NIOSOMES: AS PROMISING VEHICLE FOR NOVEL DRUG DELIVERY SYSTEM A REVIEW

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ABSTRACT

Novel drug delivery is a recent system which easily promotes and convenient route of administration and while also offering benefits over conventional dosage form. Niosomes are novel drug delivery system (NDDS). They are tiny non-ionic surfactant bilayer vesicles that are formed by hydrating synthetic non-ionic surfactants in aqueous media with or without cholesterol or other lipids, resulting in a lamellar structure that encapsulates both lipophilic and hydrophilic drugs. They are structurally similar to liposomes in that they are made up of bilayers and are thought to be a better carrier for drug delivery due to characteristics such as stability, cost, and storage conditions. Niosomes are a promising vehicle for drug delivery because they are non-ionic, more stable, and less expensive. They are also biodegradable, biocompatible, non-immunogenic, and have structural flexibility.

Niosomal drug delivery is potentially applicable to many of pharmacological agents for their action against various diseases. Encapsulation of a drug in the vesicular system is expected to prolong its presence in the systemic circulation and improve penetration into target tissue, as well as potentially lowering toxicity if selective uptake is achieved. For the treatment of cancer, viral infections, and other microbial disorders, niosomes have been extensively studied for controlled release and targeted administration. This overview covers the basics of niosomes, including as their structural components, preparation methods, limits, and current applications to a various disorder.

KEYWORDS: Niosomes, Composition, Types, Method of preparation, Factors affecting, Applications.
INTRODUCTION
In a current research and development approach relies for developing drug delivery methods that allow clinically proven drugs to work at best in treatment instead for searching of new drugs. The goal of any drug delivery has always aim for highest therapeutic action with minimum side effects.[1] The targeted drug delivery referred to the selective and effective localisation of a pharmacologically active component at a pre-determined (preselected) therapeutic concentration while limiting its access to non-target normal cellular linings, hence reducing toxicity and increasing therapeutic index.[2] As carriers for drug administration, immunoglobulin, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, and niosomes have all been used.[3] Liposomes and niosomes are two well-known drug delivery vehicles.[4]

Niosomes are the novel drug delivery system (NDDS). Niosomes are microscopic lamellar structures of size range between 10 to 1000 nm³ and these are non-ionic surfactant vesicles formed by hydrating synthetic non-ionic surfactants, with or without incorporation of cholesterol or other lipids.[5] and they are formed by the self-assembly of non-ionic surfactants in the aqueous media resulting inside closed bilayer structures (unilamellar or multi-lamellar).[6] which are entraps the hydrophilic drug into the core cavity and hydrophobic drugs in the non-polar area of the bilayer therefore both hydrophilic and hydrophobic drugs can be incorporated to niosomes.[7] These are vesicular systems that are almost similar to liposomes vesicles and are used as drug carriers in amphiphilic or lipophilic environments.[8] Liposomes are first vesicular drug delivery systems however they are having number of drawbacks, including low cost, toxicity and stability issues. Due to over the disadvantages of liposomes, research interest to move towards niosomes.[9] Chemical stability, biodegradability, non-immunogenic, biocompatibility, low production cost, low toxicity, easy for storage and handling are the main goals of niosomal system development.[7] The non-ionic surfactant vesicles are microscopic lamellar structures which are formed by admixture of non-ionic surfactant such as alkyl or dialkyl polyglycerol ether is mixed with cholesterol and then hydrated in aqueous conditions. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant like Span 60 is normally stabilised with cholesterol and little quantity of anionic surfactant like dicetyl phosphate.[5] Niosomes can be used for the sustained, controlled as well as targeted delivery of drugs.[9] And niosomes can be administer by various routes such as oral, ocular, topical, parenteral, etc. In a recent years niosomal formulations are widely used as a carrier to deliver the different types of drugs such as (herbal
and synthetic), hormones, antigens, and other bioactive compounds.[10]

STRUCTURAL COMPONENTS OF NIOSOMES
In the preparation of niosomes the two main components are used that are, Non-ionic surfactant and Cholesterol. Cholesterol is used for give rigidity and appropriate shape and Surfactant is essential for the development of niosomes. The subsequent non-ionic surfactants are usually used to prepare a niosomes are spans(span20,40,60,65,80,85), tweens (tween 20,40,60,80) and brij (brij 30,35,52,58,72,76). The non-ionic surfactants have a hydrophilic head and hydrophobic tail. The entrapment of drug in structure of niosome is shown in Fig no.1.[11]

![Image of niosome structure]

**Fig. 1 Structure of niosome.**

Niosomes are mainly contain following components

**Non-ionic surfactants**
The non-ionic surfactants form closed bilayer vesicle in aqueous media based on their amphiphilic nature using some energy for instance heat, physical agitation to form this structure. The hydrophobic sections of the bilayer structure are oriented away from the aqueous solvent, while the hydrophilic heads remain in contact with the aqueous solvent. Selection of surfactant must be done on the basis of hydrophilic lipophilic balance (HLB) value. HLB number between 4 to 8 was found to be compatible with vesicle formation. The surfactants are amphiphilic, biodegradable and non-immunogenic in nature. The following types of non-ionic surfactants used for the development of niosomes.[12]

**Alkyl Ethers:** L’Oréal tell some surfactants for the creation of niosomes containing drugs such as Diglycerol ether with an average of the 7 glycerol units and molecular weight is 972. And C16 mono alkyl glycerol ether is another surfactant which has an average of three glycerol units with molecular weight of 473. An ester linked surfactant (MW 393) is another example. Additionally, alkyl glycoside, alkyl glycerol and alkyl ether carrying poly hydroxyl
head groups are also used for formulation of niosomes.

**Alkyl Esters:** Sorbitan esters are surfactants recommend commonly used in the preparation of niosomes. Vesicles prepared by the polyoxyethylene sorbitan monolaurate they are more soluble than other surfactant vesicles. For instance, polyoxyethylene (polysorbate 60) are used to encapsulate of diclofenac sodium. For example, polyoxyethylene-10-stearyl ether: glyceryl laurate: cholesterol (27:15:57) are use as a part of transdermal delivery of cyclosporine-A.

