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NIOSOMES AS NOVEL DRUG DELIVERY SYSTEM: A REVIEW ARTICLE

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Abstract

Niosomes, which consist of vesicles formed by a combination of non-ionic surfactant and cholesterol, are a subject of interest. These structures are capable of serving as carriers for drugs that possess both hydrophilic and lipophilic properties. Within the realm of drug delivery systems, niosomes represent a method by which pharmaceuticals can be enclosed within vesicles. The appealing characteristics of niosomes include their biodegradability, biocompatibility, lack of immunogenicity, and structural flexibility. The primary aim of this literature review is to shed light on the diverse therapeutic applications of niosomes in the treatment of various medical conditions. This review will explore multiple facets concerning niosomes, such as their preparation techniques, mechanisms of action, facilitation of drug permeation, utilization as permeation enhancers, diverse applications in disease management, assessment of toxicity, and approaches to mitigating toxicity through the utilization of surfactants.

Key Words: Niosomes, Encapsulation, Surfactant, Vesicles, Application, and Toxicity.

INTRODUCTION:

The inception of targeted drug delivery can be traced back to the year 1909, when Paul Ehrlich initiated the groundwork for delivering therapeutic agents directly to infected cells. The concept of drug targeting revolves around the precise delivery of medication to specific sites within the body, thereby ensuring targeted action on the intended tissues. Niosomes, a novel drug delivery system, involve the encapsulation of medication within a polymer matrix in the form of vesicles. These vesicles, known as niosomes, consist of a dual layer of non-ionic surfactants, with examples such as Span-60, typically stabilized through the addition of cholesterol and significant amounts of anionic surfactants like dicetyl phosphate. The advantages of niosomes include the efficacy of lower drug dosages, stability due to their hydrophilic nature resulting in osmotic activity, enhanced drug stability through hydrophilicity, improved skin penetration of drugs, high patient acceptance due to the hydrophilic nature of the vesicles, and their function as depots for slow drug release. However, niosomes also present drawbacks such as the need for specialized equipment, high production costs, inefficient drug loading, fusion, aggregation, leakage of entrapped drugs, and limitations in shelf life due to drug hydrolysis.

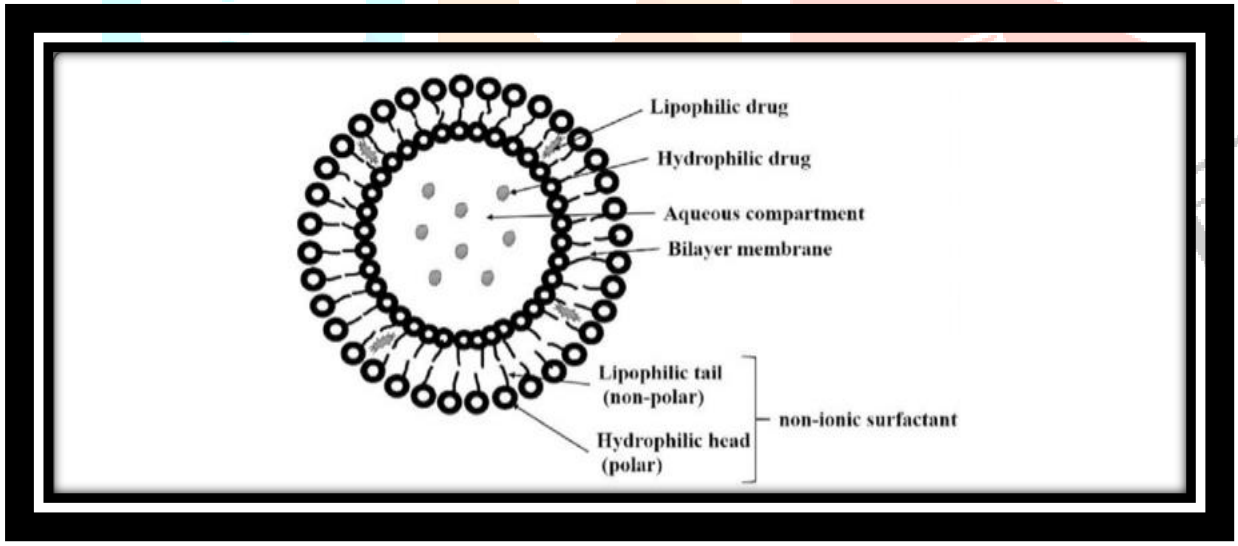
Merits Of Niosomes

• A reduced dosage is sufficient to achieve the desired therapeutic effect.
• Niosomes exhibit stability due to their utilization of a hydrophilic system, which enhances osmotic activity.
• The hydrophilic nature of niosomes results in improved stability of the entrapped drugs. • Ability to facilitate enhanced drug delivery through the skin.
• The hydrophilic vesicles in the suspension contribute to higher patient acceptance compared to oil-based systems.
• Vesicles serve as reservoirs for gradual drug release.

