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Niosomes: A Comprehensive Review Of Their Preparation, Characterization, And Applications In Drug Delivery.

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Abstract: As an alternative to lipid-solid carriers (like liposomes), niosomes are vesicular nanocarriers that are stable, non-toxic, biodegradable, and reasonably priced. The instability, rapid disintegration, bioavailability, and solubility of some drugs or natural substances may be improved by niosomes. When it comes to the targeted administration of antibacterial, antimicrobial, anti-inflammatory, antioxidant, and anticancer compounds, niosomes have the potential to be incredibly powerful systems. This essay will provide a summary of their makeup, the most popular methods for formulation, and their present application as delivery systems for cancer treatments.

Keywords: Niosomes, Drug delivery, Nanocarrier, Vesicles, Nano medicine.

1. Introduction:-

Drug delivery systems (DDS), which are intended to deliver therapeutic drugs to certain locations inside the body while maximizing their pharmacokinetics and reducing their adverse effects, are essential to modern medicine. These systems cover a broad spectrum of technology, including several delivery routes such parenteral, transdermal, and oral techniques. The necessity to address the special difficulties presented by novel treatment Drug delivery has been significantly impacted by modalities, especially biopharmaceuticals like proteins, peptides, and nucleic acids, which typically have stability and bioavailability issues.1 3.

One of the new DDS methods that has showed potential as an alternative to traditional carriers like liposomes is niosomes. Niosomes, which are vesicular structures composed of cholesterol and non-ionic surfactants, have advantages over liposomes, such as greater stability and lower production costs. 2 4.

Their unique composition allows them to encapsulate both hydrophilic and lipophilic drugs, making them versatile carriers for a variety of therapeutic treatments. This property is particularly beneficial for poorly soluble drugs since niosomes can boost their bioavailability by facilitating their passage across biological barriers such as the gastrointestinal tract.. 2 4.

Applications for niosomes may be found in many different therapeutic fields. For example, they have been studied for targeted medication delivery in cancer treatment, where chemotherapeutic drugs might be encapsulated to improve local effectiveness and decrease systemic toxicity. By improving drug retention at the target location and regulating release rates, niosomal formulations of medications such as doxorubicin have been shown in studies to dramatically improve survival rates in tumor-bearing animal

models. 2 4

Furthermore, compared to conventional delivery methods, niosomes' enhanced ability to cross biological membranes can more effectively activate immune responses in the administration of biologics and vaccines..4 6.
Their size and surface properties can be tailored to optimize interactions with biological tissues, enhancing localized drug action while minimizing systemic exposure and potential side effects. 2 4

Benefits of niosomal drug delivery systems, but there are obstacles to overcome before they can be commercialized. Regulatory obstacles pertaining to production procedures and quality control standards are among them. Nevertheless, current studies are aimed at removing these obstacles by improving niosome formulation methods and investigating their uses in industries other than pharmaceuticals, such as food sciences and cosmetics. 4 6

2. Niosomes' significance in contemporary medicine delivery:-Niosomes have generated a lot of attention in modern drug delivery techniques due to their unique properties and advantages over more traditional carriers like liposomes. These vesicular structures, which are composed of cholesterol and non-ionic surfactants, may encapsulate a range of therapeutic compounds, including both hydrophilic and lipophilic drugs. One of the key benefits of niosomes is their greater stability compared to liposomes, which are more likely to degrade. By allowing niosomes to maintain the integrity of encapsulated drugs during administration and storage, this stability improves bioavailability and therapeutic effectiveness.1 2.

Another crucial component of niosomes' significance in contemporary medicine is their capacity to provide tailored medication delivery. Researchers can increase the specificity of medication delivery to sick tissues while reducing systemic exposure by altering the surface properties of niosomes, for as by adding targeting ligands or using stimulus-sensitive materials. Because niosomal formulations may carry chemotherapeutic medicines directly to tumor cells, minimizing damage to healthy tissues and enhancing treatment results, this focused strategy is very advantageous in cancer therapy. 3 4.

For example, research has demonstrated that doxorubicin encapsulated in niosomal form not only prolongs the lives of tumor-bearing mice but also improves the anti-tumor efficiency of the medication while reducing its cardiotoxic side effects .3

Niosomes also solve problems with poorly soluble medications, which frequently make it more difficult to administer treatments effectively. Niosomes can enhance solubility and promote absorption through biological barriers, including the gastrointestinal system, by encapsulating these medications within their vesicular structure. For natural goods and biologics that could otherwise be challenging to administer efficiently, this feature is especially beneficial. 2 5.