**Alkyl Amides:** Alkyl amide (e.g., galactosides and glucosides) are used to deliver niosomal vesicles.

**Fatty Acid and Amino Acid Compounds:** Long chain fatty acids and amino acid moieties has also used in some niosomal preparation.[13]

**Cholesterol**
It’s a waxy steroid metabolite present in a cell membrane. Cholesterol is normally added to the non-ionic surfactants for provide stiffness and proper shape in the niosomal bilayer. Cholesterol and its derivatives are the most prevalent additives discovered in niosomal systems. Cholesterol permits to the formation of vesicles, membrane permeability, lowers aggregation and improves stability. The formation of aggregates by repulsive steric or electrostatic forces that leads to the move from the gel to the liquid phase in the niosomal systems proceed in niosomes that are less leaky in nature.[14]

**Charge Inducers**
Charge inducers boost vesicle stability by introducing charge to the surface of the produced vesicles. It works by preventing vesicle fusion caused by repulsive forces of the same charge, resulting in greater zeta potential levels. Dihexadecyl phosphate, diacetyl phosphate, and lipoamine acid are some of the most often employed negative charge compounds. Similarly, styryl pyridinium chloride and sterylamine are the well-known positively charged inducers used in the preparation of niosomes.[15] These charged molecules are mainly used to prevent aggregation of Niosomes. Maltodextrin is a polysaccharide, it’s minimum solubility in organic solvent. So, it’s possible to coat maltodextrin particles by simply adding of surfactant in organic solvent.[16] Usually, the charged molecule is added in niosomal preparation in an amount of 2.5–5 mol%. However, increasing the number of charged molecules can prevent the production of niosomes.[17]
Table 1: The materials used in niosomal preparation.[18]

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Nonionic surfactants</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Alkyl ethers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Alkyl glycerol ethers</td>
<td>Hexadecylglycerol ether (C16G2)</td>
</tr>
<tr>
<td></td>
<td>b. Polyoxyethylene glycol alkyl ethers (Brij)</td>
<td>Brij 30, Brij 52, Brij 72, Brij 76, Brij 78</td>
</tr>
<tr>
<td>2.</td>
<td>Alkyl esters</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Sorbitan fatty acid esters (Spans)</td>
<td>Span 20, Span 40, Span 60, Span 80, Span 65, Span 85</td>
</tr>
<tr>
<td></td>
<td>b. Polyoxyethylenesorbitan fatty acid esters (Tweens)</td>
<td>Tween 20, Tween 40, Tween 60, Tween 80, Tween 65, Tween 85</td>
</tr>
<tr>
<td>3.</td>
<td>Alkyl amides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Glycosides</td>
<td>C-Glycoside derivative surfactant</td>
</tr>
<tr>
<td></td>
<td>b. Alkyl polyglucosides</td>
<td>Octyl-decylpolyglucoside (OrCG110), decylpolyglucoside (OrNS10)</td>
</tr>
<tr>
<td>4.</td>
<td>Fatty alcohols or fatty acids</td>
<td>Stearyl alcohol, cetyl alcohol, myristyl alcohols</td>
</tr>
<tr>
<td></td>
<td>b. Fatty acids</td>
<td>Stearic acid, palmitic acid, myristic acid</td>
</tr>
<tr>
<td>5.</td>
<td>Block copolymer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Pluronic</td>
<td>Pluronic L64, Pluronic 105</td>
</tr>
<tr>
<td>6.</td>
<td>Lipidic components</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cholesterol and 1-α-Soya phosphatidyl choline</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Charged molecule</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Negative charge</td>
<td>Diacetyl phosphate, phosphatidic acid, lipoamino acid, dihexadecyl phosphate</td>
</tr>
<tr>
<td></td>
<td>b. Positive charge</td>
<td>Stearylamine, stearylpyridinium chloride, cetylpyridinium chloride</td>
</tr>
</tbody>
</table>

Advantages of Niosomes[4,8,12]

1. Niosomes are osmotically active and stable. As a result, they improve the stability of the entrapped drugs.
2. Niosomes are non-ionic surfactants that are biodegradable, biocompatible, and non-immunogenic.
3. It improves permeability of drugs through skin.
4. It increases the oral bioavailability of drugs.
5. Better patient compatibility and better therapeutic impact than conventional.
6. Handling and storage of surfactants do not require any specific conditions.
7. Oral, parenteral, and topical methods can all be used to get them to the site of action.
8. Improve the therapeutic effectiveness of the drug by protecting from the biological environment and restrict effects to target cells, thereby reducing the clearance of the drug.
9. Changes in vesicle composition, lamellarity, size, surface charge, tapping volume, and concentration can all be used to control vesicle performance.
10. They have an architecture that combines hydrophilic, amphiphilic, and lipophilic moieties, allowing them to contain drug molecules with a variety of solubilities.
11. The vesicles may act as a depot, releasing the drug in a controlled manner.
12. The structure of niosomes protect drug ingredients from heterogeneous factors present both inside and outside the body, so niosomes could be used for the delivery of labile and sensitive drug.

**Various Types of Niosomes**

The niosomes are classified according to the number of bilayers (e.g., MLV, SUV), the size of the bilayers (e.g., LUV, SUV), or the form of preparation (e.g., REV, DRV). The different various types of niosomes are described below:[16]

- Small Uni-lamellar Vesicle (SUV) - size = 0.025 – 0.050 µm.
- Large Uni-lamellar Vesicle (LUV) - size = > 0.100 µm.
- Multi Lamellar Vesicle (MLV) - size = > 0.050 µm.

**Small Uni-lamellar Vesicle (SUV)**

The most popular techniques of preparation are sonication, French press, and extrusion. They have a high thermodynamic instability and are susceptible to aggregation and fusion. The entrapped amount is small, and the entrapment percentage is low.[6] French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.[19]

**Large Uni-lamellar Vesicle (LUV)**

These are prepared by ether injection and reverse phase evaporation method. This form of
vesicle has a high aqueous lipid compartment ratio, allowing for larger amounts of bioactive materials to be encapsulated with a very economical use of membrane lipids. As compared to multi-lamellar vesicles, these have a range of benefits, including high encapsulation of water-soluble drugs, lipid economy, and a repeatable drug release rate. Due to large size of the vesicles can be captured, a high percentage capture rate is often achieved.\textsuperscript{[6]} large unilamellar vesicles vary in size from 100 to 3000 nm in length.\textsuperscript{[20]}

**Multi Lamellar Vesicle (MLV)**

These are prepared by thin film hydration method. They have a higher amount of trapped volume. It’s easy to produce, and they’re mechanically stable even when stored for a long time. Lipophilic compounds are well-suited to these vesicles as drug carriers.\textsuperscript{[6]}

Some Other Types of Niosomes are

**Bola surfactant containing niosome**

Bola surfactant containing niosomes are the surfactants these are made up of omegahexadecylbis-(1-aza-18 crown-6) (bolasurfactant): span- 80/cholesterol in 2:3:1molar ratio.\textsuperscript{[18]}

**Proniosomes**

Proniosomes are the niosomal formulation it will be containing both a carrier and a surfactant. Before being used, it must be hydrated. The formation of aqueous noisome dispersion occurs as a result of hydration. The number of proniosomes decreases the problem of aggregation, leakage, and fusion linked with the synthesis of niosomes. In terms of packaging, transport, and dosing, proniosomes-derived niosomes outperform traditional niosomes. Stability of dry
proniosomes is predicted to be higher than a pre-manufactured niosomal formulation. Proniosomes appear to be equivalent to conventional niosomes in release studies. Since the size distributions of proniosomes derived niosomes are slightly better than those of traditional niosomes, after oral administration and controlled release, the release will entrap proteineous drugs and protect them from enzymatic degradation.\[21\]

