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Niosomes: A promising nonionic surfactant vesicular system for enhancement of anticancer effect of phytochemicals

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***Abstract*---**In recent years, infectious illness therapy and vaccination have experienced a dramatic transformation. With the progress of biotechnology, not only have a great number of disease-specific biologicals been generated, but there has also been an emphasis on delivering these biologicals efficiently. Niosomes are non-ionic surfactant-based vesicles that are biodegradable, largely non-toxic, more stable, and less costly than liposomes. Non-ionic surfactant-based vesicles, also known as niosomes, have garnered a great deal of interest in the pharmaceutical industry due to its ability to encapsulate both hydrophilic and hydrophobic substances. In recent years, it has been shown that these vesicles can enhance the bioavailability of medications and may serve as a novel technique for delivering a variety of therapeutic agents, including chemical pharmaceuticals, protein therapeutics, and gene materials, with minimal toxicity and the desired targeting effectiveness. This page also provides an overview of niosome preparation processes, niosome kinds, characterisation, and applications. Chemoprevention is the use of phytochemicals to prevent or reduce cancers. It has been shown that several compounds produced from plants possess anticancer properties.

***Keywords*---**Nonionic surfactant, vesicular drug delivery system, phytochemicals.

Introduction

A drug-delivery system is a method of providing pharmaceutical substances at a predefined pace to generate a therapeutic impact in people or animals at a sick region, while simultaneously diminishing the medicine concentration in surrounding tissues. Localized pharmacological action increases medication effectiveness and decreases systemic tissue toxicity.

The goal of targeting drug delivery systems is to distribute the medication throughout the body in such a way that it exerts its therapeutic effect at the targeted and desired place, i.e. wherever its activity is required, while minimising unwanted interactions with non-targeted tissues. In 1909, Paul Ehrlich presented this concept and referred to it as "magic bullets." In the past decade, scientists working in the field of drug delivery systems have shown a great deal of interest in the use of vesicles to enhance drug delivery.

Anticancer Effect of Phytochemicals

Cancer is the most serious disease that affects individuals worldwide. Infectious agents induce genetic changes caused by carcinogens such as cigarette smoking, radiation, and chemicals, which are responsible for the majority of malignancies. Hepatocellular carcinoma is a lethal cancer, the fifth most prevalent and third deadliest cancer globally, and the fourth leading cause of cancer-related mortality in Asia and less developed nations. Surgical procedures, radiation, chemotherapy, immunotherapy, and interventional therapy are frequently used to treat hepatocellular carcinoma. Although therapeutic approaches and chemotherapy medications can decrease the multiplication of liver cancer cells, their negative effects may persist both temporarily and permanently. Due to the various side effects of chemotherapy, many patients prefer alternative treatments such as herbal remedies. Numerous research indicate that medicinal plants may be beneficial in the treatment of malignancies. Plant extracts and their derivatives have been utilised to treat a variety of disorders due to their high bioavailability, reduced side effects, and inexpensive cost. Recent research has shown that plant chemicals such as steroidal saponins and sapogenins possess anticancer properties.

The global proliferation of cancer registries has prompted the quest for innovative treatments that are toxic to cancer cells but have no impact on normal cells. The anticancer medications previously employed displayed relatively significant toxicity not only to tumour cells, but also to the normal cells of the affected body area. The quest for new anticancer medicines is now being done in both terrestrial and marine habitats. Plants have been used to heal ailments for millennia. As part of traditional folk medicine, numerous plants are taken for their health advantages in various regions of the world. The rising occurrence of many forms of cancer necessitates the development of novel anticancer medications. In 2017, it is anticipated that there will be 1,688,780 new cancer cases and 600,920 cancer deaths in the United States. After purification, several anticancer medicines obtained from plant materials are evaluated on cells (including diverse cancer cell lines) and experimental animals before being submitted to clinical trials. In recent years, the number of newly identified natural chemicals has

increased dramatically. In 2006, roughly 50,000 of these compounds were known; by 2014, this number had climbed to approximately 326,000. There were roughly 170,000 chemicals in the toxicity class among them. In addition, the quantitative interactions for 195,000 pharmacologically active substances are known.

Plants that have been used for ages in traditional medicine have been utilised as sources of compounds with high biological activity. One way to get these compounds is by extracting them from plant matter. Utilizing biotechnology to develop anticancer chemicals derived from plants is another strategy. The antitumor chemicals of natural origin (e.g., from plants and aquatic creatures) correspond to a variety of chemical classes, including alkaloids, diterpenes, diterpenoquinone, purine-based compounds, lactonic sesquiterpene, peptides, cyclic depsipeptide, proteins, macrocyclic polyethers, etc. Occasionally, the cost of extracting these compounds from natural sources is significantly less than the cost of synthesis. [15] Nanomedicine is one of the important components of nanotechnology, having several applications in numerous fields, including medication delivery. Various nanocarriers are utilised for medication delivery, and niosomes are among the most effective. Niosome is a vesicular nanoparticle consisting of nonionic surfactants and a helper lipid, such as cholesterol, that can enhance the bilayer's stiffness. Niosomes offer a tremendous potential for tumour cell targeting and controlled release. Niosomes are viewed as an alternative to other vehicles, particularly liposomes, because to their advantageous qualities, which include easy manufacturing, cheap cost, high stability, and simultaneous encapsulation of hydrophobic and hydrophilic medicines. [16]

Cholesterol and non-ionic surfactants constitute this type of colloidal nanocarrier. Non-ionic surfactants have a hydrophilic head coupled to an electrically neutral and largely non-toxic hydrophobic tail. In general, cholesterol functions as a helper lipid that can reduce interactions between niosomes and immune system proteins and promote their stability in bodily fluids. Niosomes are distinguished from liposomes by their chemical stability, extended storage period, high bioavailability, low toxicity, readily available and inexpensive raw materials, and the capacity to spontaneously load hydrophobic and hydrophilic compounds. By encapsulating active plant agents, niosomes can boost their resistance and durability against environmental degradation, hence enhancing the bioavailability of phytochemicals. Due to the hydrocarbon nature of phytochemicals, enhancing their solubility in aqueous fluids is a crucial aspect of loading phytochemicals into niosomes.

Vesicular Drug Delivery System

“Vesicles have become the vehicle of choice in drug delivery system called Vesicular Drug Delivery System.”, e.g. liposomes, Niosomes, Pharmacosomes etc.

Advantages [1]

Vesicular drug delivery systems have several advantages over the conventional dosages forms as well as prolonged released dosage forms as:

- Effective permeation of drugs into cells
- Prolongation of existence of drugs in systemic circulation.
- As selective uptake is taken place so reduces toxicity.

- Reduces the cost of therapy.
- Improves bioavailability.
- Hydrophilic-Lipophilic drugs can be incorporated.
- Sustained-release system function.
- Delayed elimination of rapidly metabolized drugs.
- Overcomes the problems of the drug insolubility, instability, and rapid degradations.