Demerits of niosomes

• Potential need for specialized machinery.
• Elevated production expenses.
• Inadequate drug encapsulation efficiency.
• Issues such as fusion, aggregation, and leakage of entrapped drugs.
• The detrimental impact of hydrolysis on the enclosed drugs can restrict the shelf life of a specific formulation.

STRUCTURE OF NIOSOMES[1]



Niosomes, characterized by their amphiphilic nature, consist of a non-ionic surface-acting agent like Span-60, which is stabilized by cholesterol and an ample amount of anionic surfactant such as dicetyl phosphate to maintain the stability of the vesicles.

COMPOSITION OF NIOSOMES: [1]

The components utilized in the formulation of niosomes include:
1. Cholesterol
2. Non-ionic surface acting agent

1. CHOLESTEROL:
Which is a steroid derivative employed to provide flexibility, rigidity, and appropriate shape.

2. NON-IONIC SURFACE ACTING AGENT:-

Examples of non-ionic surfactants commonly integrated into niosome preparations are Spans (e.g., Span20, 40, 60, 80, 85), Tweens (e.g., Tween 20, 40, 60, 80), and Brijs (e.g., Brij 30, 35, 52, 58, 72, 76), characterized by a hydrophilic head and a hydrophobic tail.

PREPARATION OF NIOSOMES:

Sonication Method:

Various methods are employed for the preparation of niosomes. One such method involves adding the drug solution into a buffer system, followed by the addition of this mixture into a surfactant or cholesterol mixture in a 20ml glass vial. The combination is then sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to produce niosomes.

Hand shaking method (Thin film hydration techniques):

In this technique, surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether, chloroform, or methanol in a round bottom flask. The organic solvent is evaporated at 20°C using a rotary evaporator, leaving a thin layer of solid mixture on the flask surface. The dried film of surfactant can be rehydrated with an aqueous phase at 0-60°C with gentle agitation to form multilamellarniosomes.

Micro fluidization method:

A modern approach to preparing unilamellar vesicles with a well-defined size distribution involves the use of micro fluidization. This method relies on two fluidized streams at ultra-high velocities interacting with each other. By directing the narrow liquid film onto a typical surface, the level of energy supplied to the system is preserved at a suitable level for the creation of niosomes.The outcome is niosomes with enhanced uniformity, smaller size, and improved reproducibility.

Reverse Phase Evaporation Technique (REV):

In the REV method, a 1:1 ratio of cholesterol and surfactant mixture is dissolved in organic solvents like chloroform and ether. The drug is dissolved in the aqueous phase and added to the above mixture to form two phases, which are then sonicated at 4-5°C. A clear gel is formed and further sonicated after the addition of phosphate buffered saline. The organic phase is removed at 40°C under low pressure. The resulting niosomes solution is viscous and is diluted with phosphate buffer, followed by heating in a water bath at 60°C to obtain niosomes with high yield.

The Bubble Method:

This method involves the use of a foaming unit consisting of a round-bottom flask with three necks, placed in a water bath for temperature control. Cholesterol and surfactant are dispersed in a buffer solution (pH 7.4) at 70°C, mixed for 15 seconds with a high shear homogenizer, and then bubbled at 70°C using nitrogen gas to generate niosomes.

FACTORS AFFECTING NIOSOMES FORMULATION[13]

1. DRUGS
2. NATURE AND TYPE OF
3. SURFACTANT
4. CHOLESTEROL CONTENT AND
5. CHARGE
6. RESISTANCE TO OSMOTIC STRESS
7. TEMPERATURE OF HYDRATION

1. Drugs:-Upon entrapment of drugs in niosomes, there is an alteration in the charge and rigidity of the niosomes bilayers, disrupting the hydrophilic and lipophilic balance of the drugs and affecting the degree of entrapment.