Furthermore, niosomes have a regulated release profile that enables long-term drug activity, which is essential for drugs that need exact dosage schedules or have limited therapeutic indices.Beyond their use in cancer treatment, niosomes are also being investigated for use in gene therapy, vaccine administration, and diagnostic imaging. Their promise in immunotherapy is highlighted by their capacity to boost immune responses when employed as vaccine carriers. 1 2.

Additionally, research is also being done to improve niosomal formulations and investigate new preparation methods that might maximize their effectiveness in a range of medicinal domains.

3. Preparation of Niosomes:-

A) Techniques for Making Small Unilamellar Vesicles

1) The Micro-Fluidization Method: This technique uses the submerged jet principle to create consistently small unilamellar niosomes. The two streams—the lipid dispersion phase and the aqueous phase—are forced to move at a very high pressure and speed to the membrane + pressurized vessel, where they converge, by use of pneumatic pumps. A uniform pressure profile at very high pressure is necessary to achieve niosome dispersion and compact size. This is created by turbulent mixing in the membrane + pressurized vessel, a continuous micro-channel. This approach offers several advantages, including increased uniformity, decreased size, maximal aqueous phase encapsulation, and high production rates. Degradation of the lipid phase is one potential negative effect of the high pressure in the interaction chamber.

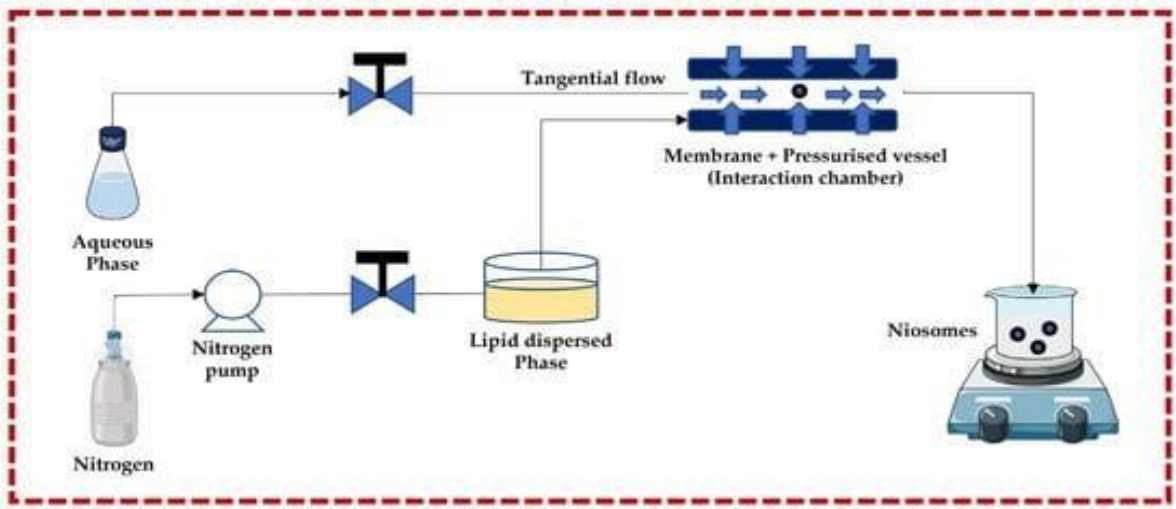

Figure 1. Schematic representation of the micro-fluidization technique.

2) The Sonication Method

Using a buffer solution containing the dissolved drug or organic material, cholesterol and a non-ionic surfactant are dispersed. This mixture is also run through a bath sonicator to create niosomes. Despite the advantages of rapid size reduction and accurate temperature control, heat production could be the main disadvantage.