Vesicular systems are highly organised assemblages of one or more concentric lipid bilayers that are generated when certain amphiphilic building materials are exposed to water. Vesicles may be constructed using a wide variety of amphiphilic building elements. Bingham originally discovered the biological origin of these vesicles in 1965, and they were given the term Bingham bodies. A drug carrier can be designed to decay slowly, respond to stimuli, and be site-specific. The ultimate objective is to reduce medication degradation and loss, avoid adverse side effects, and improve drug availability at the illness site. Encapsulating a medication in vesicular structures is projected to extend the drug's time in systemic circulation and, if selective absorption can be achieved, lessen its toxicity. As controlled delivery vehicles, lipid vesicles are one of several experimental models of biomembranes that have successfully evolved. Due to limited medication absorption into cells, traditional chemotherapy is ineffective for the treatment of intracellular infections. This can be circumvented by using vesicular drug delivery methods. [2]

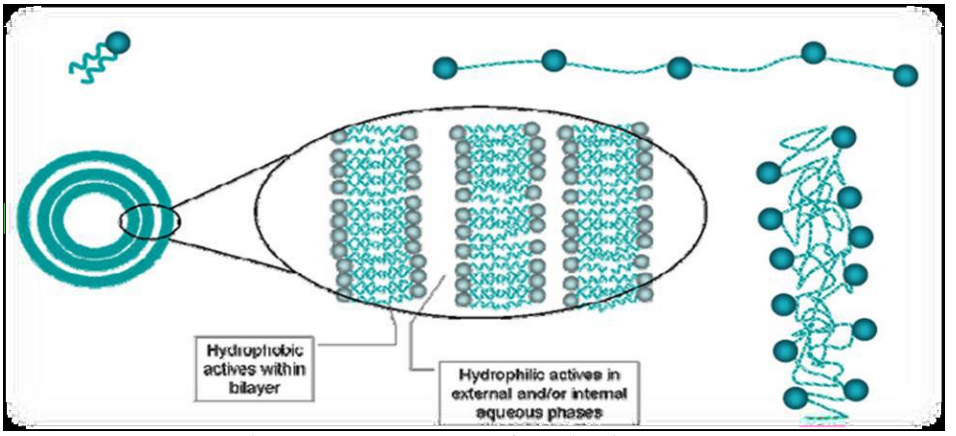


Figure 1. Structure of Vesicular system

Objectives of Vesicular Drug Delivery Systems:

1. Prolongs the medication's presence in the systemic circulation and, perhaps, decreases its toxicity if selective absorption can be achieved by delivering the drug directly to the site of infection.
2. Increases bioavailability, particularly for poorly soluble medicines.
3. The incorporation of both hydrophilic and lipophilic medicines is possible.
4. Delays the clearance of medicines that are rapidly metabolised and hence functions as sustained release systems.

Why Do We Use VDDS?

The ineffectiveness of conventional chemotherapy un the treatment of intracellular infections is a result of the restricted penetration of medicines into cells. To increase bioavailability at the site of disease, eliminate negative side effects of traditional and controlled release drug delivery methods, and solve the problem of drug and/or dosage degradation. [3]

Types of VDDS:
The targeted vesicles are classified on the basis of their composition[4]
a) Lipoidal biocarriers b) Non-lipoidal biocarriers

a. Lipoidalbiocarriers
1. Liposomes
2. Emulosomes
3. Enzymosomes
4. Sphingosomes
5. Ethosomes
6. Transferosomes
7. Pharmacosomes

b. Non-lipoidal biocarriers:
1. Niosomes
2. Bilosomes
3. Aquasomes

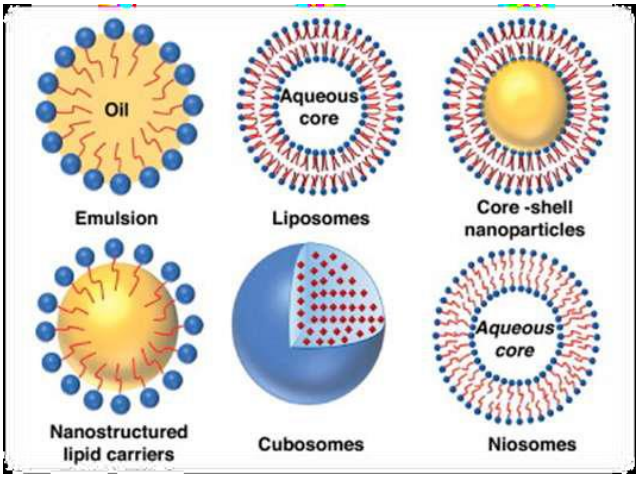


Figure 2. Types of Vesicular Drug Delivery Systems

Strategies to Improve VDDS

To improve VDDS mainly 2 strategies are reported:
- Pro-vesicular drug delivery:

Developed to overcome the stability problems associated with vesicular drug delivery systems composed of dry products or liquid crystalline gel that can be hydrated immediately before use.

e. g., Proliposomes, Proniosomes

Characterization:

Morphology, Angle of repose, Rate of hydration, Degree of deformity & permeability measurements, Size & Size distribution etc.
Types of pro-vesicular drug delivery system:
1. Proliposomes 2. Proniosomes

- Improve permeability:

a. Physical means b. chemical means

- To enhance drug delivery, vesicular systems such as liposomes, niosomes, transferosomes, pharmacosomes, and ethosomes provide an alternative. Among these several carriers, niosomes are among the most efficient drug delivery mechanisms. [5]
- Targeted medication delivery can be described as the capacity of a therapeutic substance to exert its effect directly on the desired site with minimal or no interaction with non-targeting locations. The niosome is composed of non-ionic surfactant including cholesterol and a little amount of ionic surfactant, such as diacetyl phosphate, which is utilised for stability. L'Oréal Company manufactured and sold the first non-ionic surfactant product for cosmetic applications. Due to the multi-environmental structure of niosomes, several types of drugs may be delivered to a specific place by integrating them.
- Niosomes may be unilamellar or multilamellar vesicles composed of non-ionic surfactant, cholesterol, and ionic surfactant that is used to minimise formulation aggregation. The hydrophilic, lipophilic, and amphiphilic drug can be encapsulated within the niosome's bilayer structural vesicle. Niosome is more stable than liposome due to the lipophilic nature of liposomes, which makes them susceptible to degradation and oxidation. Due to its non-ionic surfactant, niosomal formulations have a longer half-life in the blood and, as a result, a greater effect on their intended targets. Niosomes are minuscule and diminutive in size. The range of niosome size on the nanometric scale is 20 nm to 100 nm. Niosomes are fundamentally identical to liposomes but have additional benefits than liposomes. Their size is measured in nanometers, which is extremely tiny; as a result of their small size, they easily pass through all transdermal administration routes. Niosome exhibits reduced metabolism and removal by the reticular-endothelium system due to its nanometric size. Numerous benefits are associated with niosomal vesicle-containing medications. Not only does it boost the drug's stability, but it also improves its physicochemical properties. Often, niosomes have various charges on their surfaces, such as (+) and (-), which causes flocculation or aggregation and necessitates the use of less ionic surfactant to retain the same charge in formulation. Span-60 is typically utilised as a non-ionic surfactant in niosome formulation. As opposed to liposomes, niosomes do not require any specific preparation or storage conditions. The niosome preparation method is entirely based on the liposome preparation method. During niosomal formulation, medicine is frequently unencapsulated; this unencapsulated drug is frequently isolated by gel filtering or centrifugation. Several pharmacological substances have the potential to

be encapsulated in niosomes for the treatment of numerous diseases. Non-ionic surfactants utilised in the manufacture of niosomes exhibit greater stability than phospholipids employed in the formation of liposomes. Due to the ester bond present in liposomal phospholipid, phospholipid undergoes hydrolysis. Niosome demonstrates the controlled release of medication into the bloodstream at a predetermined time and pace. Pro-niosomes are water-soluble carrier particles that are coated with surfactant, or, to put it another way, they are the dry version of niosome. The pro-niosome mitigates several issues, such as its physical stability. Pro-niosomes are an additional formulation for drug administration; they exhibit strong transdermal penetration because they include surfactant, which acts as a penetration enhancer; they are non-toxic, biodegradable, and may entrap both hydrophilic and lipophilic drugs.