**Aspasomes**
Aspasome is a nano carrier that is made by combining highly charged particles like cholesterol, palmitate, and lipid diacetyl phosphate. Niosomes are made by hydrating aspasomes with water or an aqueous solution and then sonicating them. Aspasomes are frequently employed in transdermal medication administration systems to improve medication penetration into the skin. Because of their built-in antioxidant property, aspasomes have become more important for reducing diseases induced by reactive oxygen species (ROS).\[8\]

**Discomes**
Discomes are niosomes that look like huge discs. Uchegbu and colleagues previously used mechanical agitation and sonication to manufacture discomes from hexadecyl di-glycerol ether, cholesterol, and dicetyl phosphate. They discovered that discomes were large (11–60 m) and that their size increased by after sonicatation. Discomes are also thermoreponsive; as the temperature rises over 37 °C, their structure becomes less or gained. Abdelkader et al. looked into discomes for naltrexone ocular administration in the treatment of diabetic keratopathy.\[22\]

**Elastic niosomes**
Elastic niosomes are niosomes that are flexible enough to pass through opening that are smaller than their size without losing their structure. Surfactants, cholesterol, water, and ethanol are all components of these vesicles. Because of their capacity to penetrate through microscopic pores and hence improve penetration through the skin barrier, they are often utilised in topical or transdermal medication delivery. Manosroi and colleagues developed elastic niosomes for transdermal administration of diclofenac diethyl ammonium, which had a deformability index 14 times that of conventional niosomes. Another study by the same group of researchers discovered that elastic niosomes produced with sodium cholate increased papain transdermal delivery for scar therapy.\[22\]

**Transfersomes**
Transfersomes are deformable vesicular carrier systems that self-assemble into a lipid bilayer
in an aqueous media and close to form vesicle. To increase lipid bilayer flexibility and permeability, a lipid bilayer softening component is applied. This is called edge activator. An edge activator is usually a non-ionic single-chain surfactant that destabilises the lipid bilayer, enhancing its fluidity and elasticity. Both hydrophobic and hydrophilic transfersomes exist as a result, drug molecules can be accommodated by hydrophilic moieties a diverse variety of solubilities. They have the ability to transport both low and large molecular weight drugs.\[22\]

**Polyhedral Niosomes**

Polyhedral niosomes are spherical vesicles but these are non-uniform vesicles. Polyhedral niosomes have 4 to 12 sides that are all the same length. The niosomes were made from a mixture of hexadecyl diglycerol ether (C16G2) and solulan C24 by Uchegbu and Florence, 1995; Uchegbu et al., 1997; and Uchegbu and Vyas, 1998. A small amount of cholesterol also be added to this mixture to form these. Polyhedral niosomes can also be made by combining C16EO5 with solulan-C24 in a low alcohol concentration.\[9\]

**PEGylated niosomes**

Niosomes coated with polyethylene glycol (PEG) have the capacity to escape the mononuclear phagocytic system's (MPS) absorption, allowing the encapsulated medication to stay in the circulation for longer. By connecting monostearate to the hydrophilic PEG chain, He et al. created PEGylated paenol niosomes. The lipid core of the vesicles is easily integrated with these molecules. To overcome these problems of poor solubility and bioavailability, Lin et al. produced PEGylated niosomes of gambogenic acid. And Span 60, cholesterol, and dicetylphosphate can be used to make these niosomes. The preparation is done using the ether injection method. These are then changed with polyethylene glycol monostearate -15 once they have been prepared. For cancer treatment, Ashraf Alemi et al. produced cationic PEGylated niosomes for the co-administration of paclitaxel and curcumin.\[9\]

**Niosome incorporated with carbopol gel**

Drugs, spans, and cholesterol was used to form a niosomes. The resulting niosomes were then mixed into a carbopol-934 gel (1 percent w/w) base containing propylene glycol (10% w/w) and glycerol (30% w/w). In vitro diffusion experiments of niosomal gel, plain drug gel, and marketing gel was carried by in a diffusion cell using human cadaver skin. When niosomal gels were compared to ordinary drug gels, the mean flow value and diffusion co-efficient were found to be five to seven times lower.\[21\]
Vesicles in water and oil system (v/w/o)
When an aqueous niosomes are emulsified in an oil phase, a nano carrier water is formed in the oil emulsion (v/w/o). Which produces nano vesicles in water in oil gel (v/w/o gel) after cooling to room temperature? The v/w/o gel for controlled release of drug or protein can capture proteinous drugs or drugs that are protected from enzyme breakdown after being administered orally, such as a solution made up of sorbitol monostearate, cholesterol, and solulan C24.[8]

Niosomes of hydroxyl propyl methyl cellulose [HPMC]
For this form of formulation, a base was first made with 10% HPMC and then niosomes were added, result in the greater bioavailability of the pharmaceuticals in this system.[8]

Separation of Unentrapped Drug
The various procedures, such as dialysis, gel filtration and centrifugation, can be used to remove unentrapped solute from vesicles.

Dialysis
Niosomal dispersions are extremely soluble in both aqueous and organic media, and the detergent molecules in a water phase and the micelle mixture are in balance. The critical micelle concentration can indicate where this equilibrium is located. Dialysis can used to remove detergent molecules from mixed micelles when the concentration of detergent in the bulk aqueous phase is reduced. A larger CMC shows the equilibrium has shifted strongly towards the bulk solution, making dialysis removal from the mixed membrane easy. At appropriate intervals, samples are removed from the medium, centrifuged, and tested for drug content using appropriate methods (U.V. spectroscopy, HPLC etc).[12]

Gel filtration
The unentrapped drug are removed by gel filtration of niosomal dispersion using a Sephadex-G-50 column, which is then eluted with appropriate mobile phase and evaluated using appropriate analytical techniques.[23]

Centrifugation
The free drug are separated after 30 minutes of centrifugation of niosomal suspension. To get a niosomal suspension free of unentrapped drug, the supernatant solution is decanted, and the precipitate is washed and resuspended in phosphate buffer.[24]
Comparison of liposomes and niosomes

Non-ionic surfactants and cholesterol make up niosomes. Most surfactants, such as sodium dodecyl sulphate, have a single hydrophobic tail. Liposomes, on the other hand, contain phospholipid and may or may not contain cholesterol. The hydrophobic tails of phospholipids are two.\[^5\] The Behaviour of niosomes *invivo* is just like liposomes. Niosomes can modify metabolic stability and medication supply to specific organs by increasing the presence of encapsulated drugs in systemic circulation.\[^25\] Niosomes are usually more resistant to oxidative degradation because liposome phospholipids are more prone to oxidative degradation. Liposomes are more expensive and require particular storage and handling, whereas niosomes are less expensive and easier to make and store.\[^5\]

Mechanisms of Niosomes Penetration Through Skin Delivery

There is no one mechanism that can adequately explain niosomes potential to promote drug transfer through the skin, and various mechanism has been proposed, including: change of the stratum corneum's barrier function as a result of reversible lipid organisation; reduction of transepidermal water loss, which increased hydration of the stratum corneum loosens its tightly packed cellular structure and adsorption and/or fusion of niosomes on the skin's surface, As revealed by freeze fracture electron microscopy and small angle X-ray scattering, resulting in a high thermodynamic activity gradient of drug at the interface, which is the driving force for drug permeation.