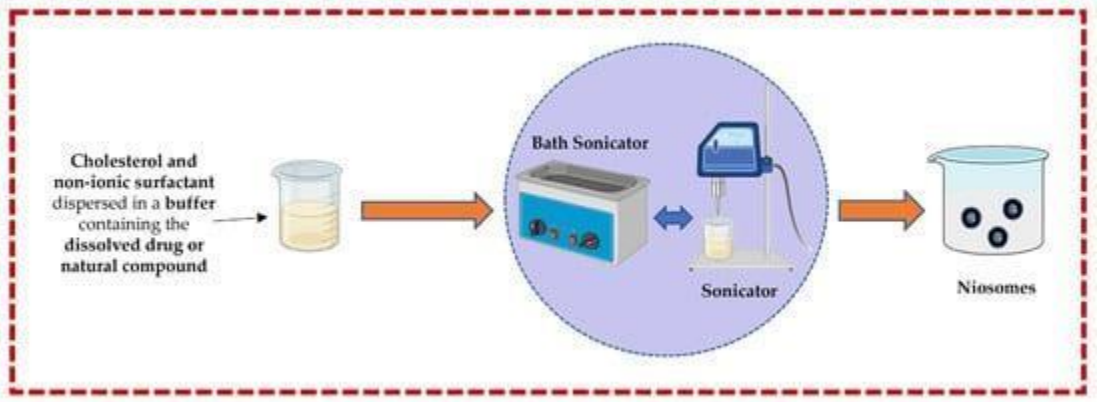

Figure 2. Schematic representation of the sonication technique.

3) The Technique of Multiple Membrane Extrusion

Niosome size may be controlled using this technique. Surfactant, cholesterol, and diacetyl phosphate are dissolved using an organic solvent (such chloroform). The thin film is then hydrated with an aqueous solution containing the drug or natural ingredient after the solvent is eliminated by rotational evaporation. The fluid is extruded through polycarbonate membranes to produce the niosomes. Better control of niosome size and the resulting reduction in polydispersity are important advantages. However, there are also disadvantages, such increased product loss and lengthier formulation times.

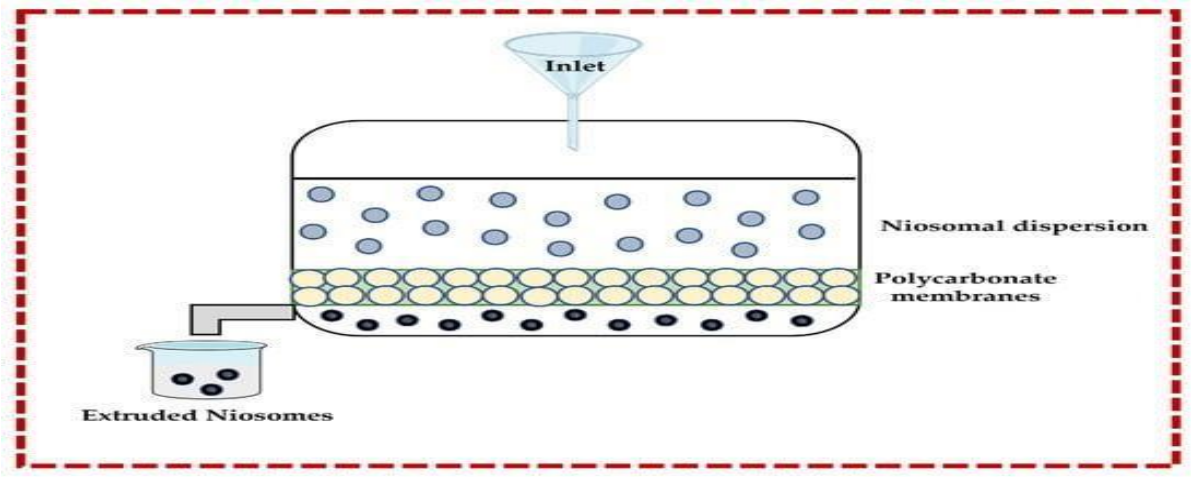

Figure 3. Schematic representation of the Multiple Membrane Extrusion Technique.

B) Techniques for Making Big Unilamellar Vesicle Niosomes

1) The technique of injecting ether

The lipidic component (cholesterol) and non-ionic surfactant are dissolved in ether and then gradually injected via a needle into the drug- or natural-molecule-containing aqueous phase while being stirred at a temperature higher than 60 °C in a heated water bath. The incredibly long procedure and the small quantity of ether present in the vesicle suspension are the drawbacks.