- The niosomal formulation reduces the nonselective systemic toxicity of an anticancer medication. Liver and the enzyme lysosomal lipase also take up niosome-containing drugs. This results in the disintegration of niosome and the release of the drug into the bloodstream; however, the degradation and breakdown of niosome in the liver occur extremely slowly, resulting in a longer prolonged impact. Cholesterol is essential to the construction of the niosome; it provides rigidity to the vesicle. However, when cholesterol is introduced in excess to the vesicle, it not only alters the fluidity, but also the drug's penetration and permeability. The administration routes for niosomal formulations include transdermal, parenteral, oral, ophthalmic, and subcutaneous. In targeted drug delivery, several carriers, such as immunoglobulin, plasma protein, microsphere, synthetic polymers, and occasionally erythrocytes and liposome, are utilised; nevertheless, liposome and niosome are the most thoroughly studied drug delivery systems. [6]
- Niosomes are non-ionic surfactant vesicles produced by the hydration of synthetic non-ionic surfactants, with or without cholesterol or other lipid incorporation. This category of vesicles was established. Similar to liposomes, these are vesicular structures that can transport amphiphilic and lipophilic medicines. One of the motivations for producing niosomes is the expected greater chemical stability of the surfactants than that of the phospholipids used to make liposomes. Because phospholipids contain ester bonds, they are quickly hydrolyzed. Scientists have sought for vesicles created from alternative substances, such as non-ionic surfactants, since unreliable reproducibility resulting from the use of lecithin in liposomes creates additional issues. Niosomes are a promising drug delivery vehicle because they are non-ionic, less toxic, and increase the therapeutic index of the medication by limiting its action to target cells. Niosomes or non-ionic surfactant vesicles are tiny lamellar structures generated by hydration of a combination of alkyl or dialkyl polyglycerol ether non-ionic surfactant and cholesterol in aqueous environments. The vesicle-forming amphiphile in niosomes is often a non-ionic surfactant such as Span – 60, which is stabilised by the addition of cholesterol and a little quantity of an anionic surfactant such as diacetyl phosphate.

- The vesicle is formed of lipid bilayer nonionic surface-active substances, thus the term niosomes.
- Niosomes are extremely minute, microscopic in size. The size resides in nanometric scale. • Niosomes are unilamellar and multilamellar vesicles.
- Niosomes are composed of a variety of substances, including sucrose, ester, surfactants, and polyethylene alkyl ether surfactants. Surfactants containing alkyl ether, alkyl ester, alkyl amides, fatty acids, and an amino acid molecule. [7]

A niosome is a vesicle composed of a non-ionic surfactant. Niosomes are predominantly composed of non-ionic surfactant and cholesterol incorporation. Other excipients are also acceptable. They share a bilayer structure with liposomes, but the ingredients employed to produce niosomes render them more stable.

Salient Features of Niosomes

- Niosomes are osmotically stable and capable of entangling the solution and increasing the drug's rigidity.
- Niosomes are biocompatible, non-immunogenic, and biodegradable non-ionic surfactants.
- Niosomes have a structure that is generally deliquescent and hydrophobic, which permits the drug molecules to have a wide range of solubility.
- Niosomes facilitate the delivery of unstable and sensitive drugs.
- Niosomes are often architecturally flexible, allowing them to be tailored to specific circumstances.
- Securing the medicine from its biological environment increases the drug's accessibility at a particular location.
- Niosomes increase the solubility and oral bioavailability of poorly soluble medications, as well as the skin penetrability of topically administered pharmaceuticals.

Advantages of Niosomes:

1. As a water-based vehicle, the vesicle suspension delivers greater patient compliance than oil-based dose formulations.
2. The architecture of niosomes, which consists of hydrophilic, lipophilic, and amphiphilic components, may accept drug molecules with a broad spectrum of solubilities.
3. The features of vesicles may be altered by modifying their composition, size, lamellarity, surface charge, tapping volume, and concentration.
4. They can release the medicine in a regulated and continuous manner.
5. Surfactants require no specific conditions for storage and handling, such as low temperature and an inert environment.
6. They can function as a depot formulation, allowing for the regulated release of the medicine.
7. They increase the oral bioavailability of medicines with low solubility.
8. They have a structure that is stable even in emulsion form.
9. They are cost-effective for mass manufacturing.
10. They can prevent the medication from being metabolised by enzymes.

11. They can boost the skin's ability to absorb medicines.
12. Therapeutic performance of drug molecules can be enhanced by delaying elimination from circulation.
13. They can safeguard the active ingredient from biological circulation.
14. Niosomes can be delivered to the site of action by oral, topical, and parenteral methods.

Disadvantages of Niosomes:

1. Physical instability
2. Aggregation
3. Fusion
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf-life of the dispersion.

Structure of Niosomes

Niosomes are spherical and composed of lamellar (unilamellar or multilamellar) structures at the microscopic level (Figure 3). Nonionic surfactants, with or without cholesterol and a charge inducer, produce the bilayer. Niosomes are formed using several types of surfactants in varying combinations and molar ratios. Alkyl ethers, alkyl glyceryl ethers, sorbitan fatty acid esters, and polyoxyethylene fatty acid esters are examples of surfactants. The addition of cholesterol preserves the bilayer's stiffness, resulting in less permeable niosomes. In the meantime, charge inducers deliver charge to the vesicles and increase vesicle size, enhancing the efficacy of drug entrapment. Negative charge inducers, such as dicetyl phosphate, dihexadecyl phosphate, and lipoamino acid, as well as positive charge inducers, such as stearylamine and cetylpyridinium chloride, assist stabilise the vesicles.

