FUTURE TARGETED DRUG DELIVERY SYSTEMS: NIOSOME.

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In recent years, there has been a revolutionary shift in how infectious disease management and immunization procedures are carried out. Biotechnology and genetic engineering have advanced, an emphasis has been made on the effective delivery of these biologicals, in addition to the creation of a large number of drugs targeted at certain ailments. Vesicles make up niosomes produced with cationic surfactants that are degradable, safer, stronger, and less expensive than liposomes. With a focus on their application in medicine, this text explores the present expansion of curiosity niosomes of curiosity across a number of scientific domains. A basic overview of niosome preparation techniques, types, characterization, and applications is also provided in this article.

Keywords: Bilayer, lamellar, niosomes, surfactants, and drug entrapment.

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DOI: 10.48047/ecb/2023.12.si5a.0431

1.INTRODUCTION

The goal of targeted drug delivery is to elevate the medication's relative concentration in the target tissues while lowering it in the non-target tissues. This concentrates the medicine where it is needed. As a result, the medication has no effect on the nearby tissues. Furthermore, localization of the medicine avoids drug loss, leading to the highest level of pharmacological effectiveness. Numerous carriers, including serum proteins, synthetic polymers, and immunoglobulin liposomes, erythrocytes, niosomes, and microspheres have been used to target drugs. [1] Niosomes are one of these superior carriers. Non-ionic surfactants' ability to self-assemble into vesicles was initially discovered by scientists working in the cosmetics sector in the 1970s. Niosomes are microscopic lamellar structures that go by the name of non-ionic surfactant vesicles. created when cholesterol is combined with a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class. [2] Non-ionic surfactants' ability to self-assemble into vesicles was initially discovered by scientists working in the cosmetics sector in the 1970s. One can change the properties of the vesicle by varying its composition, size, lamellarity, tapping volume, surface charge, and concentration. A few of the forces at play on the object include Forces of Van der Waals between molecules of surfactants, electrical discharges between detergent molecules' charged groups and entropic forces between surfactant short-acting forces, head groups, etc. The niosomes' vesicular structure is preserved by these stresses. However, the stability of niosomes is influenced by a variety of factors, including the type of surfactant used, the makeup of the medication that is included, the temperature of storage, detergents, using lipids that cross membranes, the in-situ interfacial polymerization of surfactant monomers, and the presence of charged molecules. The water-loving, amphiphilic, and lip-loving components of an establishment allow it to receive pharmacological components that include solubilities.[3] They could possibly work as a storehouse, producing the medication. By delaying clearance from circulation, shielding the medication from its biological environment, and limiting the effects to target cells, drug molecules can also act therapeutically more effectively. [4] Alpha, omega-hexadecyls-(1-aza-18-crown-6) (Bola-surfactant)-Span 80-cholesterol (2:3:1) is the main component of noise-making bola surfactant.[5] Niosome preparation requires the use of nonimmunogenic, biocompatible, and biodegradable surfactants. Dry protostomes can be wet right when making watery niosome dispersion forms. It is now easier to transport, distribute, store, and administer medications, and niosome issues like aggregation, fusion, and leaking are handled. [6Like liposomes, niosomes affect the medication's organ distribution and metabolic stability while boosting drug circulation in vivo. [7] Similar to liposomes, the nature of the bilayer and the manufacturing procedure have an impact on the properties of niosomes. According to reports, cholesterol's intercalation It reduces the trapping volume of the formulation, and as a result, the effectiveness of the trap. [8] However, liposomes and niosomes have differing qualities from one another, in part because noisomes are created from neutral or charged cholesterol and single-chain uncharged surfactant while liposomes are made from double-chain phospholipids. Liposomes contain a large amount of cholesterol than niosomes do. Liposomes are therefore less efficient than niosomes at encasing pharmaceuticals. Phospholipids, one of the components of liposomes, are chemically fragile and demand careful handling and storage due to their tendency for oxidative disintegration. The grade of phospholipids that occur in nature also varies. Niosomal medication delivery may be used by many pharmaceuticals to treat a variety of diseases. It can also be utilized to create a cutting-edge drug delivery system for medications that are difficult to absorb. By overcoming the anatomical barrier of the gastrointestinal system through the transcytosis of M cells from Peyer's patches in the intestinal lymphatic tissues, it increases bioavailability. [9] The reticule-endothelial system absorbs niosomal vesicles. Such targeted medicine accumulation is used to treat disorders like leishmaniasis, a parasitic infection that affects the liver and spleen cells. [10,11] Immunoglobulins and other non-reticuloendothelial systems can also detect the lipid surface of this delivery mechanism. [2-8,10-12] Encapsulating several antineoplastic drugs in this carrier vesicle aims to reduce the drug's adverse effects while keeping or occasionally increasing activity against tumors. [13] The acycline medication doxorubicin has an irreversible, dose-dependent cardiotoxic effect and has broad-spectrum anticancer activity. [14,15] When the drug was given orally to mice with S-180 carcinoma, it improved their lifespans and inhibited sarcoma growth. After receiving methotrexate trapped in niosomes intravenously, mice with S-180 tumors completely regressed, and methotrexate plasma levels and elimination slowed. Particularly for treating severe brain cancer, It regulates successfully the medication's release rate. [16] Studies investigating the characteristics of the immune system reaction triggered by pathogens have used niosomes. [17]