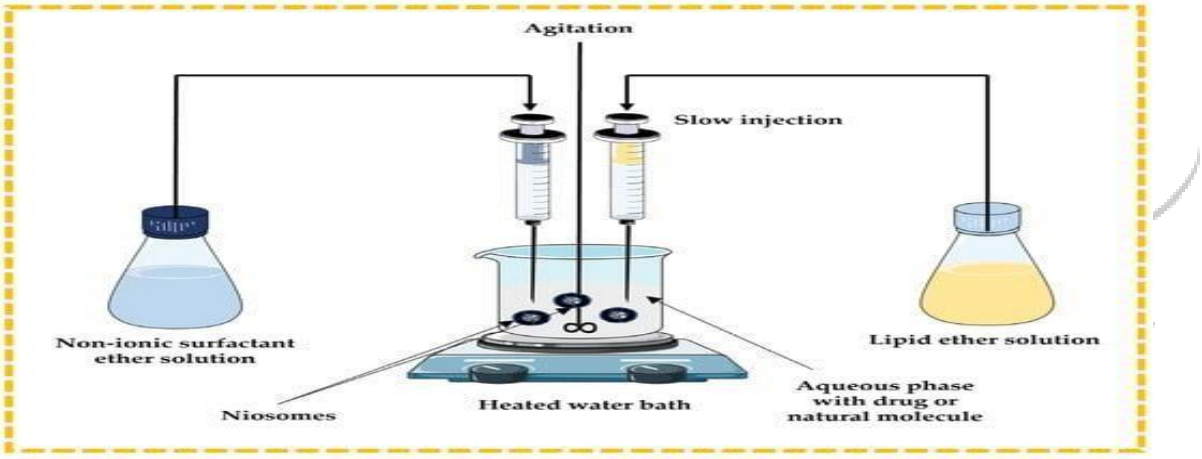

Figure 4. Schematic representation of the ether injection technique.

2) The Lipid Injection Method

There are no organic solvents used in this process. Melted cholesterol and surfactant are quickly injected into a heated aqueous phase containing the dissolved drug or natural substances to form niosomes.

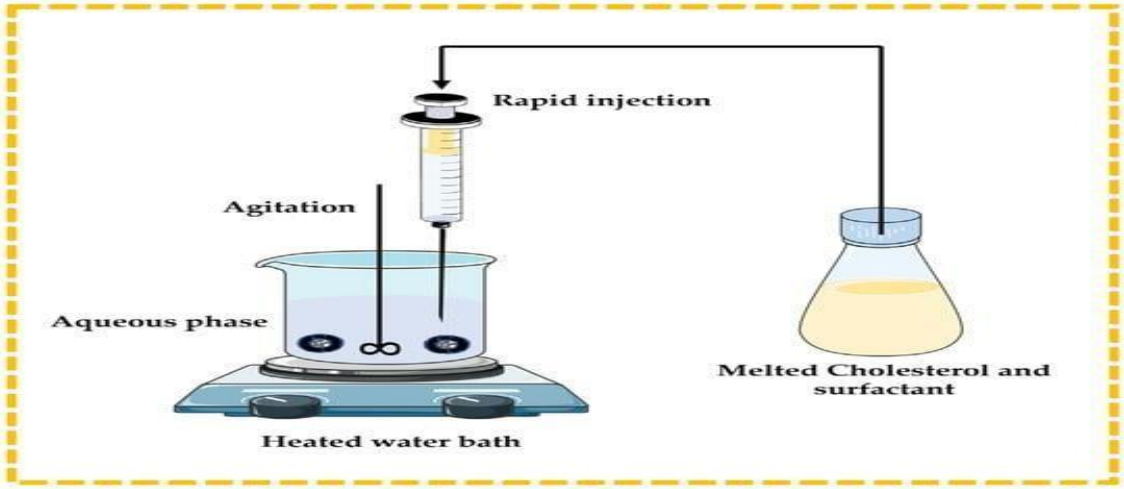

Figure 5. Schematic representation of the lipid injection technique.

3) The Bubble Method

This new one-step process creates niosomes without the need of an organic solvent, which is very useful for creating big unilamellar vesicles. Cholesterol, buffer solution, and non-ionic surfactant are mixed in a three-neck round-bottom flask. The third neck supplies nitrogen, and the temperature is controlled by a thermometer and water-cooled reflux. The dispersion is put to a water bath that has been heated to 70 °C in order to create niosomes.