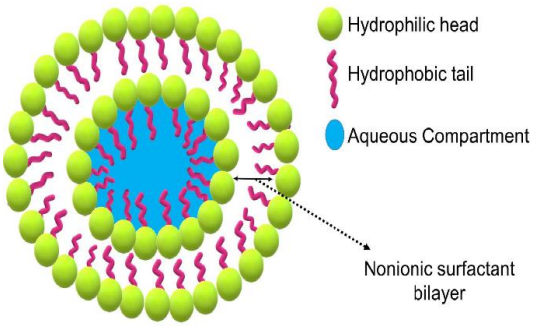


Figure 3. Typical Structure of Niosome

Nonionic surfactants in niosomes prefer to position themselves such that the hydrophilic end faces outward (toward the aqueous phase) and the hydrophobic end faces inward to produce a closed bilayer structure that encloses solutes in an aqueous solution. Niosomes have a closed bilayer structure with hydrophilic inner and outer surfaces and a lipophilic region sandwiched in between. The formation of the closed bilayer structure requires energy, such as heat or physical agitation. Various forces within the vesicles, such as van der Waals and repulsive

interactions between the surfactant molecules, were discovered to play a significant role in maintaining the vesicular structure. Changing the vesicle's constituents (including type, content, and concentration), size, surface charge, or volume will probably alter the niosomes' characteristics. On the basis of their vesicle size, niosomes may be divided into three groups: tiny unilamellar vesicles (0.025–0.05 mm), multilamellar vesicles (>0.05 mm), and giant unilamellar vesicles (>0.10 mm). [8]

Components of Niosomes

Non-ionic surfactants

Non-ionic surfactants are one of the most essential niosome components. To produce niosomes, various types and their combinations are employed to entrap various drugs. The nature of non-ionic surfactants is amphiphilic, biodegradable, biocompatible, and non-immunogenic. The features of formed niosomes are determined by their composition, concentration of additives, size, lamellarity, and surface charge. For the creation of niosomes, non-ionic surfactants such as Span (60, 40, 20, 85, and 80) and Tween are applied (20, 40, 60, 80).

Cholesterol
It is a crucial ingredient in the formation of niosomes. Cholesterol is not only necessary for the production of niosomes, but its presence also impacts other niosome features. It influences the membrane's permeability, stiffness, entrapment efficiency, rehydration ease of freeze-dried niosomes, stability, and storage time. If cholesterol is combined with low HLB surfactants, it enhances the vesicle's stability, and if the HLB value is more than 6, it facilitates the creation of bilayer vesicles. The inclusion of cholesterol enhances the formulation's viscosity and, thus, its stiffness.

Charged molecule
Some charged compounds are introduced to niosomes to increase their stability by preventing collisions via electric repulsion. As negatively charged compounds, dicetyl phosphate (DCP) and phosphotidic acid are used. Likewise, stearyl amine and stearyl pyridinium chloride are well-known charged compounds used in niosomal preparations.

Hydration medium
In the creation of niosomes, the hydration medium is one of the most essential components. Phosphate buffer is typically utilised as a hydration medium. However, the buffer's pH relies on the solubility of the encapsulated medicine. [9]

Types of Niosomes
The various types of niosomes are as:

1. Multi lamellar vesicles (MLV),
2. Large unilamellar vesicles (LUV),
3. Small unilamellar vesicles (SUV) [17].

1. **Multilamellar vesicles (mlv):** It comprises of many bilayers encircling the aqueous lipid compartment individually. The diameter of these vesicles is

around 0.5-10 m. Multilamellar vesicles are the most often employed niosomes due to their ease of production and mechanical stability during long-term storage. These vesicles are ideally suited for transporting lipophilic substances.

2. **Large unilamellar vesicles (luv):** This kind of vesicle has a high ratio of aqueous to lipid compartments, allowing for the encapsulation of greater amounts of bioactive substances with less membrane lipid consumption.
3. **Small unilamellar vesicles (suv):** Small unilamellar vesicles are often generated by sonication from larger multilamellar vesicles. 10-100 nm is the approximate size of tiny unilamellar vesicles. [10]

Figure 2. Types of Niosomal vesicles

Methods of Niosome Preparation

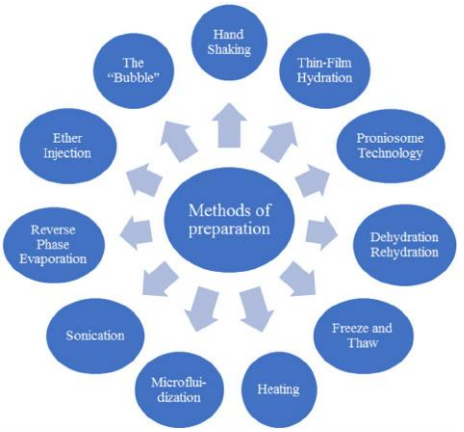


Figure 3.Methods of Preparation of Niosomes

Thin film hydration technique

Thin film hydration, commonly known as the hand-shaking method, is a straightforward procedure that uses organic solvents to dissolve surfactant and cholesterol. Surfactants and cholesterol are dissolved in a round-bottomed flask, then the organic solvent is evaporated to leave a thin coating on the flask's bottom. The addition of hydration media causes the formation of vesicles, which are subsequently processed to generate unilamellar vesicles.

Ether injection method
The process consists of gently introducing a solution of surfactant dissolved in diethyl ether into warm water on a magnetic stirrer equipped with a hot plate while maintaining a temperature of 60°C. Through a 14-gauge needle, the surfactant combination in ether is gently injected into the medication solution. Solvent vaporisation results in the creation of monolayer vesicles. The niosome vesicle's particle size ranges from 50 to 1000 nm.

Hand shaking method
This method is also known as thin hydration. In this technique, a mixture of surfactants and cholesterol is dissolved in volatile organic solvents such as ether, chloroform, and methanol. Using a rotary evaporator at room temperature, the organic solvent is extracted, leaving behind a thin coating of solid mixture placed on the flask wall. This procedure generates multilamellar niosomes. The rehydration of the dried surfactant film in an aqueous phase at 60°C with mild agitation resulted in the production of niosomes.

Sonication techniques
In this method, an aliquot of a medication solution in buffer is transferred to a combination of surfactant and cholesterol in a glass vial. The mixture is sonicated for three minutes at 60°C using a probe sonicator with a titanium probe to produce niosomes.

Reverse phase evaporation technique (REV)
This procedure involves dissolving the surfactant and cholesterol in a combination of ether and chloroform. To this, a drug-containing aqueous phase is introduced, and the resultant two phases are sonicated at 4-5°C. A translucent clear gel is created. After adding hydration medium, the substance is sonicated again. At 40°C, the aforementioned organic phase is eliminated. Niosomes are formed by diluting the resultant niosome suspension with phosphate buffer saline and heating it at 60°C for 10 minutes.

Micro fluidization method
In this technology, two fluidized streams (one containing medication and the other containing surfactant) contact at ultrahigh velocity, in carefully defined micro channels within the interaction chamber, such that the energy provided to the system remains in the region of niosome formation. The term for this is submerged jet principle. It leads in improved homogeneity, reduced size, and repeatability in niosome formulation.

Extrusion method
Using a rotating vacuum evaporator, the solvent of a combination of cholesterol and dicetyl phosphate is evaporated to create a thin layer. The film is then hydrated with the drug solution, and the resultant suspension is extruded through a polycarbonate membrane and passed up to eight times to create niosomes of uniform size.

Transmembrane pH gradient drug uptake
Surfactant and cholesterol are dissolved in chloroform in a flask with a circular bottom. Under lowered pressure, the solvent evaporates to produce a thin layer on

the flask's wall. To produce multilamellar vesicles, the coating on the wall is hydrated with citric acid (pH 4) by vortex mixing. The samples are then freeze-thawed three times and sonicated to yield niosomes.

