milky-looking niosomal dispersion. For example, niosome-entrapped morin hydrate (MH) [16], diclofenac sodium (DCS) [17], luteinizing hormone releasing hormone (LHRH) [18], adriamycin [19], and flurbiprofen [20] have all been prepared using HSM.

3.2 Thin Film Hydrated method-

The thin-film hydration method (TFH) is a popular and easy preparation technique. This process involves dissolving the surfactants and some additives, like cholesterol, in an organic solvent in a round-bottomed flask. After that, a thin layer is created on the interior wall of the flask by rotational vacuum evaporating the organic solvent. The dry film is hydrated above the transition temperature (Tc) of the surfactant by adding an aqueous solution, such as water or PBS (phosphate buffer saline), which contains a medication. During the hydration, MLVs were created [21,22]. **Fig. 1** shows the design for the technique for making niosomes using TFH. TFH has been utilised to create niosomes that are trapped in minoxidil [23], nimesulide [24], insulin [25], hydroxycamptothecin [26], beclometasone dipropionate (Bdp) [27], glucocorticoids [28], salicylic acid and p-hydroxyl benzoic acid [29], methotrexate [30], doxorubicin [31], antioxidants [32], etc

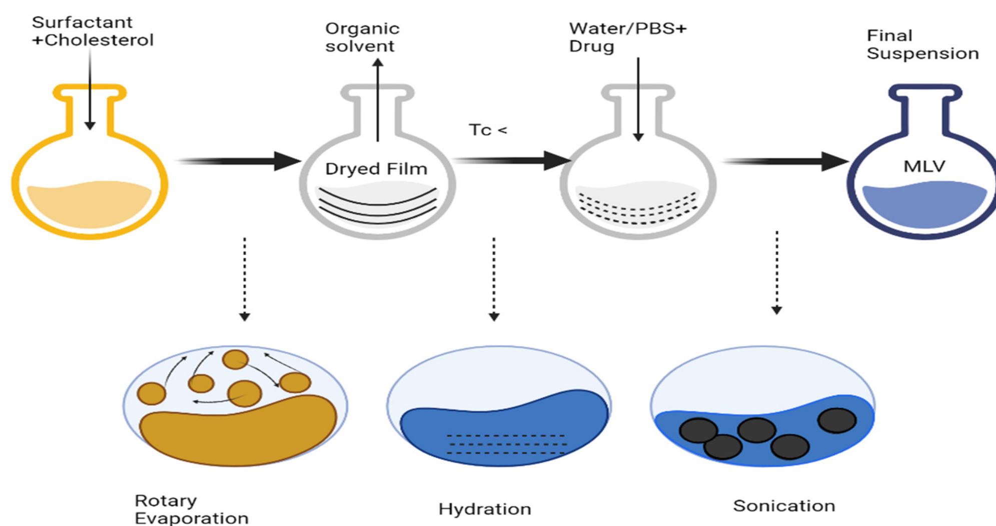


Fig No- 1 Niosome preparation of Thin Film Hydrated Method

3.3 Bubble method-

The "bubble" method is an approach to niosome preparation that does not include organic solvents. This procedure involved transferring surfactants, additives, and (Buffered Saline) PBS (pH 7.4) into a glass reactor with three necks. For temperature control, the reactor is placed in a water bath. The first neck is where the thermometer is located, the second neck is where nitrogen is fed, and the third neck is where water-cooled reflux occurs. Niosome components are dispersed at 70 °C, and the dispersion is blended for 15 seconds with a high-

shear homogenizer. Nitrogen gas is then bubbled at 70 °C immediately after the dispersion [15].

3.4 Ether Injection Method-

In the ether injection technique (EIM), the surfactants and additives are dissolved in an organic solution, such as diethyl ether, and slowly injected through a needle in an aqueous solution [containing medication] kept at constant temperature (approximately 60 °C). Surfactants are added to help single-layered vesicles form while ether is being vaporised. SUVs and LUVs made with the solvent injection process have a lot of aqueous fluid trapped inside. The ultimate vesicle's diameter varies from 50 to 1000 nm [21,22,15] depending on the circumstances. **Fig. 2** EIM has been used for the preparation of niosome entrapped gadobenate, diclofenac sodium (DCS), fluconazole, rifampicin, adriamycin, etc.