Niosomes are capable of carrying hemoglobin. It is possible to change the curve that separates hemoglobin from oxygen to mimic that of non-encapsulated hemoglobin, and oxygen can pass through vesicles [18,19]. The sluggish absorption of medications through the main disadvantage of transdermal administration is the skin. [20] Niosomes are frequently given by epidermal technique to improve the therapeutic efficacy of numerous medications that inhibit inflammation, such as flurbiprofen and piroxicam, as well as sex hormones, such as estradiol and levonorgestrel. When medications are administered topically, parenterally, or orally also provides improved medication saturation at the site where it works because of its cellular structure. The continuous release activity of niosomes makes it Drugs having low therapeutic indices and water solubilities may be delivered. Niosome drug administration is one strategy for producing localised drug activity because of their small size and weak capacity to penetrate connective tissue or epithelium. This method confines the drug to the site for administration. For instance, mononuclear cells absorb antimonial contained in niosomes, causing the drug to be localized, increasing its effectiveness and making it less toxic and needing lower doses. Localized pharmacological action lessens systemic negative effects while enhancing drug potency and efficiency. [13] Although liposomal drug delivery technology is still in its infancy, illness, and tumor chemotherapy have already shown promise.

1.1. VARIOUS TYPES OF NIOSOMES

Based on the size of the vesicle, niosomes can be divided into three groups. The three types are multilamellar vesicles (MLV, size 0.05 m), large unilamellar vesicles (LUV, size 0.1 m), and small unilamellar vesicles (SUV, size 0.025-0.05 m). m).

Methods of Preparation

Depending on the vesicle morphologies and distribution, the number of multiple sections, liquid phase entrapment efficiency, and pores of vesicles, various ways are utilized to produce niosomes.

- ✓ **1.1.1. Making tiny unilamellar vesicles**
- ✓ *Sonication:*
- ✓ The surfactant and cholesterol combination are mixed with the drug-containing aqueous phase in a scintillation vial using sonication. [11] Utilizing a sonic probe, the mixture is homogenized for three minutes at 60 °C. The vesicles are all identically modest in size.
- ✓ *Micro fluidization*

1.1.1. In Two fluidized streams go forward through a carefully designed tunnel in the connection chambers before crashing together at incredibly high speeds. [21] To make sure because what is supplied to the system remains contained within the clamorous space, a common gateway is established up in this instance. Increased reproducibility, reduced size, and improved uniformity are the outcomes.