Multiple membrane extrusion technique:
By evaporation, the combination of cholesterol, surfactant, and dicetyl phosphate in chloroform forms a thin layer. The thin film is hydrated by a drug medium using polycarbonate membranes, which is an effective method for adjusting niosome size, and the final solution is extruded via a series of up to eight membranes.

The "Bubble" method
It is a one-step method for producing liposomes and niosomes without the need of organic solvents. To obtain the dispersion, all components are dispersed in the appropriate aqueous solutions and then homogenised. The three necks of a flask with a round bottom are positioned in a water bath to adjust the temperature. The water-cooled reflux and thermometer are located in the first and second necks, respectively, while the nitrogen supply is located in the third neck. Cholesterol and surfactant are disseminated inside a buffer (pH 7.4) at 70°C, mixed for 15 seconds with a high shear homogenizer, and then "bubbled" at 70°C with nitrogen gas.

The single pass technique
The solution or suspension of lipids is extruded with air mass through a porous device and a nozzle, followed by mixing, to form niosomes with a narrow size distribution within the range of 50-500 nm.

Characterization
Using a light microscope, photon correlation microscopy, freeze-capture microscopy, entrapment efficiency, and in vitro release rate, several characteristics of niosomes, such as vesicle diameter, are studied. Other variables such as drug stability, drug leakage in saline and plasma during storage, pharmacokinetics, and toxicity are also investigated.

Therapeutic applications of niosomes
The potential applicability of niosomal drug delivery to several pharmacological agents for their activity against diverse disorders exists. Below are few of their therapeutic uses.

Targeting of bioactive agents

To reticulo-endothelial system (RES)
The vesicles are taken up preferentially by RES cells. Niosomes are taken up by cells via circulating serum factors known as opsonins, which mark them for elimination. Such localised drug accumulation has been utilised in the treatment of animal cancers known to metastasis to the liver and spleen, as well as in the therapy of parasitic liver infection.

To organs other than RES
Immunoglobulins appear to attach rather readily to the lipid surface, providing a straightforward method for drug carrier targeting. Numerous cells contain the innate ability to identify and bind certain carbohydrate determinants, which may be utilised to route transport systems to specific cells.

Neoplasia
Doxorubicin, an anthracyclic antibiotic with broad-spectrum antitumor action, has an irreversible cardiotoxic effect proportional to dosage. The administration of this medication via niosomes to mice with S-180 tumour extended their lifespan and lowered the rate of sarcoma growth. Encapsulation of the medication into niosomes boosted its half-life, lengthened its circulation, and changed its metabolism.

Immunological application of niosomes
Niosomes have been utilised to investigate the antigen-induced immune response. Brewer and Alexander showed that niosomes are a strong immunostimulant due to their immunological specificity, minimal toxicity, and durability. [11]

Ophthalmic drug delivery
Due to tear formation, impermeability of corneal epithelium, non-productive absorption, and transitory residence period, it is challenging to attain optimal bioavailability of a medication from ocular dosage forms such as ophthalmic solution, suspension, and ointment. To obtain good drug bioavailability, however, other vesicular systems, such as niosomes and liposomes, are recommended for experimental usage. Bioadhesive-coated niosomal formulation of acetazolamide produced from span 60, cholesterol stearylamine, or dicetyl phosphate demonstrates a greater propensity for intraocular pressure decrease than the commercially available formulation (Dorzolamide). The chitosan-coated niosomal formulation of timolol maleate (0.25 percent) had a greater effect on intraocular pressure reduction than a commercially available formulation with a lower risk of cardiovascular adverse effects.

Surfactants:
The word surfactant (short for surface-active-agent) refers to a chemical that demonstrates some level of surface or interfacial activity. It is important to note that not all amphiphiles exhibit this behaviour; only those with more or less balanced hydrophilic and lipophilic inclinations are likely to migrate to the surface or contact. If the amphiphilic molecule is excessively hydrophilic or hydrophobic, it remains in one of the phases and does not undergo phase separation.

Amphiphiles display qualities other than tension reduction, which is why they are frequently branded according to their primary application, such as soap, detergent, wetting agent, disperssant, emulsifier, foaming agent, bactericide, corrosion inhibitor, antistatic agent, etc. In other instances, they are known by the structure they can form, such as membrane, microemulsion, liquid crystal, liposome, vesicle, or gel.

Some molecules, such as short-chain fatty acids, are amphiphilic or amphipathic, meaning that they have a component with an affinity for nonpolar media and a component with an affinity for polar media. These molecules exhibit surface activity and form directed monolayers at interfaces (i.e., they lower the surface or interfacial tension of the medium in which they are dissolved). In certain contexts, surfactants are described as molecules that can form micelles. These compounds are known as surfactants, amphiphiles, surface-active agents, tensides, or paraffin chain salts in extremely ancient literature. The word surfactant was initially registered as a trademark for some surface-active goods and then released into the public domain. Surfactants are soaps (salts of fatty acids having at least eight carbon atoms). Detergents are surfactants or combinations of surfactants whose solutions possess cleaning capabilities. Thus, detergents modify interfacial characteristics in order to facilitate the removal of a phase from solid surfaces.

The presence of a hydrophilic head group and a hydrophobic chain (or tail) inside the molecule accounts for the peculiar features of aqueous surfactant solutions. In cases when the polar or ionic head group interacts strongly with an aqueous environment, it is solvated through dipole–dipole or ion–dipole interactions. In fact, the nature of the polar head group is utilised to categorise surfactants into several groups. Fluorocarbon-based surfactants are resistant to oxidation compared to hydrocarbon-based surfactants. Due to the smaller size of fluorine atoms compared to hydrogen atoms, the surfactants' structures are more rigid, resulting in a strong surface tension lowering action, water and oil repellency, thermal resistance, chemical resistance, and lubricating ability. In water-based paints, hybrid fluoride–hydrogen containing surfactants are utilised. Silicon added to fluorine-containing surfactants produces high-quality lubricants, effective defoamers, and even compounds with potent anti-HIV properties. In addition to chemically generated surfactants, there is a family of surfactants known as microbiological or biosurfactants, which have highly intriguing and complex structures but are more expensive to make. [12]

Despite the widespread use of surfactants in several sectors, it is rather surprising that, until very recently, the vast majority of surfactant applications were single-headed, single-tailed surfactants. The inability of typical sulphate and sulfonate surfactants to tolerate hard water or to dissolve in cold water sparked an early interest in alternative surfactant architectures. Evans began studying sulphate surfactants in which the point of substitution was altered and the micellar characteristics were associated to the site of substitution of the sulphate group in the mid-1950s. This was one of the early examples of the creation of a structure–performance link in a family of surfactants. Scientist explained the synthesis of one of the first ‘tunable’ surfactants, the disodium α-sulfocarboxylates. These surfactants were shown to have superior qualities in terms of hard water tolerance, foam stability, and detergency when compared to their single headed equivalents. They suffered from the issue that they are irritating to the skin, a problem that is confronted with most high critical micelle concentration (cmc) surfactants. Interest in generating novel amphiphiles faded when detergent formulators learned they could boost the effectiveness of existing commercial products by the judicious use of additives. By the early 1980s however, interest in surfactants derived from non-linear alkylbenzene (non-LAB)

sources began to increase as it became clear that consumer demand for “newer and better” detergents was outpacing the ability of detergent manufacturers to reformulate their products when the main component was still the conventional single-head, singletail amphiphile. Hence the synthesis of new surfactants has emerged as a feasible and relevant issue in the literature. In recent surfactant articles it is not unusual to witness the research of the characteristics of vitamin E-based surfactants, sugar-based surfactants and many others. One of the most interesting discoveries in the world of surfactant chemistry is the introduction of the Gemini surfactants in the late 1980s and early 1990s. The name Gemini surfactant, developed by Menger, has been recognised in the surfactant literature for defining dimeric surfactants, that is, surfactant molecules that have two hydrophilic (chiefly ionic) groups and two tails per surfactant molecule. These twin sections of the surfactants are joined by a spacer group of varied length (most typically a methylene spacer or an oxyethylene spacer) (most commonly a methylene spacer or an oxyethylene spacer). A block schematic of a typical Gemini surfactant is given below.