2. Nature And Type Of Surfactant[9]:- The dimensions of niosomes exhibit a direct correlation to the HLB value of the surfactant, indicating that an increase in the HLB value of the surfactant, such as span 85, leads to a proportional increase in the size of niosomes due to the decrease in surface free energy with enhanced hydrophobicity of the surfactant. A surfactant is characterized by the presence of a hydrophilic head and a hydrophobic tail, with the hydrophobic portion potentially containing alkyl or perfluoroalkyl groups, or in specific cases, a single steroidal group.

3. Cholestrol content and charge[10,21]:- The presence of cholesterol aids in enhancing the entrapment efficiency and hydrodynamic diameter of niosomes by providing membrane stabilizing properties and reducing membrane permeability. An increase in the cholesterol content of the bilayer may lead to a reduction in the release rate of the encapsulated material, consequently increasing the rigidity of the bilayers obtained. Introduction of charge results in an augmented interlamellar distance between successive bilayers within a multilamellar vesicle structure, contributing to a greater overall volume of entrapped material.

4. Resistance to osmotic stress :-The introduction of a hypertonic salt solution to the niosomes suspension results in a reduction of their diameter.

5. Temperature of Hydration :- The size and shape of niosomes are dependent on the temperature during hydration.

CHARACTERIZATION OF NIOSOMES [11]

1.Measurement Of Angle Of Repose :-

The angle of repose of dry powder niosomes can be determined using the funnel method, where the niosomes powder is funneled into a fixed position in order for the 13mm outlet orifice of the funnel to be positioned 5cm above a flat, black surface.The powder forms a conical shape on the surface, and the angle of repose is calculated by measuring the height of the cone and the diameter of its base.

2. Scanning electron microscopy [14] :-

An essential characteristic of niosomes is the particle size, which can be evaluated along with surface morphology (roundness, smoothness, and aggregation) and size distribution using scanning electron microscopy (SEM). Niosomes are sprinkled onto double-sided tape attached to aluminum stubs, which are then placed in the vacuum chamber of the scanning electron microscope for morphological characterization employing gaseous secondary electron detectors.

3. Osmotic shock[14] :-

Changes in vesicle size can be assessed through osmotic studies, where niosome formulations are exposed to hypotonic, isotonic, and hypertonic solutions for a duration of 3 hours. Subsequent to this incubation period, alterations in the vesicle size within the formulations can be observed under an optical microscope.

4. Stability Studies [15] :-

The assessment of niosomes' stability involves storing the optimized batch in airtight sealed vials at various temperatures. Parameters such as surface characteristics, percentage of drugs retained in niosomes, and niosomes derived from proniosomes are selected to evaluate stability. Any instability in the formulation may manifest as drug leakage.

5. Zeta Potential analysis[16] :-

Conducting zeta potential analysis is crucial to comprehend the colloidal properties of the prepared formulation. The diluted Niosomes derived from proniosomes dispersion are analyzed using a zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry methods at a set temperature of 25°C. The

charge on vesicles and their mean zeta potential values, along with standard deviations, are directly obtained from these measurements.

IN-VITRO METHOD FOR NIOSOMES[18]

The study of in vitro drug release from niosomes can be conducted through various methods such as

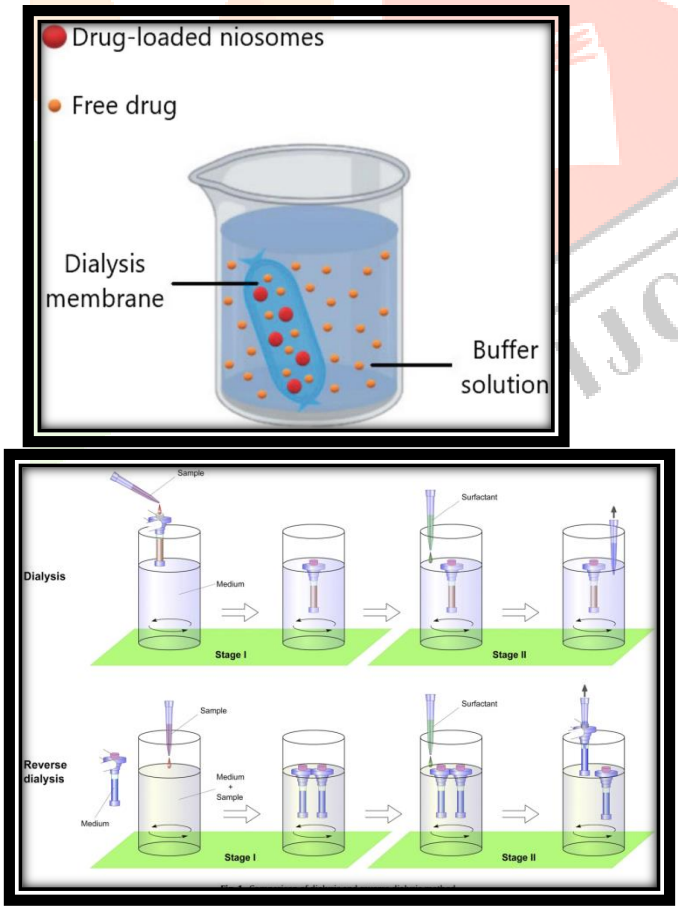
- Dialysis Tubing
- Reverse dialysis
- Franz diffusion cell