Adsorption of niosomes onto the cell surface happens with little or no internalisation of aqueous or lipid components; it can occur as a result of attractive physical forces or as a result of specialised receptors attaching to ligands on the vesicle membrane and drug transfer from vesicles to the skin. On the other hand, niosomes can fuse with the cell membrane, causing theniosomal contents to be completely mixed with the cytoplasm. Finally, niosomes can be absorbed by a cell (endocytosis), with cytoplasmic lysozymes dissolving or digesting the niosomes membrane structure, releasing the contained contents into the medium.\[^26\]
Methods of Preparation

Various methods are used for the preparation of niosomes are:

1. Hand shaking method (Thin film hydration technique).
2. Ether injection method.
4. Reverse phase evaporation technique (REV).
5. Micro fluidization.
7. Trans membrane pH gradient (inside acidic) druguptake process (remote loading).

Hand shaking method (Thin film hydration technique)

In a round bottom flask, a mixture of vesicles-forming components such as surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform, or methanol). The organic solvent is evaporated using a rotary evaporator at room temperature (20°C), leaving a thin layer of solid mixture on the flask wall. With gentle agitation, the dried surfactant film can be rehydrated with aqueous phase at 0-60°C. Multilamellar niosomes are formed as a result of this process. It is noted that addition of the drug to the system depends on the nature of the drug, a hydrophilic drug can be introduced to the aqueous phase, but a hydrophobic drug only can be dissolved in an inorganic solvent with other components.[20]
Ether injection method

The niosomes are prepared by using the ether injection method by infusing a surfactant solution mixed in diethyl ether (volatile organic solvent) into warm water kept at 60°C. With the use of a 14-gauge needle, the surfactant combination in ether is injected into an aqueous solution of material. Ether vaporization produces single-layered vesicles (volatile organic solvent).[18]
minutes using a sonicator with a titanium probe to obtain niosomes.\textsuperscript{[27]}

Fig. 6: Formulation of niosome by sonication method Reverse phase evaporation technique.

\textbf{(REV)}

The ingredients are dissolved in a mixture of volatile organic solvents (ether and chloroform). After that, a drug-containing aqueous solution is added to the mixture, and the two phases are sonicated at 4-5°C. The transparent gel generated is then sonicated with the addition of phosphate buffer. The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with phosphate buffer solution and heat it for 10 minutes on a water bath at 60°C.\textsuperscript{[28]}

**Fig. 7: Formulation of niosome by reverse phase evaporation method.**

\textbf{Micro fluidization}

Micro fluidization is a relatively new technology for producing unilamellar vesicles with a specific size distribution. The submerged jet principle is used in this technology, in which two fluidized streams contact at ultra high velocities in precisely specified micro channels within the interaction chamber. The impingement of a thin liquid sheet along a common front is
arranged in such a way that the energy given to the system stays inside the niosome formation region. As a result, the niosomes generated have improved uniformity, smaller size, and reproducibility.\textsuperscript{[29]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig8.png}
\caption{Micro fluidization method.}
\end{figure}

\textbf{Multiple membrane extrusion method}

The mixture of non-ionic surfactant, cholesterol, and di-acetyl phosphate is dissolved in chloroform and evaporated. As a result, a thin layer forms, followed by hydration of the aqueous phase; the niosome suspension is then transported through a polycarbonate membrane which are arranged in a series of eight passage. As a result, this method focuses on controlling the size of niosomes.\textsuperscript{[30]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig9.png}
\caption{Multiple membrane extrusion method.}
\end{figure}
Trans-membrane pH gradient (inside acidic) drug uptake process (Remote Loading)

The solution of surfactant and cholesterol is generated in chloroform, then the solvent is evaporated under decreased pressure to generate a thin film on the walls of the round bottom flask in the trans membrane pH gradient drug absorption process. After that, citric acid is used to hydrate the film. The freeze-thaw process is used to create multilamellar vesicles, which are then sonicated. Finally, an aqueous solution of 10 mg/ml of drug is added to the noisome suspension and vortexed, after which the pH is raised to 7.0-7.2 with 1M disodium phosphate. To make niosomes, this mixture is heated for 10 minutes at 60°C.\textsuperscript{131}

![Diagram of the preparation of niosomes via the trans-membrane pH gradient drug uptake process.](image)

**Fig. 10:** Schematic diagram of the preparation of niosomes via the trans-membrane pH gradient drug uptake process.

**Bubble method**

It is a unique technology for manufacturing liposomes and niosomes in a single step without the use of organic solvents. To adjust the temperature, the bubbling unit consists of a round-bottomed flask with three necks positioned in a water bath. The first and second necks have a water-cooled reflux and thermometer, and the third neck has a nitrogen supply. Cholesterol and surfactants are dispersed together in this buffer (PH 7.4) at, the dispersion is stirred for 15 seconds with a high shear homogenizer, and the mixture is immediately “bubbled” with nitrogen gas at 70°C.\textsuperscript{132}
Fig. 11: Schematic diagram of the preparation of niosomes via the bubble method.

**Formation of niosomes from proniosomes**

Another way to make niosomes is to use a surfactant to cover a water-soluble carrier like sorbitol. The coating technique produces a dry formulation. A thin coat of dry surfactant is applied to each water-soluble particle. This preparation is known as “Proniosomes”. The niosomes are identified by the addition of aqueous phase at $T > T_m$ and brief agitation.

$T = $ Temperature.

$T_m = $ mean phase transition temperature.

Fig. 12: Formation of niosomes from proniosomes.