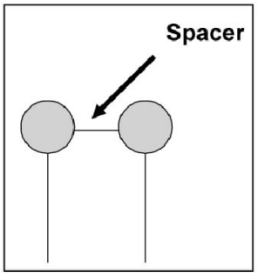


Figure 4. Illustration of a Gemini surfactant

Numerous articles discuss the characteristics of cationic and anionic Gemini surfactants. Gemini surfactants possess a number of superior properties when compared to conventional single-headed, single-tailed surfactants, with the Geminis exhibiting lower cmc values (by approximately an order of magnitude), increased surface activity (C20) and lower surface tension at the cmc, enhanced solution properties such as hard-water tolerance, superior wetting times, and lower Krafft points. Given the favourable cost/performance ratio of Gemini surfactants, their employment in a variety of surfactant applications (e.g., soil remediation, oil recovery, and commercial detergents) might be anticipated. [17-19]

Classification of Surfactants

From a business perspective, surfactants are frequently categorised according to their function. However, this is not particularly beneficial because many surfactants have many applications, which might lead to confusion. Surfactants are most often and scientifically categorised according to their dissociation in water.

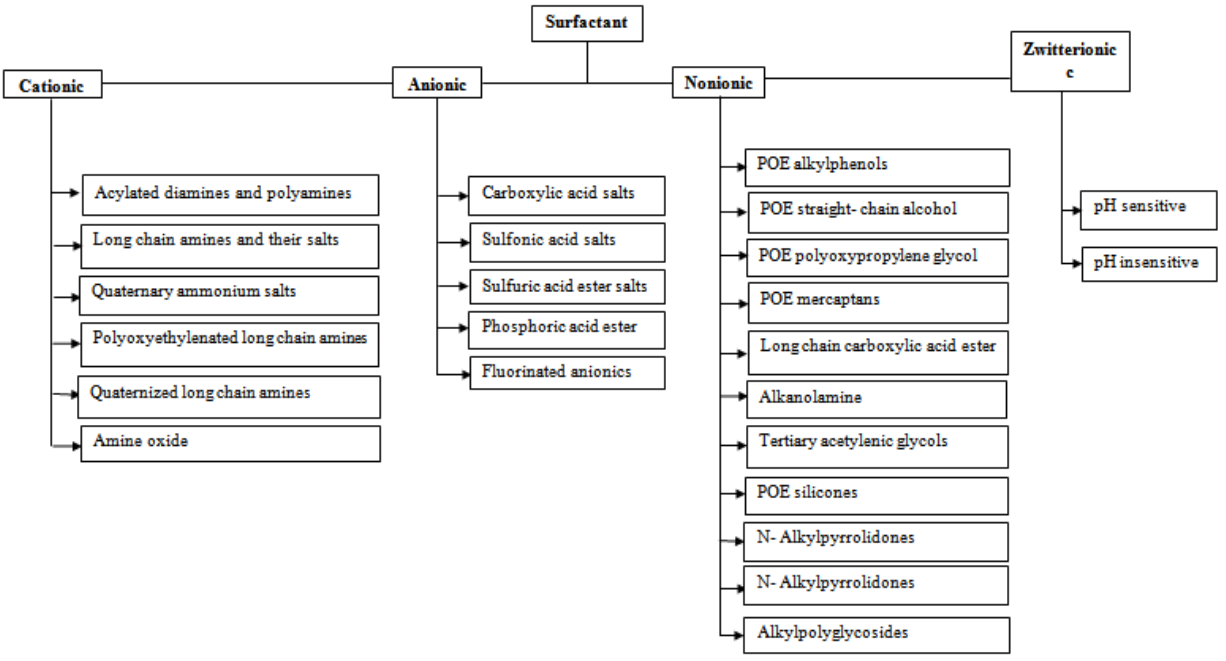


Figure 5.Systematic classification of surfactants

1. Anionic Surfactants :

In water, anionic surfactant dissociates into an amphiphilic anion and a cation that is typically an alkaline metal (Na+, K+) or quaternary ammonium. They are the most widely employed surfactants. They include alkylbenzene sulfonates (detergents), (fatty acid) soaps, lauryl sulphate (foaming agent), di-alkyl sulfosuccinate (wetting agent), and lignosulfates (dispersants), among others... Anionic surfactants constitute around fifty percent of the global output. [20]

2. Nonionic Surfactants:

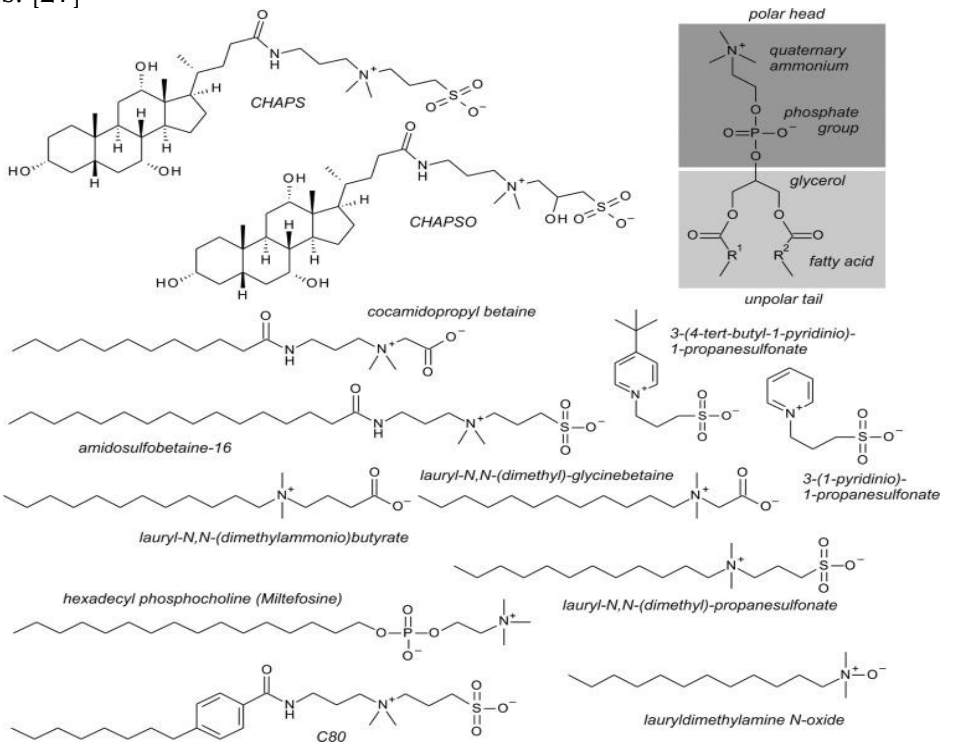
Nonionic surfactants comprise around 45 percent of the total industrial output. Their hydrophilic groups are nondissociable, such as alcohol, phenol, ether, ester, or amide, therefore they do not ionise in aqueous solution. A considerable number of these nonionic surfactants are rendered hydrophilic by the inclusion of a polyethylene glycol chain, which is the result of ethylene oxide polycondensation. These substances are known as polyethoxylated nonionics. Due of their low toxicity, glucoside (sugar-based) head groups have been brought to the market throughout the past decade. Concerning the lipophilic group, it is frequently of the alkyl or alkylbenzene type, with the former originating from naturally occurring fatty acids. In contrast to polyethylene oxide, the polyether produced via the polycondensation of propylene oxide is somewhat hydrophobic. This polyether chain is employed as the lipophilic group in the so-called polyEOpolyPO block copolymers, which are often included in a distinct class, such as polymeric surfactants, which will be discussed in further detail later. [21-24]