1.1.2 Multilamellar vesicle preparation

- ✓ **The thin film hydration process (hand shaking method)**
- ✓ Using a rotary evaporator, the mixture of surfactant and cholesterol is separated in a flammable organic solvent that includes such as diethyl ether, chloroform, or methanol. in the hand shaking method, leaving a thin coating of the solid mixture on the flask wall. [11] The dry layer is held at room temperature and gently mixed while being hydrated with a drug-containing aqueous phase.

✓Drug uptake via trans-membrane pH variation (remote loading) in an acidic environment

1.2.4 The chemical chloroform is used to dissolve detergent and lipids. [22] The solvent is subsequently vaporized at a lower temperature, leaving the round-bottom flask's wall with a thin layer of solvent concentration of 300 mM (with a pH 4.0) of the acid citric has been hydrated onto a film using vortex mixing. Before being sonicated, the multilamellar vesicles go through three cycles of freezing and thawing. This niosomal suspension is combined with the drug's 10 mg/ml aqueous solution before being spun around. The material's temperature is then increased by one million sodium phosphatases at 7.0–7.2. The mixture must then be heated for another ten minutes at sixty degrees Celsius to create the necessary multilamellar particles.

1.1.2Developing big unilamellar cells

- ✓ **Reverse phase evaporation technique (REV)**

In this procedure, a chloroform and ether solution are used to dissolve the cholesterol and surfactant. [23] This is combined with an aqueous phase that contains medication, then at a temperature of 4-5°C both components are sonicated. The translucent gel that has formed is further sonicated after just a little phosphate buffer has been added. The organic phase is removed at 40 °C using low pressure. Niosomes are created by diluting the ensuing thick nucleus dispersion with a saline solution containing phosphate before heating it for ten minutes in a bath of water at 60°C.

✓ **Ether injection method**

The 0.25 ml/min the crucial stage in the ether-based method is the administration of liposomal components into a warmed aqueous phase kept at 60°C using a 14-gauge syringe. [11,24] The ether gradient presumably stretches towards the aqueous-nonaqueous boundary as a result of the solvent's delayed vaporization, causing the development of larger unilamellar particles. The former may have facilitated the formation of the bilayer structure. The method's drawback is that it is challenging to get rid of the little amounts of ether that are frequently present in the vesicle suspension.

Miscellaneous

✓ **Multiple membrane extrusion method**

1.2. In chloroform, surfactant, cholesterol, and diacetyl phosphate mix by evaporation to bring about a light coating. [20] A water drug solution is used to wet the film, and the resultant suspension is ejected. in a series of up to eight passes via a set of polycarbonate membranes. This is an effective method for limiting the amount of noise.

1.3. Niosome preparation using polyoxymethylene alkyl ether

A different technique can be used to modify the size and quantity of cholesterol and polyoxymethylene alkyl ether bilayer vesicles. [25] When the temperature is normal, severe shaking has the reverse effect, turning into smaller unilamellar particles from multilamellar ones. However, when the temperature exceeds 60°C, little Large multilamellar vesicles (>1 m) develop from unilamellar vesicles. Due to the dissolution of hydrogen bonds between water and polyethylene glycol (PEG) moieties at higher temperatures, it is known that PEG and water mix. transformation from unilamellar to Polyoxymethylene alkyl ethanol solvent may exhibit vesicles with multiple layers at greater temperatures. The free drug is often extracted from the encapsulated medication using a centrifugation method, gel permeation chromatography, or a dialysis procedure. Although the as opposed to liposomes, noisome and the outer phase often have smaller variances in density. it can be particularly difficult to separate noisome by centrifugation. By including protamine, the vesicle suspension can be made more separable during centrifugation.

1.3.1. Emulsion method

An organic mixture of cholesterol, the surfactant used, and a water-based mixture containing the medication are combined to create an emulsion of oil and water (o/w). [26,27] Noisome are then dispersed in the aqueous phase after the organic solvent has evaporated.