1. Dialysis Tubing:-

In-vitro drug release is facilitated by placing niosomes in prewashed dialysis tubing that is hermetically sealed. This tubing is then dialyzed against a suitable dissolution medium at room temperature, and samples are withdrawn at specific intervals. Ensuring sink conditions is imperative during this process. [17]

2.Reverse Dialysis[19] :-

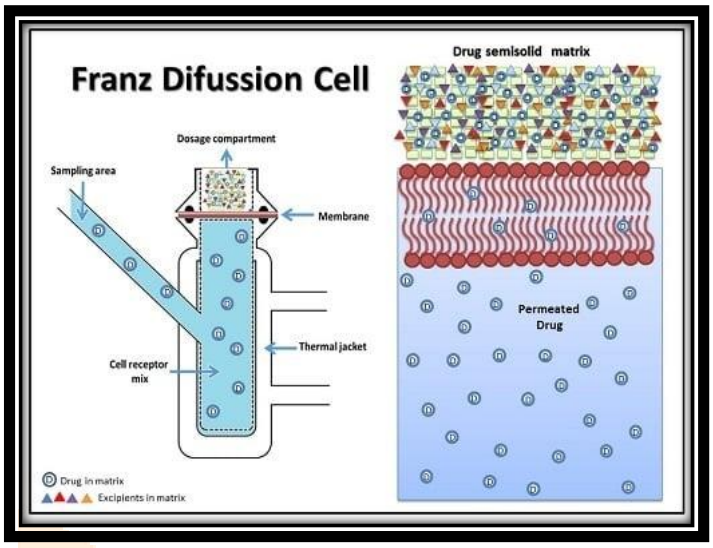
In this technique, a small dialysis sac containing 1ml of dissolution medium is placed in proniosomes, which are then introduced into the dissolution medium. This method allows for direct dilution of proniosomes, but it may not accurately quantify rapid releases. [20]



3.Franz diffusion cell :-

The Franz diffusion cell method is another approach to investigate in vitro diffusion studies. Proniosomes are positioned in the donor chamber of the Franz diffusion cell, equipped with a cellophane membrane. The proniosomes are dialyzed against a suitable dissolution medium at room temperature, and samples are

withdrawn at regular intervals for drug content analysis using appropriate methods (UV, spectroscopy, HPLC, etc.). Maintaining sink conditions is vital. [10, 21]



APPLICATIONS OF NIOSOMES [10,21]

- The utilization of niosomes has been applied to investigate the immune response elicited by antigens.
- It is extensively utilized for the examination of drug targeting.
- Niosomes can serve as a treatment modality in anti-neoplastic therapy, particularly in the context of cancer treatment. Moreover, they can function as carriers for hemoglobin.
- Presently, niosomes are employed in the delivery of peptide drugs, showcasing promising therapeutic effects in ocular drug delivery.
- Additionally, they find wide applications as diagnostic agents.

Immunological Application Of Niosomes[22]

Essentially, niosomes are instrumental in exploring the characteristics of the immune response triggered by antigens. These lipid vesicles can also facilitate drug targeting towards organs beyond the reticulo-endothelial system. A carrier system is integrated with niosomes to specifically target organs within the human body.

Sustained Release [22]

Sustained release mechanisms can be effectively employed for drugs with a low therapeutic index and poor solubility.

Localized Drug Action[22]

The contemporary approach of drug delivery through niosomes enables precise localization of drug action due to their size and limited penetration through epithelial and connective tissues, ensuring targeted drug delivery at the site of administration.