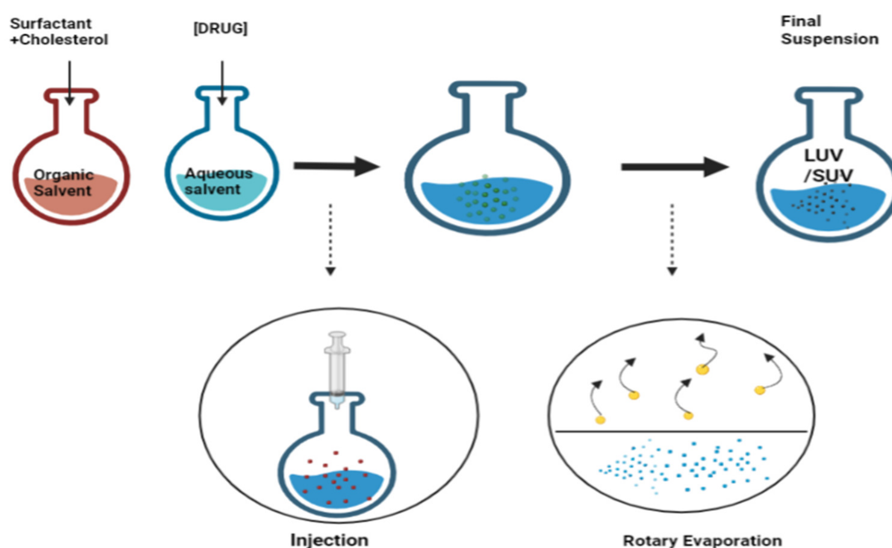


Fig No- 2 Niosome preparation of Ether injection Method

Sonication Method-

In this procedure, the surfactant/cholesterol mixture is introduced to a medication solution dissolved in a buffer. To produce niosomes, the mixture is probe sonicated for 3 minutes at

60 °C using a sonicator and a titanium probe [15]. Diallyl disulfide (DADS) loaded niosomes have been prepared using the sonication method [33].

3.5 Microfluidization Method-

Niosomes might be produced with more uniformity, smaller size, unilamellar vesicles, and improved repeatability by applying the micro fluidization approach. The submerged jet principle, which involves two fluidized streams interacting at extremely high speeds in carefully planned microchannels inside an interaction chamber, is used in this technique. The arrangement of a thin liquid sheet impinging along a common front ensures that the system's energy supply remains inside the region of niosome production [15].

3.6 Heating Method-

Surfactants and other additives, including cholesterol, were individually hydrated in PBS (pH = 7.4) for an hour at room temperature in a nitrogen atmosphere. The solution is then heated (to a temperature of around 120 °C) on a hot-plate stirrer to dissolve the cholesterol after roughly 15-20 minutes. The temperature is then lowered to 60 °C, and while stirring for an additional 15 minutes, the additional ingredients—surfactants and other additives—are added to the buffer in which the cholesterol has been dissolved. Niosomes produced at this stage are maintained at 4-5 °C under a nitrogen environment until usage, after which they are retained at ambient temperature for 30 min [34–37].

3.7 Dehydration & Rehydration Method-

Multilamellar vesicles can be produced using the "freeze and thraw" technique (FAT-MLVs). Using the TFH approach, niosomal suspensions were frozen in liquid nitrogen for 1 minute and then thawed in a water bath at 60 °C for a further 1 minute [38].

3.8 Proniosome Technology-

Niosome preparation has been using Proniosome technology for almost two decades. Proniosomes have been used as stable precursors for the quick creation of niosomal carrier systems, which is an unique drug carrier preparation technique [40]. Niosomes entrapped in vinpocetine, valsartan, 17-estradiol, tenoxicam, etc. have all been prepared using PT. In general, SUVs are made by transforming MLV dispersions into (Small Unilamellar Vesicles) SUVs using high pressure homogenization (using a microfluidizer, bath, or probe sonicator), extrusion under high pressure, or sonication (using French pressure cell). Energy application

causes the MLV structure to disintegrate, resulting in the formation of SUVs with a large radius of curvature [16,21,22,45]. Due to the decreased pH inside the niosome, the drug precipitates and ionises. After being enclosed, it is unable to escape the vesicle. The thin layer of cholesterol and surfactant can be hydrated using this method experimentally by vortex mixing citric acid (pH 4.0). The MLVs are so frozen and thawed. Aqueous solution with drugs is added, and the suspension is vortexed. The pH is then increased to 7.0–7.2, and niosomes are produced by heating the solution to 60 °C for 10 minutes [46,47].

3.9 Reverse phase Evaporation Method –

When creating LUVs, reverse phase evaporation is used to dissolve niosomal components, surfactants, and additives in an organic solvent. The organic phase is combined with the aqueous phase, which contains the medication, and the mixture is then sonicated to create an emulsion. The organic phase is then slowly removed using a rotary vacuum evaporator at a temperature of between 40 and 60 °C. **Fig. 3** Until the process of hydration is finished, the evaporation will continue. When an organic solvent evaporates, LUVs are created [48,38]. In addition, a number of techniques, such reverse phase evaporation and ether or ethanol injection procedures, require for strenuous circumstances, including the use of organic solvents, sonication, and high temperatures for extended periods of time [38,21,22,40,49].