1.3.2. Lipid injection method

With this approach, there is no pricey organic phase necessary. Here, the first melting of the lipid and surfactant mixture is preceded by the introduction of a heated, vigorously agitated a phase of water that contains the absorbed medication. A melted triglyceride can then be used to dissolve the medication. injected into an agitated, heated, and surfactant-containing aqueous phase.

1.3.3. Micelle-based niosome preparation

The enzymes from a combination of the micellar mixture can likewise be employed to create niosomes. When polyoxymethylene cholesteryl subacetate diester (PCSD), calcium hydrogen phosphate, and C16 G2 are combined in a micellar solution, esterase's cause the creation of a noisy dispersion. The esterase's break down PCSD, which results in the production of polyoxymethylene, sebacic acid, and cholesterol. C16 G2 niosomes are produced when cholesterol, C16 G2, and DCP are combined.

1.3.4. Characterizations of niosomes

✓ ***Size***

✓ The laser light scattering technique can be used to determine the average diameter of niosomal vesicles, which are believed to have a spherical shape. [28] Additionally, freeze-fracture electron microscopy, photon correlation microscopy, optical microscopy, ultracentri fugation, and molecular sieve chromatography can all be used to quantify the diameter of these vesicles [29,30]. The increase in vesicle diameter brought on by niosome freeze-thawing may be due to vesicle fusion during the cycle.

✓ ***Bilayer development***

✓ Under light polarization microscopy, an X-cross formation is an indication of the assembly of non-ionic surfactants into a bilayer vesicle. [31]

✓ ***The quantity of lamellae***

Nuclear magnetic resonance (NMR) spectroscopy is used for determining it., electron microscopy, and X-ray small-angle scattering. [29]

✓ **Membrane stiffness**

By tracking the temperature-dependent mobility of a fluorescent instrument, or cell rigidity can be determined. [31]

✓ **Entrapment success**

The amount of drug remaining present After complete vesicle breakdown with 50% the n-prop or 0.1 percent Triton X-100 and examination of the remaining solution using the right test procedure for the medication, in niosomes is determined. Following the creation of niosomal dispersion, unentrapped medication is separated. The entrapment efficiency (EF) = (Amount ensnared / Total Quantity) 100 can be used to symbolize [32].

✓ ***Study of In Vitro Production***

Dialysis tubing was utilized in disclosed in a method to analyze the release into the environment in vitro rate. [33] distilled water has been used to soak a cleaned dialysis bag. The cell dispersion was put into the tubing-based bag and then sealed. Then, the bag containing the vesicle was filled with a 250 ml beaker that contained 200 ml of buffer solution. At either 25°C or 37°C, this beaker was vigorously shaken at all times. The appropriate assay method was used to periodically check the buffer for drug content. A different technique involved After being soaked in water that had been double-distilled for a period of 48 hours in order for the isoniazid encapsulated to swell, Sephadex G-50 powder underwent gel filtration. [34] The ready-to-use niosome suspension was initially added to the top of the column in a volume of 1 ml, and ordinary saline was used for elution. Before becoming a free drug, isoniazid that is bound to niosomes first emerges as a somewhat thick, opalescent white liquid. Niosomes that had been separated were put within a hemodialysis line with an end linked to a Sigma hemodialysis bag. The potassium phosphate buffer mixture had a pH of 7.4. as the suspension medium for the dialysis tube, which was then agitated using a magnetic stirrer. In order to analyze the samples, HPLC (high-performance liquid chromatography) was used. at predetermined intervals.

✓ **In vivo Release Research**

This study made use of rats with albinism. There were different types of these rats. The appropriate disposal syringe for the in vivo research was used to inject orally administered niosomal solution (into the tip of the artery).

✓ **Physico-Chemical Characteristics of Niosomes: Influencing Components**

On a number of factors that influence the physicochemical properties of niosomes, more detail is provided.