3. Cationic Surfactants

In water, cationic surfactants disintegrate into an amphiphilic cation and an anion, which is often of the halogen type. A relatively substantial part of this class consists of nitrogen compounds, such as fatty amine salts and quaternary ammoniums, with one or more long alkyl chains, frequently derived from natural fatty acids. In general, these surfactants are more costly than anionics since their production requires a high-pressure hydrogenation process. As a result, they are only used in two instances where there is no cheaper alternative, namely as a bactericide and as a positively charged substance that can adsorb on negatively charged substrates to produce an antistatic and hydrophobant effect, which is frequently of great commercial significance, such as in corrosion inhibition. When a single molecule of a surfactant exhibits both anionic and cationic dissociations, it is referred to as amphoteric or zwitterionic. This is the case with manufactured chemicals like betaines and sulfobetaines, as well as natural molecules like amino acids and phospholipids. [25,26]

4. Zwitterionic Surfactants

Surfactants that contain both a positive and negative charge called zwitterionic or amphoteric. As previously indicated, these charges may be permanent or pH-dependent. The cationic component is often an amine or quaternary ammonium cation, whereas the anionic component is typically a carboxylic, sulfuric, or phosphoric acid (or esters thereof). They are commonly employed in cosmetics, the purification of proteins, the separation of proteins, and the solubilization of proteins. [27]



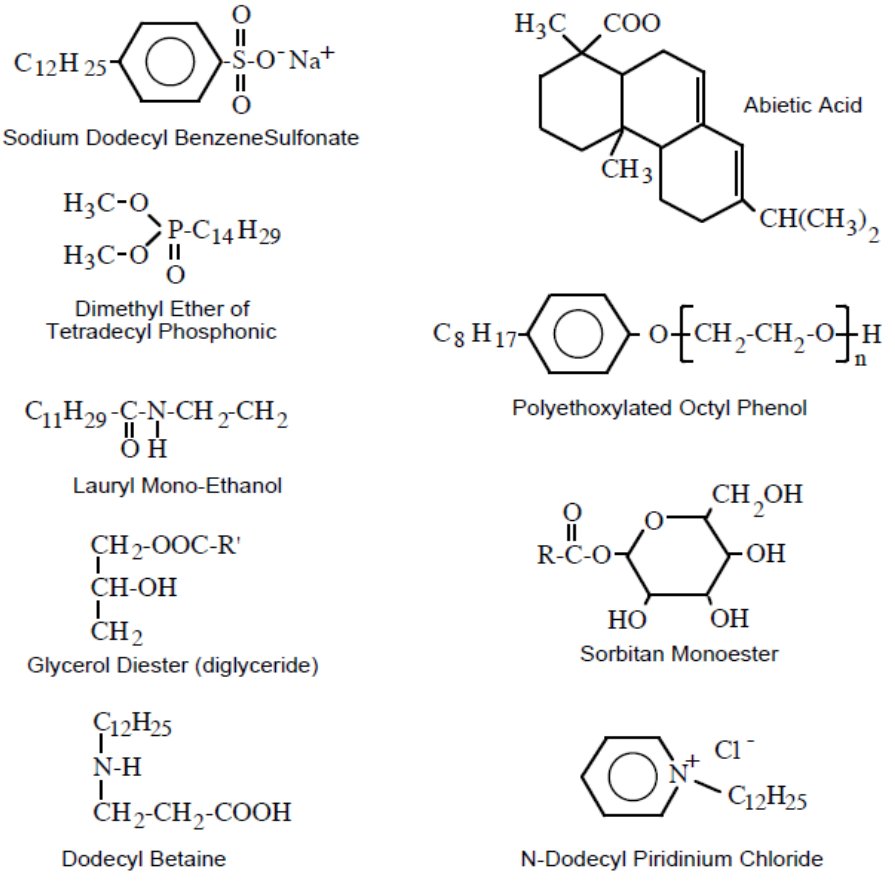


Figure 6. A few commonly used surfactants

Some amphoteric surfactants are pH-insensitive, whereas others are cationic at low pH, anionic at high pH, and amphoteric at intermediate pH. The high cost of amphoteric surfactants restricts their employment to extremely specialised applications, such as cosmetics, where their excellent biological compatibility and low toxicity are of key concern. In the past two decades, a new class of surface active substance has been developed, known as polymeric surfactants or surface active polymers. These substances are the result of the association of one or more macromolecular structures exhibiting hydrophilic and lipophilic properties, either as separate blocks or as grafts. They are currently widely employed in the formulation of cosmetics, paintings, foodstuffs, and additives for the manufacturing of petroleum. [28-31]

Mechanism of Action of Surfactants [32-35]

Surfactants can show its action in three different ways:

1. Roll-up procedure

The surfactant drops the oil/solution and fabric/solution interfacial tensions and boosts the fabric's stain in this way.

2. Emulsification
The surfactant sinks the oil solution interfacial tension and prepares simple oil emulsification.

3. Solubilization
By interacting with the micelles of a surfactant in a solvent (water), a component readily liquefies to form a consistent and pure solution. Surfactants are also commonly referred to as wetting agents and foaming agents. Surfactants are not only used to create emulsion, but also to remove dirt and stains from cloth. Surfactants reduce the surface tension of a molten substance's medium. The surfactant contributes significantly to the entrapping oil phase by decreasing the interfacial tension between two interfaces or media (such as stain/fabric, water/stain, air/water). The water reduces the surface tension and makes it easy to emulsify oil, which is the source of washing filth and lubricating dull dishes, clothing, and other exteriors, and aids in keeping oily dust or grease postponed in the water, therefore forming emulsions. The hydrophilic head or water-loving head lies in the water and tugs the oil towards the water.