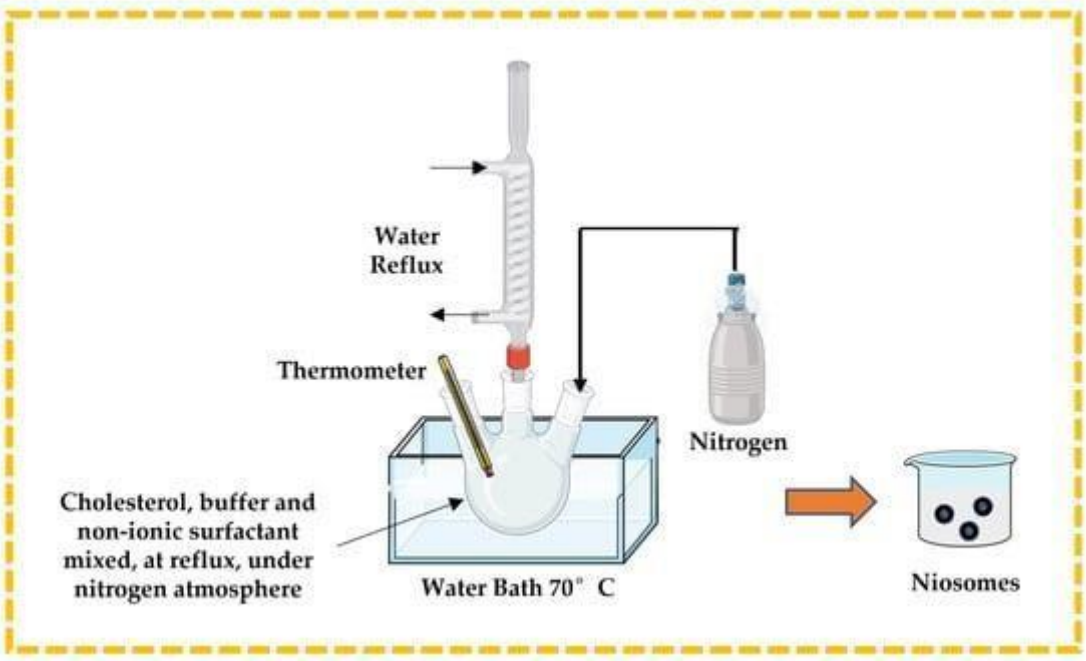

Figure 6. Schematic representation of the bubble technique.

4) The Method of Reverse-Phase Evaporation

An suitable organic solvent, such as chloroform or ethyl ether, is used to dissolve the cholesterol and surfactant. An aqueous phase containing the drug or natural chemical is then added, and the two immiscible phases are homogenized and sonicated. The organic solvent is extracted from the resultant emulsion using rotary evaporation in order to create niosomes.

Figure 7. Schematic representation of the reverse phase evaporation technique.

C) Techniques for Multilamellar Vesicle Niosome Preparation

1)Method of Trans-Membrane pH Gradient

This technique is effective for ionizable hydrophobic compounds. The cholesterol, surfactant, and hydrophobic molecule are dissolved using an appropriate solvent, such chloroform. The solvent is removed by rotary evaporation, leaving a thin film on the wall of a round-bottom flask, and the residue is then hydrated with citric acid at a pH of 3.0 or 4.0 in a beaker. After that, the resultant suspension is frozen, thawed, and sonicated. Next, an aqueous solution containing a drug or natural molecule is added to the suspension and agitated using a vortex mixer. The liquid is heated to 60 °C to create niosomes after the pH is raised to 7.0 using a