✓ **Main additives and surfactants of choice**

A surfactant needs to have a hydrophilic head and a hydrophobic tail in order to prepare niosomes steroidal, perfluoroalkyl, or alkyl groups that include a single, two, or more. may make up the hydrophobic tail. [35] Due to their single-chain alkyl tail, surfactants of the ether kind are riskier than dialkyl-type surfactants. Esterases convert ether-linked surfactants into triglycerides and fatty acids in living tissue, making them less toxic and chemically unstable than ether-type surfactants. [36] For the manufacture of noisy, solvents having chains of alkyl groups between C12 and C18 are suitable. Vesicles can be produced by Span range detergents with an HLB number of 4 to 8. [37] Table 1 lists numerous non-ionic surfactant types along with illustrations. [38] In addition to surfactants and medications, a variety of additives can be used to create stable niosomes. The niosomes that are produced have Different forms can be modified in terms of their permeability and durability by changing the parameters of the membrane with different additions. When a small The steric restriction that's going to ordinarily induce grouping is unaffected by the amount of solution C24 (cholesteryl poly-24-oxyethylene ether) applied to the polygonal nuclei. However, spherical niosomes are created when C16G2: cholesterol: solution (49:49:2) is introduced. [39] The structure of the membrane affects niosomes' typical size. When cholesterol is added, the niosomal membrane stiffens, which lessens medication leaking from the noisy. [40]

✓ **Hydration temperature**

The niosome's dimensions and shape are influenced by the hydration temperature. It should be higher for optimal outcomes above the point when the mixture transitions from the state of water to the solid form. the formation of nanoparticles by chemicals is influenced by variations in niosomal system temperature, which also alter vesicle shape. [35,39] a C16G2: solulan C24 (91:9) polygonal particle is heated to become a spherical vesicle at 48 degrees Celsius. However, the vesicle initially transforms into a collection of smaller, spherical niosomes at 49 degrees Celsius after being cooled from 55 degrees Celsius, and then, at 35 degrees Celsius, it transforms into polyhedral structures. Solulan C24 (49:49:2), cholesterol levels, and C16G2 formed a vesicle. in contrast, is unaffected by heat or cold. [27] Along with the above-mentioned crucial variables, other significant ones include the amount of the water media and time spent hydrating the niosomes. If these components are chosen incorrectly, poor niosomes may be produced or there may be issues with drug leakage.

Table 1: various non-ionic surfactant types

Different Type of non-ionic surfactant	Examples
Fatty alcohol	Stearyl, stearyl acetate, cetostearyl acetate, and oleyl acetate
Ethers	Brij, Nonoxynol-9 Glyceryl Laurate, Decyl Glucoside, Lauryl Glucoside, Octyl
Esters	Glucoside, Polysorbates, and Spans
Block copolymers	Poloxamers

✓ **Nature of encapsulated drug**

2. The charge and rigidity of the niosome bilayer are influenced by the physio-chemical characteristics of the medication that is enclosed. In order to increase vesicle size, the medication provides a force that causes surfactant layers to oppose one another when it mixes with hydrophobic heads in groups. [29] The bilayer's generation of charges prevents vesicle agglomeration.

3.

Table 2 lists the drug's nature's impact on vesicle production.

4. **Elements impacting the size, effectiveness of entrapment, and properties of vesicles upon release**

✓ **Drug**

✓ The interaction When a drug gets stuck in niosomes, the interaction of the solute with the head groups of the surfactant raises the charge and mutual repulsion of the surfactant bilayers, expanding the volume of the particle inside. extended PEG chains in the polyoxymethylene glycol (PEG) coated vesicles surround the medicines, decreasing their tendency to expand. The polar liquid equilibrium of the medicine affects the level of retention.

✓ **The quantity and kind of surfactant**

The mean size of niosomes improves in accordance with an increase in the hydrophilic-lipophilic balance (HLB) of surfactants such as Spans 85 (HLB 1.8) to Span 20 (HLB 8.6).