Role of surfactants

Surfactants play a crucial role in the development of various medication delivery systems. For the manufacture of chemicals that are not completely soluble in water, pharmaceutically acceptable surfactants or co-solvents are traditionally employed to improve solubility. Polymeric micelles produced with surfactants exhibit a comprehensive set of distinctive characteristics that make them ideal drug carriers for a wide variety of medicines. The low solubility in biotic solutions exhibited by roughly 50 percent of the medications imposes restrictions on oral, transdermal, and parenteral delivery methods. The encapsulation of hydrophobic pharmaceuticals into polymeric micelles composed of surfactants is one of the brightest alternatives among the existing methods for overcoming such issues. Surfactant plays an important function in both the pharmaceutical and non-pharmaceutical fields. A thorough investigation of surfactant inclusion and action in the medical profession would reveal a vast array of tonic applications for this substance. The area of medical science would benefit from a reduction in research on each surfactant if it led to an improvement in the treatment of a variety of illnesses. A surfactant, such as pulmonary surfactant, has many effects beyond reducing surface tension and changing mechanical characteristics that reduce work activity. For instance, the epithelium of the lung is in constant touch with the environment, and surfactant protects against infection by enhancing the clearance of pathogens, changing the inflammatory cell response, and enhancing the biophysical function of the lung. Hydrophilic proteins that play a little part in surfactant production have a profound effect on antibacterial action. Surfactant is a well-known therapy for RDS (respiratory distress syndrome) in premature newborns; however, there has been no significant therapeutic benefit associated with the use of exogenous surfactant in adult patients with ARDS (acute respiratory distress syndrome) to far. [36-38]

To investigate the potential of surfactants as an immune-modulating treatment or as small molecules that influence the accessibility of surfactant ingredients in respiratory illnesses, more research is required. In double emulsion synthesis,

surfactants play an essential role in controlling the particle size of the polymeric nan- particulate system, such as nanocapsules containing penicillin-G; the classification and release of drug-loaded polybutyl adipate (PBA) nanocapsules containing penicillin-G are discussed here. Utilizing techniques such as double emulsion solvent evaporation, exhausted span and tween as surfactants, and dichloromethane as an organic solvent, nanocapsules were created. Nanocapsules containing penicillin-G and tiny amounts of both surfactants likely to have a greater burst discharge. Under optimal formulation circumstances, the trapping of penicillin-G may reach 60 percent and the release of the burst may fall below 45 percent. In this circumstance, the nanocapsules' narrow diameter of only 130 nm will be crucial. The forces at work within micellar foam are seen in (Figure 7) [14]

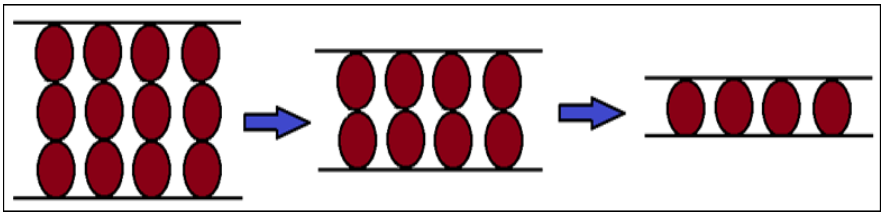


Figure 1. Structural forces in foam film (micelle)

- **Nonionic Surfactants:**

Nonionic surfactants are chargeless. They are often included in laundry and dishwashing detergents. After anionic, they are the second most often used surfactants. In hard water, these molecules are less likely to form'soap scum' due to their lack of charge. They are often less effective than anionic, but produce less skin irritation for certain individuals. [39-41]

If anionic surfactants are the most common, nonionic surfactants are a close second, employed in a variety of cleaning, personal care, and disinfection products as well as industrial activities. These are the most prevalent anionic surfactants:

- Cocamide monoethanolamine (Cocamide MEA)
- Cocamide diethanolamine (Cocamide DEA)
- Fatty alcohol ethoxylates
- Amine oxides
- Sulfoxides

Nonionic surfactants are actively promoted in regions with hard water (high mineral content) because they are less prone to develop soap scum. [10] Nonionic surfactants are less prone to cause skin irritation, but they are also less effective in cleaning. Most cleaning solutions include anionic and nonionic surfactants to strike a balance between cleaning efficacy and skin irritation risk.

Nonionic surfactants are substances containing hydrophobic and hydrophilic surface-active groups. These surfactants do not ionise in aqueous solutions. Typically, commercial nonionic surfactants are a combination of homologous structures made of alkyl chains with varying numbers of carbons and hydrophilic moieties with varying numbers of ethylene oxide (ethoxylate, EO), propylene oxide

(propoxylate, PO), and butylenes oxide (butoxylate, BO) units. These compounds rank second in terms of global surfactant usage and account for 35% of overall surfactant consumption. Nonionic surfactants are frequently utilised in consumer items such as detergents, cleaning agents, and personal care products.

Due to their extensive use and features that facilitate transport across immiscible interfaces (oil/water and water/biological membranes), these surfactants are ubiquitous in the natural environment. Some of their metabolites are more dangerous than their parent chemicals, although not being categorised as very toxic poisons. Consequently, there is a growing demand for a rapid and reliable means of detecting their existence.

Non-ionic surfactants, consisting of a hydrophilic head group and a hydrophobic tail, are employed in the synthesis of niosomes; they are non-charged and relatively non-toxic. The hydrophobic portion of a surfactant can be alkyl (T), fluoroalkyl, or steroidal. The number of hydrophobic moieties in vesicle-forming surfactants is currently restricted, whereas a broad range of hydrophilic head groups are accessible. Diverse non-ionic surfactants, such as polyglycerol alkyl ethers, glucosyl dialkyl ethers, crownethers, ester-linked surfactants, polyoxyethylene alkyl ethers, Brij, Spans (sorbitan esters), and Tweens (Polysorbates), used for the preparation of niosomes are GRAS-approved and safe for human consumption.

Nonionic surfactants offer an advantage over ionic surfactants in that it is possible to generate surfactants with a wide range of hydrophile-lipophile balance (HLB) by modifying molecular structures, particularly the hydrophilic moiety. As is the case with nonionic polyoxyethylene-type surfactants, the HLB is modified by varying the polymerization degree of the polyoxyethylene group. In water/polyoxyethylene-type surfactant systems, a broad range of surfactant aggregates with both positive and negative curvatures are seen in a phase diagram as a function of the HLB number of the surfactant. [38,41]

Conclusion

Niosomes may serve as an excellent nanovesicle delivery platform and offer a potential way for the administration of chemical medications, protein therapeutics, and gene materials for the prevention and treatment of illness. They offer several benefits over liposomes, including high chemical and physical stability, cheap cost, and simple manufacture. In the realm of pharmaceutics, they may prove to be an alternative to liposomes and have garnered a great deal of attention. Niosomes are biodegradable, generally non-toxic, more stable, and less expensive than liposomes. The capacity of non-ionic surfactant-based vesicles, also known as niosomes, to encapsulate both hydrophilic and hydrophobic molecules has piqued the interest of the pharmaceutical sector. In recent years, it has been demonstrated that these vesicles can improve the bioavailability of medications and may serve as a novel method for delivering a wide range of therapeutic agents, including chemical pharmaceuticals, protein therapeutics, and gene materials, with minimal toxicity and the desired targeting effectiveness.

Conflict Of Interest

Authors declares that there is no any conflict of interest.

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