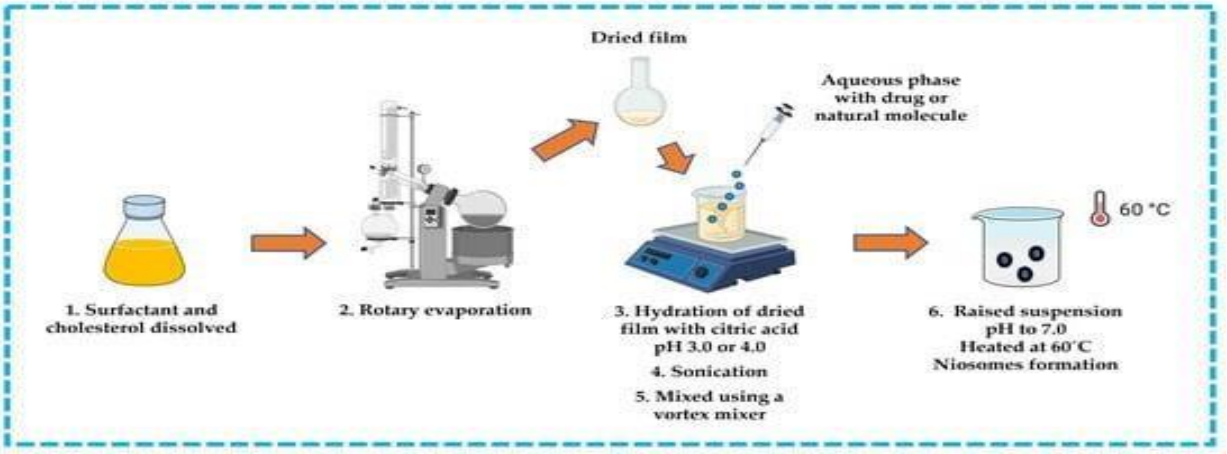

Figure 8. Schematic representation of the trans-membrane pH gradient technique

2) The Thin-Layer/Thin-Film Hydration Method

The formation of niosomes frequently use this technique. The cholesterol and surfactant are dissolved using a suitable organic solvent (such as ether, ethanol, or chloroform). A dry thin- film layer forms within the flask after the organic solvent is removed by vacuum/rotary evaporation. The drug is dissolved in an aqueous solution and then added to the resultant film to hydrate it. To create niosomes, the hydrated film must be incubated in a water bath above the transition temperature of the surfactants.

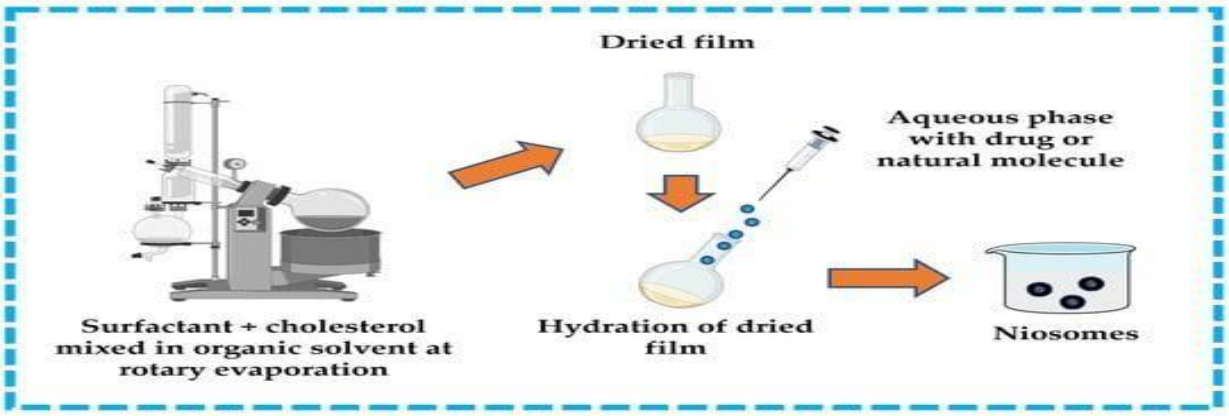

Figure 9. Schematic representation of the Thin-Film/Thin-Layer Hydration Technique

4. New Developments in Niosome Delivery Systems for Cancer Treatment

Currently available therapeutic treatments for cancer, one of the world's most lethal diseases, including immunotherapy, gene therapy, radiation, chemotherapy, surgery, magnetic hyperthermia, and more. Surgery is necessary for many cancer therapies, but it can be challenging to conduct timely, safe, and successful cancer surgery. Inadequate biodistribution and solubility, adverse effects, reduced therapeutic efficacy, or even treatment failure are some of the issues that usually restrict other therapeutic clinical treatments that rely on molecules with anticancer characteristics.

The development of novel techniques, strategies, and materials to fight cancer has been the focus of massive scientific efforts over the last few decades. Nanotechnologies have been thoroughly researched for cancer treatment as biotechnology has developed in order to increase safety, accuracy.

Figure 10. Schematic representation of the Recent progress in niosomes in the most common types of cancers found worldwide.

5. Niosome Characterization

Niosomes are vesicular systems based on non-ionic surfactants that require careful characterization to guarantee their effectiveness in drug delivery applications. Numerous methods are used to assess their stability, shape, efficacy of encapsulation, and drug release patterns.

A) Morphology

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are the main methods used to determine the morphology of niosomes. While TEM produces high- resolution pictures that show the internal structure and dimensions of individual vesicles, SEM offers comprehensive images of the surface structure that enable the evaluation of size and form. Furthermore, the average size of niosomes in suspension may be determined by measuring Dynamic Light Scattering (DLS) is used to determine the particle size distribution and polydispersity index.