The formation of niosomes from maltodextrin-based proniosomes has been reported by Blazek-Walsh A.I. et al. This allows for quick niosome reconstitution with minimum residual carrier.
The maltodextrin and surfactant slurry were dried into a free-flowing powder that could be rehydrated with warm water.\[^{33}\]

**Table 2: Recent researches loading various drugs on to noisome.**

<table>
<thead>
<tr>
<th>NO.</th>
<th>Drug used</th>
<th>Application</th>
<th>Components</th>
<th>Method used</th>
<th>Route of administration</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Baclofen</td>
<td>For anti-inflammatory effect</td>
<td>Span-40,60 Cholesterol</td>
<td>Thin film hydration (TFH) method</td>
<td>Topical</td>
<td>[34]</td>
</tr>
<tr>
<td>2.</td>
<td>Salbutamol sulphate</td>
<td>Anti-asthmatic drug</td>
<td>Tween-20,40,60,80 Span-20,40,60,80 Brij 35 Cholesterol diethylether</td>
<td>Transmembrane pH gradient method</td>
<td>Oral</td>
<td>[35]</td>
</tr>
<tr>
<td>3.</td>
<td>Benzoyl peroxide and Adapalene</td>
<td>Treatment for acne</td>
<td>Cholesterol Span-40,60,85 Chloroform</td>
<td>Thin film hydration method</td>
<td>Transdermal</td>
<td>[36]</td>
</tr>
<tr>
<td>4.</td>
<td>Metformin hydrochloride</td>
<td>To enhance bioavailability</td>
<td>Span-40 Cholesterol Dicetyl phosphate</td>
<td>Reverse phase evaporation (REV)</td>
<td>Oral</td>
<td>[37]</td>
</tr>
<tr>
<td>5.</td>
<td>Methotrexate</td>
<td>To improve the therapeutic efficacy of drug in cancer therapy, parasitic, viral &amp; microbial disease</td>
<td>Span-20,40,60 Tween-40,60,80</td>
<td>TFH</td>
<td>Intravenous</td>
<td>[38]</td>
</tr>
<tr>
<td>7.</td>
<td>Erythromycin</td>
<td>To enhance skin penetration as well as to improve skin retention of drug</td>
<td>Span-20,60,80 Cholesterol Chloroform Methanol</td>
<td>TFH</td>
<td>Topical</td>
<td>[40]</td>
</tr>
<tr>
<td>8.</td>
<td>Zidovudine</td>
<td>Treatment of AIDS</td>
<td>Span-60,80 Tween-20,40,60,80</td>
<td>TFH</td>
<td>Oral</td>
<td>[41]</td>
</tr>
<tr>
<td>9.</td>
<td>Aceclofenac</td>
<td>Treatment of rheumatoid arthritis</td>
<td>Span-20,60 Cholesterol methanol</td>
<td>Ether injection method</td>
<td>Oral</td>
<td>[42]</td>
</tr>
<tr>
<td>10.</td>
<td>Azithromycin &amp; Prednisolone</td>
<td>Treatment of osteoarthritis and ankylosing spondylitis</td>
<td>Cholesterol Span-40,60 Diethyl ether</td>
<td>Ether injection method</td>
<td>Topical</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Etoricoxib</td>
<td>Treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gout arthritis</td>
<td>Span-60 Tween-80 Cholesterol Diethyl ether Chloroform Methanol</td>
<td>TFH &amp; Ether injection method</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Ciprofloxacin</td>
<td>Treatment for pulmonary diseases</td>
<td>Tween-40,60 Span-40,60 Cholesterol</td>
<td>Transmembrane pH gradient uptake process</td>
<td>Pulmonary</td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Oxcarbazepine</td>
<td>To improve anticonvulsant activity</td>
<td>Cholesterol Span Chloroform Methanol</td>
<td>TFH</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>Prednisolone sodium phosphate</td>
<td>To increase bioavailability and sustained action</td>
<td>Span-60,80 Tween- 20,80 Cholesterol Methanol</td>
<td>TFH &amp; Ethanol injection method</td>
<td>Ocular</td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>Etodolac</td>
<td>To improve oral bioavailability</td>
<td>Span-20,40 Tween- 20,40 Diethyl ether</td>
<td>Ether injection method</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>Minoxidil</td>
<td>To improve the low skin permeation &amp; bioavailability</td>
<td>Brij-52,76 Span-20,40,60 Dicetyl phosphate</td>
<td>TFH</td>
<td>Topical</td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>Atorvastatin calcium</td>
<td>Treatment for hyperlipidemia</td>
<td>Span-20,40 Tween- 20,40 Cholesterol</td>
<td>Ether injection method</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Doxycycline hyclate</td>
<td>To increase bioavailability &amp; improve their efficacy</td>
<td>Span-20,60,80 Tween-60 Cholesterol</td>
<td>TFH &amp; Reverse phase evaporation (RFV)</td>
<td>Ocular</td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>Acyclovir</td>
<td>To improve oral bioavailability of the drug</td>
<td>Span-80 Cholesterol Diethyl ether</td>
<td>Hand shaking process &amp; Ether injection</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Acetazolamide</td>
<td>Treatment of glaucoma &amp; also to improve low corneal penetration &amp;</td>
<td>Span-40,60 Cholesterol Diethyl ether Chloroform Methanol</td>
<td>TFH &amp; RFV</td>
<td>Ophthalmic</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Drug</td>
<td>Application</td>
<td>Methods</td>
<td>Route</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>-----</td>
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<td>-------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>Rosuvastatin calcium</td>
<td>To improve dissolution &amp; permeability</td>
<td>Span-80 Cholesterol Methanol, TFH</td>
<td>Oral</td>
<td>[54]</td>
<td></td>
</tr>
<tr>
<td>22.</td>
<td>Paclitaxel</td>
<td>Treatment of cancer such as lung, ovarian, breast, neck cancer</td>
<td>Span-40 Dicetyl phosphate Cholesterol, TFH</td>
<td>Intravenous</td>
<td>[55]</td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>Asenapine maleate</td>
<td>To increase bioavailability &amp; treatment of schizophrenia</td>
<td>Span-60 Cholesterol Chloroform, Hand shaking &amp; sonication method</td>
<td>Oral</td>
<td>[56]</td>
<td></td>
</tr>
<tr>
<td>24.</td>
<td>Clotrimazole</td>
<td>To increase retention time in the dermis layer through controlled release of the drug</td>
<td>Span-40 Cholesterol Chloroform, Thin film evaporation method</td>
<td>Topical</td>
<td>[57]</td>
<td></td>
</tr>
<tr>
<td>25.</td>
<td>Capecitabine</td>
<td>Treatment for colorectal cancer &amp; breast cancer</td>
<td>Span-40,60 Tween-40,60 Cholesterol, TFH</td>
<td>Oral</td>
<td>[58]</td>
<td></td>
</tr>
<tr>
<td>26.</td>
<td>Ibuprofen</td>
<td>Treatment of rheumatoid arthritis</td>
<td>Span-20,60,80 Cholesterol, TFH &amp; Ether injection method</td>
<td>Topical</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>27.</td>
<td>Lornoxicam</td>
<td>To improve the permeation &amp; anti-inflammatory activity</td>
<td>Span-40 Dicetyl phosphate Sterylamine, TFH</td>
<td>Transdermal</td>
<td>[60]</td>
<td></td>
</tr>
<tr>
<td>28.</td>
<td>Beclomethasone dipropionate</td>
<td>Anti-asthma drug</td>
<td>Span-60 Cholesterol, TFH</td>
<td>Pulmonary</td>
<td>[61]</td>
<td></td>
</tr>
<tr>
<td>29.</td>
<td>Itraconazole</td>
<td>To enhance the antifungal activity</td>
<td>Span-20,40,60 Cholesterol, TFH</td>
<td>Topical</td>
<td>[62]</td>
<td></td>
</tr>
<tr>
<td>30.</td>
<td>Lamivudine</td>
<td>Treatment of AIDS &amp; Hepatitis</td>
<td>Span-60 Cholesterol, TFH</td>
<td>Transdermal</td>
<td>[63]</td>
<td></td>
</tr>
<tr>
<td>31.</td>
<td>Dexamethasone</td>
<td>Treatment of anti-inflammatory condition, cerebral edema, in alcohol withdrawal syndrome &amp;</td>
<td>Span-60 Tween 20,80 Cholesterol Dicetyl phosphate Sterylamine, Hand shaking method</td>
<td>Topical</td>
<td>[64]</td>
<td></td>
</tr>
</tbody>
</table>
congenital
adrenal
hyperplasia,
cerebral malaria