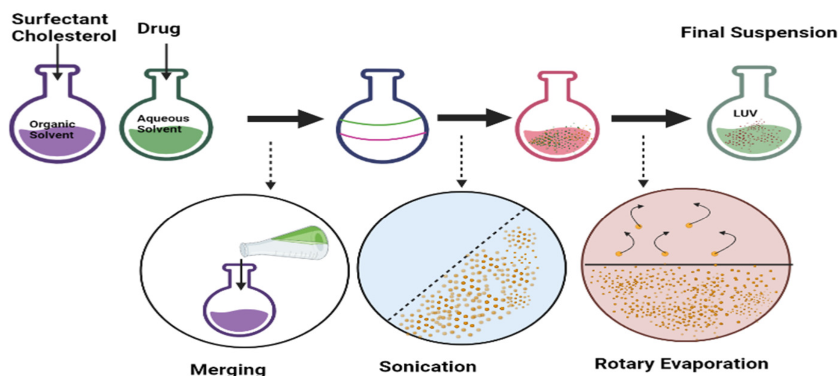


Figure No- 3 Niosome Preparation of Reverse phase Evaporation Method

4 Factor Affecting Niosomes Formulation-

4.1 Drug -

Drug entrapment in niosomes affects the stiffness and charge of the noisome bilayer. The degree of entrapment is influenced by the drug's hydrophilic lipophilic equilibrium. [50].

4.2 Nature and types of Surfactant-

Due to the surface hydrophobicity of the surfactant, the mean size of niosomes increases correspondingly as HLB surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) are used. Hydrophilic head and hydrophobic tail are necessary characteristics of a surfactant. In other cases, a single steroidal group may make up the hydrophobic tail instead of one or two alkyl or perfluoroalkyl groups [51].

4.3 Cholesterol content and charge-

Cholesterol increases the hydrodynamic diameter and trapping effectiveness of niosomes. It increases membrane stabilising action and lessens membrane leakiness. A higher cholesterol content in the bilayers led to a slower rate of material release from the encapsulation, which increased the stiffness of the resulting bilayers. In multilamellar vesicle structures, the presence of charge tends to increase the interlamellar distance between succeeding bilayers and increases the overall volume entrapped [52].

4.4Resistance to osmotic stress -

The diameter is reduced by addition of hypertonic salt solution to suspension of niosomes.

Resistance to osmotic stress: By adding a hypertonic salt solution to the niosome suspension, the diameter is decreased.

4.5 Temperature of Hydration-

Hydration temperature influences the shape and size of niosome.

4.6 Structure of surfactants

The geometry of vesicle to be shaped from surfactants is inuenced by surfactant's structure, which can be characterized by basic pressing parameters. Geometry of vesicle to be shaped can be predicated on the premise of basic pressing parameters of surfactants. Critical packing parameters can be defined using following equation,

CPP (Critical Packing Parameters) =V/lc × a0

Where,

V = hydrophobic group volume,

lc = the critical hydrophobic group length,

a0= the area of hydrophilic head group

Critical packing parameter value type of miceller structure

formed can be ascertained as given below,

If CPP < ½ formation of spherical micelles,

If ½ < CPP < 1 formation of bilayer micelles,

If CPP > 1 formation inverted micelle[53].

5 Evaluation-

[1]**Size**

Niosomal vesicles are thought to be spherical in shape, and the laser light scattering method can be used to measure their mean diameter [28]. Additionally, utilising various methods like electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy, optical microscopy, and freeze fracture electron microscopy, the diameter of these vesicles can be determined. In order to enhance the vesicle width of niosomes, freeze-thawing is used, which might be described as a fusing of vesicles during the cycle. [54-56].

[2] Bilayer formation:

By observing the creation of an X-cross using light polarisation microscopy, it is possible to identify the bilayer vesicle formed by the assembly of non-ionic surfactants.

[3] Number of lamellae:

The number of lamellae in niosomes is counted using nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering, and electron microscopy [57-58].

[4] Membrane rigidity

A fluorescent probe's mobility as a function of temperature can be used to calculate the flexibility of a membrane.

[5] Entrapment efficiency

Unentrapped drug is first separated from niosomal dispersion, then drug still in niosomes is determined by completely interrupting vesicles with 50% n-propanol or 0.1% Triton X-100 and analysing the resulting solution using the appropriate drug assay method. It can be explained by the formula:

Entrapment efficiency (EF) = (Amount entrapped / Total amount) 100. [59].