Together, these methods verify that niosomes usually have a spherical form, which is essential for their stability and usefulness in drug delivery applications. Additionally, surface morphology may be examined at the nanoscale using Atomic Force Microscopy (AFM), which can provide topographical data to supplement SEM and TEM findings 1,2.

B) Encapsulation Efficiency

To evaluate the therapeutic potential of medications, it is essential to ascertain how well they are encapsulated within niosomes. One popular method for comparing the quantity of medication injected into the niosomal system with the amount encapsulated is High- Performance Liquid Chromatography (HPLC).

Accurately calculating the entrapment efficiency is made possible by this technology, which is crucial for guaranteeing that the target region receives adequate therapeutic concentrations. Drug concentration in niosomal formulations may also be evaluated using other methods, such as spectrophotometry 3,4.

C) Stability Studies

For assessing chemical and physical stability under a range of environmental circumstances, stability studies are essential. In these investigations, niosome integrity is usually evaluated over time at various temperatures, pH levels, and storage settings. Freeze-thaw cycles are one technique that may be used to examine possible niosomal structural leakage or degradation and to imitate storage conditions. Additionally, physical stability may be visually monitored for aggregation or sedimentation, while chemical stability can be assessed using HPLC to detect any degradation products generated during storage. 1.5

D) Drug Release Profiles

Understanding the kinetics of a drug's release from niosomes is necessary to forecast its therapeutic efficacy. In vitro dissolution assays, commonly used to analyze release patterns, allow researchers to evaluate the rate and efficiency of a drug's release from its niosomal carrier under physiologically similar settings. Knowing this information is necessary to design niosomal formulations that provide controlled or sustained release patterns appropriate for a given therapeutic requirement. Release kinetics may be studied using a range of models, such as zero-order, first-order, and Higuchi models, depending on the drug's composition and how it interacts with the niosomal matrix.2, 3

6. Applications in Drug Delivery

Niosomes are now versatile carriers in modern drug delivery systems because they may encapsulate a range of therapeutic chemicals while enhancing bioavailability and targeting capabilities.

A) Cancer Therapy

One of the most potential applications for niosomes is the treatment of cancer. They can encapsulate chemotherapeutic medications like as doxorubicin or paclitaxel, reducing systemic toxicity and allowing for tailored administration to tumor sites. Researchers can modify the surface characteristics of niosomes, such as by adding targeting ligands, to increase the selectivity for cancer cells over healthy tissues. This targeted approach reduces the side effects of conventional chemotherapy while simultaneously improving therapeutic outcomes.1, 2

B) Antimicrobial Delivery

Niosomes may also effectively transport antimicrobial substances, including antibiotics and antifungal drugs. Because of their potential to improve solubility and bioavailability, they can be utilized to give antimicrobial drugs that are poorly soluble. Studies show that niosomal formulations can increase the efficacy of antibiotics against resistant bacteria by enhancing drug retention at infection sites and encouraging better transit across biological barriers..3, 4

C) Vaccine Delivery

Since niosomes increase immune responses and antigen stability, they are crucial for vaccine delivery. They can contain adjuvants or antigens, providing a controlled release feature that encourages long-term immune stimulation. Research indicates that niosomal vaccines can elicit stronger humoral and cellular immune responses than traditional immunization formulations. 1, 2

D) Gene Therapy

Niosomes have attracted attention in gene therapy applications because of their capacity to transfer genetic material. Niosomes have the ability to encapsulate nucleic acids, such as DNA or RNA, preventing their degradation and facilitating their uptake by cells. This characteristic positions niosomes as possible delivery vehicles for gene editing tools like as CRISPR-Cas9 or RNA interference therapies.3, 4

E) Topical and Transdermal Delivery

Niosomes are also utilized in topical and transdermal drug delivery systems due to their potential to improve skin permeability. By encapsulating drugs inside niosomes, researchers can improve drug penetration through the stratum corneum barrier. This will increase local concentrations at particular locations while reducing systemic absorption.

7. Preclinical and Clinical Research

To assess niosomal formulations for safety and efficacy in a variety of medical applications, extensive preclinical and clinical research is necessary.