FACTORS AFFECTING FORMULATION OF NIOSOME

Drug

Entrapment of drugs in niosomes increases vesicle size, most likely through raising the charge and mutual repulsion of surfactant bilayers or the interaction of solute with surfactant head groups. However, because some drugs are imprisoned in long PEG chains in polyoxyethylene glycol (PEG)-coated vesicles, the tendency to increase in size is reduced. The drug's hydrophilic lipophilic balance influences the degree of entrapment.\[3\]

Amount and type of surfactant

Because the surface free energy drops as the hydrophobicity of the surfactant increases, the mean size of niosomes grows proportionally as the HLB of the surfactant increases, such as from Span 85 (HLB 1.8) to Span 20 (HLB 8.6). Depending on the temperature, the type of lipid or surfactant used, and the presence of additional components such as cholesterol, the bilayers of the vesicles are either liquid or gel. Alkyl chains are present in a well-ordered form in the gel state, whereas the structure of the bilayers is more disordered in the liquid state. The gel-liquid phase transition temperature distinguishes surfactants and lipids (TC). Entrapment efficiency is also affected by the phase transition temperature (TC) of the surfactant; for example, Span 60 with a higher TC has better entrapment.\[29\]

Cholesterol content and charge

Cholesterol was added to niosomes, which enhanced their hydrodynamic diameter and trapping effectiveness. Cholesterol has a two-fold effect: on the one hand, it raises the chain order of liquid-state bilayers, and on the other hand, it decreases the chain order of gel-state bilayers. The gel state is changed into a liquid ordered phase at high cholesterol concentrations. The release rate of encapsulated material was reduced as the cholesterol content of the bilayers increased, resulting in an increase in the rigidity of the bilayers. In a multilamellar vesicle structure, the presence of charge tends to increase the interlamellar distance between successive bilayers, resulting in a larger overall entrapped volume.\[23\]

Resistance to osmotic stress

When a hypertonic salt solution is added to a niosome suspension, the diameter of the niosomes
shrinks. Slow release with small enlargement of vesicles occurs in hypotonic salt solution, possibly due to inhibition of eluting fluid from vesicles, followed by faster release, possibly due to mechanical loosening of vesicle structure under osmotic stress.\textsuperscript{[4]}

**Temperature of hydration**

Hydration temperature influences the shape and size of the noisome. For ideal condition it should be above the gel to liquid phase transition temperature of system. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation.\textsuperscript{[11]}

**Characterization of niosomes**

Niosomes are characterized for the following parameters

**Visual appearance**

To examine for turbidity, flocculation, and sedimentation, niosomal dispersion is placed in clear containers.\textsuperscript{[6]}

**Bilayer formation**

Under light polarisation microscopy, niosomes are created by the interaction of surfactants to form bilayer vesicles, which are characterised by the development of X-crosses. Under light polarisation microscopy, niosomes are generated by the interaction of surfactants to form bilayer vesicles, which are characterised by X-cross formation.\textsuperscript{[31]}

**Number of lamellae**

This is used to determine a nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy.\textsuperscript{[33]}

**Angle of repose**

The angle of repose test, which is used to create the heap, is an extremely delicate procedure. Heap form measurement can be used to determine the angle of repose. The angle of repose can be measured using the traditional approach. The grains were allowed to freely flow out of the funnel onto the clean surface. The funnel was positioned so that the bottom tip did not contact the apex of the granule heap.

The following equation is used to calculate the angle of repose. \( \tan \Theta = \frac{h}{r} \) (1)
\[
\Theta = \tan^{-1} \left( \frac{h}{r} \right)
\] (2)
Where $\Theta$ is the angle of repose, $h$ is the height of heap in cm and $r$ is the radius of the circular support (cone) in cm.$^{[12]}$

**Average vesicle size, morphology and size distribution**

Light microscopy and coulter counter (for particles with diameters over 1 m), photon correlation spectroscopy, electron microscopic analysis (scanning electron microscopy (SEM), transmission electron microscopy (TEM), freeze fracture replication-electron microscopy (FF-TEM)), and light scattering are all techniques that can be used to determine the size of niosomes. The size distribution of niosomes and the polydispersity index (PdI) can also be determined using a dynamic light scattering particle size analyzer. The size of vesicles can range from 20 nm to 50\,\mu m.$^{[65]}$

**Vesicle diameter**

Light microscopy, photon correlation microscopy, and freeze fracture electron microscopy can all be used to estimate the diameter of niosomes. Freeze thawing (vesicles suspended at 20°C for 24 hours, then heated to Niosomes (at room temperature) increase vesicle diameter, which could be due to vesicle fusion during the cycle.$^{[19]}$

**Bilayer Rigidity and Homogeneity**

The bilayer that forms in niosomes should be stiff in order to preserve its specific shape and homogenous in nature in order to achieve optimal drug distribution. Thus, p-NMR, differential scanning calorimetry (DSC), and Fourier transform-infrared spectroscopy (FT-IR) techniques can be used to measure bilayer stiffness and structural homogeneity. Fluorescence resonance energy transfer (FRET) was recently employed to gain a better understanding of the shape, size, and structure of niosomes.$^{[31]}$

**Surface charge**

Zeta Potential Measurement (Zeta Sizer)Free Flow Electrophoresis.$^{[6]}$

**Viscosity**

Viscosity is measured using viscometers and rheometers of various sorts. The measurement of fluid resistance to progressive deformation by shear stress or tensile stress is known as viscosity. The Ostwald viscometer is used to determine the viscosity of niosomes. As a result, the temperature maintained is at $25 \pm 0.5\, ^\circ C$ and $35 \pm 0.5\, ^\circ C.$$^{[66]}$
**PH Measurement**
A pH metre can be used to determine the pH of niosomes. The pH measurement is carried out at a temperature of 25°C.[13]

**Zeta Potential Measurement**
A zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method is used to determine the zeta potential of properly diluted niosome dispersion. The temperature is set at 25 °C. As a result, the charge on vesicles and their mean zeta potential values can be directly determined.[13]