Table 2Effect of a drug's composition on niosome development

Nature of the drug	Leakage from the vesicle	Stability	Other properties
Hydrophobic drug	Decreased	Increased	Improved transdermal delivery
Hydrophilic drug	Increased	Decreased	-
Amphiphilic drug	Decreased	-	Increased encapsulation, altered
Macromolecule	Decreased	Decreased	-

because A rise in buffer hydrophilic properties coincides with a decrease in interface energy that is free. [41] several factors, including the ambient temperature, the type of phospholipid or surfactant, and whether there are additional substances like cholesterol, the bilayers of the vesicles can either be in the so-called liquid state or the gel state. While the structure of lipid layers is more chaotic in the liquid state, the chain reactions are present in a well-ordered form in the gel state. The surfactants or lipids are characterized by the temperature at which the gel-to-liquid phase transition takes place (TC). The efficiency of trapping is additionally affected by the phase transition temperature (TC) of the surfactant; for example, Span 60 with a greater TC produces greater trapping.

✓ **Cholesterol charge and content**

Niosome physicochemical size and entrapment efficiency are both increased by cholesterol. Lipid frequently has two separate impacts. Bilayer chain orders are altered by cholesterol. in both their liquid and gel states. A liquid-ordered phase develops from the gel state at high cholesterol concentrations. The bilayers were stiffer as the concentration of cholesterol increased because it slowed the rate of material release from their encapsulation. In multilamellar vesicle systems, the Charge has a propensity to increase the distance between consecutive bilayers, increasing the overall volume of material trapped. [41]

5. Techniques for Preparation

The vesicles generated by the hand shaking approach are larger (0.35–13 nm) than those generated by the method of ethanol infusion (50–1,000 nm). Smaller nuclei are able to be produced using the Reverse Phase Evaporation (REV) technique. The micro fluidization procedure results in smaller, more uniform vesicles. Protection against osmotic stress the diameter of the niosomes

shrinks when niosomes are suspended in a highly concentrated salt solution. It is believed that the blocking of membrane liquid extraction is what causes the slow initial dissolution in a hypotonic salt solution. This follows by a quick release that may be brought on by the physical loosening of the membrane formation during osmotic pressure. [2,42] The medications listed in Table 3 have undergone various routes of animal testing.

6. CONCLUSION

Recent developments in scientific study have supported tiny particles, particularly enzymes and medication, as a key class of therapeutic agents. They do, however, come with a variety of pharmaceutical-related challenges, such as limiting the bioavailability of appropriate medication administration techniques, physical as well as chemical unpredictability, and possible adverse reactions.

Table 3: Drugs used in niosomal delivery

Routes of drug administration	Examples of Drugs
Intravenous route	insulin, cisplatin, amarogentin, daunorubicin, amphotericin B, 5-fluorouracil, calprotectin, Adriamycin, cytarabine hydrochloride, vincristine, sodium stibogluconate, centchroman, indomethacin, colchicine, rifampicin, tretinoin, and glucose
Peroral route	amino acids, peptides, insulin, DNA vaccines, ciprofloxacin, norfloxacin, ergot alkaloids,
Transdermal route	Ketoconazole, annonacin, estradiol, nimesulide, dithranol, piroxicam, levonorgestrel, and ketorolac
Ocular route	cyclopentolate with timolol maleate

Although niosomes have come under fire for their failure to effectively carry peptides and biological substances, they are able to encapsulate lethal drugs such as those for AIDS, cancer, and viruses. It offers a workable carrier system as opposed to ionic drug carriers, which are typically toxic and inappropriate. However, niosome technique is still in its early stages. As an outcome, because it is a viable method for administering customized pharmaceuticals, research is being done to develop a technique that is acceptable for bulk manufacture.

Acknowledgment

I am incredibly grateful for Dr. Atul Bendale Sir guidance and assistance as I prepare this review paper. I also want to express my gratitude to all of the co-authors who provided suggestions and helped make this article helpful for our readers.

Conflict of interest

No conflict of interest has been declared.

Funding source

There is no funding source.

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