A) Research *in-Vitro*

In vitro studies are an essential initial step in assessing the stability and efficacy of niosomal formulations before moving on to animal models or human trials. Stability under different conditions, cytotoxicity against target cells, release patterns, and encapsulation efficiency are often assessed in laboratory studies. These studies provide essential information on how well a formulation works in controlled circumstances

and help uncover any potential issues before proceeding to more complex in vivo investigations. 1,2

A) *In-Vitro* Research

In order to evaluate the safety profiles and therapeutic outcomes of niosomal preparations, in vivo studies must employ animal models. These studies help assess pharmacokinetics, which includes absorption rates, distribution patterns, metabolism rates, and potential side effects, when administered in vivo. For example, using animal models, researchers have examined the anti-tumor efficacy of doxorubicin-loaded niosomes compared to free drug delivery. The results of these studies aid in establishing dosage regimens and guiding further studies toward clinical trials. 3, 4

8. Difficulties and Restrictions

Despite the advantages of niosomes in drug delivery systems, several barriers limit their widespread application.

A) Problems with Stability

For niosomal formulations, stability problems with degradation and leakage over time are a significant challenge. Temperature or pH variations may result in the premature leakage or structural breakdown of encapsulated drugs. To solve these stability issues, careful formulation methods are required, such as increasing surfactant concentrations or using stabilizers that enhance vesicle integrity during storage.6, 7

B) Scalability

Scalability is another challenge when niosomal compositions are manufactured on a big scale after being produced in a lab. Many preparation methods that are successful for small batches may not be economical for larger batches due to increased costs or the challenge of maintaining consistent quality across batches. One of the biggest obstacles to commercializing niosomal products is currently developing scalable and reproducible manufacturing techniques. 3, 4

C) Barriers to Regulation

Navigating regulatory norms presents additional challenges for individuals producing niosomal substances. Regulatory agencies usually need thorough information on safety profiles, manufacturing processes, quality control techniques, and clinical efficacy before authorizing a product for human use. Following these stringent guidelines might lead to more expensive and time-consuming development processes for bringing new medications to market.

D) Prospects for the Future

Future prospects for niosomes in medication delivery systems are promising due to ongoing advancements in nanotechnology integration. Including Nanotechnology According to recent advancements, there is growing interest in enhancing niosome performance even more by fusing nanotechnology with traditional formulation methods. Better treatment efficacy or targeted capabilities against challenging diseases like infectious or malignant disorders may arise from innovations like the use of nanoparticles or modifications to surfactant compositions. 5, 7

E) Customized Healthcare

Another exciting prospect is tailoring niosome formulations for uses in personalized medicine. Traditional drugs may have fewer adverse side effects while enhancing therapeutic outcomes if therapies are tailored to each patient's needs. This approach could involve changing formulation features like size distribution or surface qualities, depending on patient- specific factors like ailment kind or genetic profile. 3, 4

F) Eco-Friendly Methods

Not to mention, there is an increasing emphasis on developing eco-friendly production methods that minimize the negative effects on the environment while maintaining cost- effectiveness throughout the manufacturing processes of niosome manufacture. Adopting sustainable methods might benefit global efforts to promote environmentally friendly healthcare in addition to assisting businesses. 1, 2.

9. Future Prospects: Possible effects of niosomal advancements on medication administration::-

Niosomes are gaining popularity in the drug delivery sector because to their unique properties and versatility. Being vesicles based on non-ionic surfactants, they provide a good alternative to traditional

drug delivery techniques, particularly in terms of concentrating on specific illnesses and minimizing adverse effects. Future advancements in niosomal technology might drastically change how drugs are delivered, increasing patient adherence and treatment effectiveness.One of the most appealing aspects of niosomes is their ability to encapsulate both hydrophilic and hydrophobic drugs, which makes them perfect for a range of therapeutic applications. This flexibility enables the development of formulations that effectively deliver poorly soluble drugs, which typically provide significant pharmacotherapy challenges. Niosomes can guarantee this by increasing these substances' solubility and bioavailability.1,2

The potential for customized drug delivery is another area where niosomal advancements may have a big impact. By changing the surface properties of niosomes, such as adding ligands or antibodies, researchers may create formulations that preferentially concentrate in disease regions, such as tumors or inflammatory tissues. This targeted approach improves the therapeutic index of drugs while reducing systemic exposure and associated side effects.
Recent studies have demonstrated that niosomal formulations significantly improve the pharmacokinetics of anticancer medications as compared to conventional administration methods, leading to better treatment outcomes.3,4.

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