**Entrapment efficiency (EE)**
The entrapment efficiency (EE) can be expressed as,

\[
\text{(% EE)} = (\text{Amount of drug entrapped/ total amount of drug}) \times 100.
\]
It can be determined after the medication has been partitioned and the vesicle has been completely destroyed with either 1ml of 2.5 % sodium lauryl sulphate or 50 % n-propanol. This is then mixed and centrifuged, and the resulting supernatant is tested for drug using appropriate dilutions.[8]

**Osmotic shock**
Osmotic investigations can be used to determine the change in vesicle size. For 3 hours, niosome formulations are incubated with hypotonic, isotonic, and hypertonic solutions. Optical microscopy is then used to examine the changes in the size of vesicles in the formulations.[23]

**In-vitro drug release**
In vitro drug release of niosomes can be determined by the following methods:
1. Dialysis
2. Franz diffusion cell

**Dialysis**
Dialysis is performed by depositing niosomal dispersion in a pre-washed and pre-soaked dialysis bag that is tied at both ends. The dialysis bag is suspended in a 37 °C dissolving media that is constantly stirred. At regular intervals, samples are withdrawn and replaced with new samples. The drug content of the removed samples is determined.

**Franz diffusion cell**
The donor and receptor compartments are divided by a cellophane membrane or a dialysis
membrane in this cell assembly. Niosomal dispersion is kept at 37°C in the donor compartment, while the dissolving media, phosphate buffer, is kept in the receptor compartment and Magnetic stirrer is used to stir continuously. The samples are taken out at regular intervals, replaced with fresh medium, and the drug content is determined.[24]

**Stability studies**

Stability studies are done by storing niosome at two different conditions, commonly 4 ± 1 °C and 25 ± 2 °C. Formulation size, shape and number of vesicles per cubic millimetre can be examined before and after storing for 30 days. After 15 and 30 days, residual drug can also be measured. The size of vesicles is determined using a light microscope and the numbers of vesicles per cubic millimetre is determined using a hemocytometer.[18]

**Table 3: Methods of Evaluation of Niosomes.**[71]

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Evaluation Parameter</th>
<th>Method/ Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Size distribution, Polydispersity index</td>
<td>Scanning electron microscopy (SEM), Dynamic light scattering particle size analyzer, Anderson cascade impactor, Malvern Mastersizer, Optical microscopy, Klotz® particle sizer</td>
</tr>
<tr>
<td>2.</td>
<td>Morphology</td>
<td>SEM, Optical microscopy, TEM, Quasi elastic light scattering technique, freeze fracture tech Phase Contrast microscopy, small angle X-ray diffraction (SA-XRD)</td>
</tr>
<tr>
<td>3.</td>
<td>Zeta potential</td>
<td>Malvern Zetasizer (zetameter) Microelectrophoresis meter</td>
</tr>
<tr>
<td>4.</td>
<td>Thermal analysis</td>
<td>DSC, Hot stage microscopy, DTA</td>
</tr>
<tr>
<td>5.</td>
<td>Membrane microstructure</td>
<td>Negative staining TEM</td>
</tr>
<tr>
<td>6.</td>
<td>Lamellarity</td>
<td>TEM, Optical microscopy</td>
</tr>
<tr>
<td>7.</td>
<td>Conductivity</td>
<td>Conductometer</td>
</tr>
<tr>
<td>8.</td>
<td>Viscosity</td>
<td>Oswalt-U-tube, Low shear rheoanalyser</td>
</tr>
<tr>
<td>9.</td>
<td>Permeation study</td>
<td>Franz diffusion cell</td>
</tr>
<tr>
<td>10.</td>
<td>Entrapment efficacy</td>
<td>Centrifugation, Dialysis, gel chromatography</td>
</tr>
<tr>
<td>11.</td>
<td>In-vitro release study</td>
<td>Dialysis membrane</td>
</tr>
</tbody>
</table>

**Applications of Niosomes**

**Drug Targeting**

Drug targeting is one of the most useful applications of niosomes. Niosomes have the ability to target both the reticuloendothelial system (RES) and other organs. The niosome vesicles are taken up by RES cells. The serum factor opsonin regulates the uptake of vesicles and marks them for elimination. This causes the drug to accumulate at the target site, and it is used to treat tumours in animals as well as parasite diseases of the liver. Antibodies, immunoglobulins and
other carrier systems can be coupled to niosomes to target specific organs.\(^{[67]}\)

**Leishmaniasis**

Leishmaniasis is a parasitic disease that infects the liver and spleen spread via a through female sandfly bite. Therapeutic efficacy of amarogentin (an antileishmanial, secoiridoid glycoside derived from Indian medicinal plant *Swertia chirata*) was investigate in an experimental model of leishmaniasis in hamster. The efficacy of amarogentin was compared using liposomes and niosomes as delivery vehicles to the infected region. Amarogentin encapsulated in niosomes was more effective than liposomes at the same level of membrane microviscosity.\(^{[67]}\)

**Anti-cancer drug**

**Daunorubicin HCl**

When compared to free medication, niosomal daunorubicin hydrochloride had a higher anticancer effectiveness. The niosomal formulation was able to kill Dalton's ascitic lymphoma cells in the peritoneum on the third day of treatment, whereas the free medication required six days and was ineffective. Hematological investigations also show that the niosomal formulation outperforms free drug therapy. The niosomal formulation resulted in a longer mean survival time, proving the formulation's overall efficacy.

**Doxorubicin**

Rogerson et al., looked at the distribution of niosomal doxorubicin made from C16 monoalkyl glycerol ether with or without cholesterol. The doxorubicin level in tumour cells, serum, and lungs was enhanced by the niosomal formulation, but not in the liver or spleen. Doxorubicin-loaded cholesterol-free niosomes reduced tumour proliferation and increased the lifespan of tumor-bearing mice. The cardiotoxicity of doxorubicin was minimised when it was formulated in a niosomal form. Doxorubicin's overall metabolic route is altered by niosomal formulation.

**Methotrexate**

According to Azmin et al., the niosomal formulation of methotrexate has a greater AUC than methotrexate solution, which can be delivered intravenously or orally. When compared to simple drug solution, noisomely-formulated methotrexate has a greater tumoricidal efficacy.

**Bleomycin**

Niosomal formulation of bleomycin containing 47.5 % cholesterol shows higher levels of drug in the liver, spleen, and tumour when compared to plan drug solution in tumor-bearing mice.
When comparing the niosomal formulation to the plain drug solution, there is no significant difference in drug concentration in the lungs. In addition, niosomal formulations result in less drug build-up in the stomach and kidney.