[6]Application:

Niosome as a carrier for hemoglobin-

Niosomal solution can be utilised as a carrier for haemoglobin since it exhibits a visible spectrum that is superimposed onto that of free haemoglobin. The haemoglobin dissociation curve of vesicles can be modified similarly to that of non-encapsulated haemoglobin, and they are also permeable to oxygen [60].

Ophthalmic drug delivery-

Due to tear formation, the impermeability of the corneal epithelium, non-productive absorption, and transient residence time, it is challenging to achieve optimal bioavailability of drugs from ocular dosage forms as ophthalmic solution, suspension, and ointment. However, niosomal vesicular systems have been suggested [61].In order to ensure good bioavailability of the medication.

Delivery of peptide drugs-

In an in vitro intestinal loop model, niosomal entrapment oral administration of 9-desglycinamide, 8-arginine vasopressin was investigated, and it was found that peptide stability considerably increased18. Applications of niosomes in immunology Niosomes have been utilised to explore the nature of the immune response triggered by antigens. According to reports, niosomes are a powerful adjuvant with regard to immunological specificity, low toxicity, and durability [62].

Transdermal delivery of drugs by niosomes-

When a medicine is included in niosomes for transdermal delivery, skin penetration of the drug is increased [63].

Neoplasia-

A dose dependent antirreversible cardiac toxic effect is produced by anthracyclic antibiotics like Doxorubicin, which exhibits broad spectrum anti tumour action. When given to mice

with the S-180 tumour through niosomal administration, this medication lengthened their lives and slowed the pace of sarcoma proliferation [30].

Use in studying immune response:

Niosomes are used to study the concept of the immune response triggered by antigens due to their immunological selectivity, low risk, and more notable solidity. Non-ionic surfactant vesicles have demonstrably shown that they can function as adjuvants following parenteral administration of a variety of unique antigens and peptides. [64].

Anti-inflammatory agents [31]

Anti-inflammotry agents:

When compared to the free medication, the niosomal formulation of diclofenac sodium with 70% cholesterol had higher anti-inflammator action. In comparison to the free medication, the niosomal formulation of nemesulide and flurbiprofen has higher anti-inflammatory activity [53,65].

Leishmaniasis:

Niosomes can be used to concentrate medication for the treatment of diseases when the contaminated life form resides in the reticulo-endothelial organ. Leishmaniasis is an infection in which the parasite targets the liver and spleen cells [66,67,68].

Immunological application:

The nature of the immune response triggered by antigens has been studied using niosomes. Niosomes have been described by Brewer and Alexander as an effective adjuvant due to their immunological specificity, low toxicity, and stability [68].Transdermal delivery of drugs by niosomes Those drug have slow penetration of medicament through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate

has been achieved by transdermal delivery of drug incorporated in niosomes. From the above discussed studies, and confocal microscopy, it was seen that

non-ionic vesicles could be formulated to target pilosebaceous glands. Topical niosomes may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

Transdermal delivery of drugs by niosomes:

One of the main drawbacks of transdermal distribution is the delayed uptake of some medications via the skin. The transdermal distribution of a medication integrated with niosomes has increased the penetration rate. It was discovered that non-ionic vesicles might be created to target pilosebaceous glands from the experiments previously mentioned using confocal microscopy. Topical niosomes can behave as a solubilization matrix, local depot for sustained release of dermally active chemicals, penetration enhancers, or rate-limiting membrane barrier for regulating medication systemic absorption [69].

Niosomes as carriers for Hemoglobin:

Hemoglobin can be transported by niosomes. Niosomal suspension exhibits a visible spectrum that can be superimposed, and is most likely to be or, onto that of free haemoglobin. Oxygen can pass through vesicles, and the haemoglobin dissociation curve can be changed in a manner comparable to that of non-encapsulated haemoglobin. Anti-neoplastic Treatment The majority of antineoplastic medications have serious side effects. Niosomes can modify metabolism, extend drug circulation, and lengthen drug half-life, all of which reduce drug side effects. Niosomes are associated with a slower rate of tumour clearance and greater plasma levels as well as a slower rate of tumour proliferation [69].

Diagnostic imaging with niosomes –

It can serve as a diagnostic tool. An encapsulated paramagnetic agent tested with MRI that is in a conjugated niosomal formulation of gadobenate dimeglumine with [N-palmitoyl glucosamine (NPG)],PEG 4400, and both PEG and NPG exhibit much superior tumour targeting [70].

Conclusion:

Niosomes may function as a fantastic nano-vesicle delivery platform and provide a promising method for the delivery of chemical drugs, protein drugs and gene materials for the purpose of disease prevention and treatment. Compared with liposomes, they have some advantages, such as good chemical and physical stability, low cost and easy formulation. They may prove to be an alternative to liposomes and attract extensive attention in the field of pharmaceutics. More work may be undertaken in the fields below to yield more information for niosome development

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