**Vincristine**

When compared to the plain drug formulation, the niosomal formulation of vincristine had a greater tumoricidal activity (Parthasarathi G et al., 1994). In addition, in S-180 lung carcinoma-bearing mice, the niosomal formulation of carboplatin has a stronger tumoricidal activity and has a lower bone marrow toxic effect than the standard drug solution.\[68\]

**Anti-infective agents**

Niosomes can be used to targeting of drug in the treatment of diseases in which the infectious organism is found in the organ of reticuloendothelial system. Leishmaniasis is a disease in which parasite infects cells of liver and spleen. The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney.\[69\]

**Antiviral**

After an intravenous bolus administration of zidovudine (ZDV), an anti-HIV medicine, the distribution of proniosomes and niosomes in the lungs, kidney, heart, liver, and spleen of mice was investigated. At 4 degrees Celsius, a Tween 80-based formulation was shown to have improved half-life, mean residence duration, and drug leakage. When compared to free drug solution, employing niosomes as a drug delivery vehicle improved ribavirin liver targeting by up to 6 times. Ribavirin niosomes have a considerable liver targeting property, which could improve ribavirin efficacy at low dosages while reducing harmful side effects at higher levels. The compositional parameters in tenofovir niosomes have a considerable impact on drug release. The niosomes were made with various compositions and their vesicular sizing parameters, electrical properties, drug entrapment data, and drug release characteristics were all investigated. The results showed that microfluidization can be used to produce anti-HIV niosomes with very small mean vesicular diameters and scale them up.\[15\]

**Delivery of Peptide Drugs**

The problem of bypassing the enzymes that would break down the peptide in oral peptide medication administration has long been a problem. Niosomes are being studied to see if they may successfully protect peptides from gastrointestinal peptide degradation. An in vitro
investigation using oral delivery of a vasopressin derivative entrapped in niosomes revealed that the drug's entrapment substantially increased the peptide's stability.\cite{70}

**Transdermal drug delivery**

Although there are benefits to administering medications via the transdermal method, such as avoiding the first pass effect, there is one significant disadvantage is the sluggish rate of drug penetration through the skin. To counteract the slow penetration rate, various techniques are used, one of which is niosomal formulation. The ketorolac flux across the skin is larger in proniosomal ketorolac formulations prepared from span 60 than in proniosomal ketorolac formulations prepared from tween20, according to a study. The bioavailability and therapeutic efficacy of drugs including diclofenac, flurbiprofen, and nimesulide are also increased by niosomal formulation, according to the research.\cite{27}

**Ophthalmic drug delivery**

Various bioadhesive polymers can be employed to deliver niosomes for ophthalmic drug delivery. The acetazolamide bioadhesive coated niosomal formulation made from span 60, cholesterol stearylamine or dicetyl phosphate has a greater tendency to lower intraocular pressure. When compared to the marketed formulation, the chitosan coated niosomal formulation timolol maleate (0.25%) has a greater effect for lowering intraocular pressure and has a lower risk of cardiovascular side effects. Instead of typical drug solution, the water-soluble antibiotic gentamicin sulphate showed maximum drug release in the form of niosomal drug delivery.\cite{12}

**Niosomes as carriers for Hemoglobin**

Niosomes can be used as a carrier for haemoglobin. The visible spectrum of niosomal suspension is superimposed over that of free haemoglobin. Vesicles are oxygen permeable, and the haemoglobin dissociation curve can be altered in the same way that non-encapsulated haemoglobin.\cite{15}

**In Immune Response Study**

The niosomes can be utilised to study the features of the immune response elicited by antigens due to their great stability, low toxicity, and immunological selection. The ability of niosomes to work as an adjuvant treatment in conjunction with I.V injection of various peptides and antigens has been demonstrated.\cite{8}
Diagnostic imaging with niosomes

The niosomal system has the potential to be employed as a diagnostic tool. Gadobenate dimeglumine in a conjugated niosomal formulation with [N-palmitoylglucosamine (NPG)], PEG4400, and both PEG and NPG have dramatically improved tumour targeting of an encapsulated paramagnetic drug as measured by MR imaging.\[^{16}\]

Delivery of Vaccines

Niosomes are becoming increasingly important as carriers for peroral and topical vaccination. Non-ionic surfactant-based vaccine delivery systems are immunogenic on a weekly basis. Studies on the topical delivery of Hepatitis B surface antigen encapsulated in niosomes and nasal mucosal delivery of influenza antigen have demonstrated comparable outcomes to other vaccine delivery techniques.\[^{25}\]

Hormone delivery

The study looked at the in-vitro penetration of estradiol from vesicular formulations through the human stratum corneum. Non-ionic n-alkyl polyoxyethylene ether surfactants were used to make the vesicles (CnEOm). The penetration-enhancing impact of surfactant molecules and the influence of vesicular structures generated by their adsorption at the stratum corneum suspension interface are two processes reported to play a role in vesicle–skin interactions.\[^{70}\]

Niosomes used in Cosmetic formulations

As both hydrophilic and hydrophobic medicines in topical formulations are easily manufactured, a variety of cosmetic treatments are prepared as niosomes. N-acetyl glucosamime (NAG) has been proposed as a therapy for melanocyte tyrosinase enzymes. As needed in hyperpigmentation diseases, prepared formulations improved the amount of medication localization in the skin. Both elastic and non-elastic niosomes were prepared in the formulation of anti-aging niosomes; the elastic niosomes demonstrated a higher rate of penetration into the skin, resulting in a greater topical anti-aging effect.\[^{31}\]

Other Applications are

Sustained Release

After niosomes are taken up by liver cells, Azmin et al believe that the liver acts as a depot for methotrexate. Drugs having a low therapeutic index and low water solubility can benefit from the sustained release action of niosomes since they can be kept in the circulation via niosomal encapsulation.\[^{4}\]
Localized Drug Action
Drug delivery using niosomes is one method for achieving localised drug activity, as their small size and low penetrability through epithelium and connective tissue maintains the drug localised at the administration site. Localized drug action improves the medicine's efficacy and potency while reducing the drug's systemic adverse effects, for example. Antimonials encapsulated in niosomes are taken up by mononuclear cells, resulting in drug localization, increased potency, and thus reduced dose and toxicity. Although the development of niosomal drug delivery technology is in its early stages, it has showed promise in cancer chemotherapy and anti-leishmanial therapy.\textsuperscript{[21]} 

CONCLUSION
Niosomes drug delivery system is a novel approach for entrapping drugs in nanocarriers such as niosomes. The concept of drug targeting at specific tissue site by incorporating drug into niosomes is widely accepted by researchers and academicians. Niosomes is a well preferred drug delivery system and present a structure similar to liposomes. They can be used as alternative drug delivery system and also having various advantages over liposomes such as cost and stability etc. Niosomes have been extensively studied for various applications such as oral, topical, ophthalmic, parental, transdermal various other routes are used for targeting the drug to the site of action for better efficacy. And also, they can be used to encapsulate natural origin of drugs such as peptides, enzymes, vaccines, genes, anti-cancer and virtually any other type of drug.

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47. Chaudhari PD, Desai US. Formulation and evaluation of niosomal in situ gel of