Transdermal delivery of drugs by niosomes[22]

The challenge of slow drug penetration through the skin in transdermal drug delivery can be overcome through enhanced transdermal drug delivery rates facilitated by niosomes. Topical niosomes can act as a solubilization matrix and a local depot for sustained release of dermally active compounds, enhancing penetration.

Leishmaniasis[22]

Leishmaniasis is a disease characterized by the infiltration of Leishmania parasites into liver and spleen cells. Niosomes are utilized to achieve high drug concentrations in the body without inducing adverse effects.

ROUTE OF APPLICATION OF NIOSOMES DRUGS [1]

Intravenous route
Intravenous Route Examples include Doxorubicin, Comptothecin, Insulin, Zidovodin.

Inhalation
Inhalation Illustrative instances encompass all trans-retinoic acids.

Transdermal route
Transdermal Route Instances comprise Piroxicam, Estradiol, Nimesulide.

Ocular route
Ocular Route Examples are Timolol Maleate, Cyclopentol.

Nasal route
Nasal Route Examples include Sumatriptan, Influenza Viral Vaccine.

TOXICITY OF NIOSOMES:

The toxicity associated with niosomes is dependent on the nature of their components. Non-ionic surfactants exhibit higher biocompatibility and lower toxicity compared to anionic, amphoteric, and cationic surfactants. The presence of surfactants in vesicular systems in equivalent amounts significantly reduces the properties of niosomes. Hofland et al. conducted a study evaluating the toxicity of various surfactants utilized in niosomal formulations on human keratinocytes. They suggested that ester-type surfactants are less toxic due to enzymatic degradation of ether bonds. The hemolytic test is utilized to predict surfactant toxicity, with implications for vesicular systems derived from such assessments. Hofland et al conducted an investigation into the cytotoxicity of various surfactants utilized in niosomal formulations on human keratinocytes. They also presented a hypothesis suggesting that ester-based surfactants are less harmful due to enzymatic breakdown of ether bonds. The hemolytic assay was employed to assess the toxicity of surfactants, and vesicular systems were developed based on these findings. Recent studies have shown that the ability of niosomes to disrupt red blood cells depends on the length of the alkyl chain in the surfactant and the size of the colloidal particles in suspension. Shorter carbon chains tend to insert more effectively into erythrocyte membranes, disrupting their molecular structure; however, niosomes encounter challenges in interacting with biological membranes, resulting in significant hemolysis. Niosomes formulated with bolaform surfactants demonstrated favorable safety and tolerability profiles both in vitro with human keratinocytes and in vivo with human subjects, who did not exhibit skin redness when treated topically with a drug-free bolaformniosome formulation.

Niosomes As Percutaneous Enhancers:

When utilizing niosomes on the skin, it is essential to differentiate between the desired effects, whether it is a local impact within the skin (dermal drug delivery) or a systemic impact involving absorption through the skin (transdermal drug delivery). Achieving systemic circulation is the objective of transdermal targeting, which has become a key focus for many pharmaceutical research groups investigating conditions such as inflammation, cancer, psoriasis, alopecia, and acne. The transdermal route offers several advantages over conventional routes of drug administration: it avoids peak and trough levels in the bloodstream (associated with intravenous therapy); bypasses first-pass hepatic metabolism and gastrointestinal degradation (affected by pH, enzymatic activity, and interactions with food, beverages, and other orally administered drugs), leading to enhanced drug bioavailability and efficacy; and can serve as an alternative to oral drug administration when that route is not feasible (e.g., vomiting and diarrhea). Other advantages of transdermal administration include the accessibility of the skin, its relatively large surface area for absorption, and the painless nature of the procedure, enhancing patient comfort. However, a major drawback of transdermal drug delivery is the low rate of penetration through the skin. Only a limited number of drugs can be formulated as transdermal delivery systems due to the barrier posed by the stratum corneum, which acts as a limiting factor in drug permeation. This barrier is highly selective in terms of the types of molecules it allows to pass through the skin; therefore, only molecules with specific physicochemical properties can effectively cross the skin barrier.

The movement of drugs through the stratum corneum layer predominantly involves passive interactions and can occur through three pathways: intercellular, transcellular (paracellular), and transappendageal. Once penetrated the epidermis, a substance may undergo dermal diffusion or be transported to deeper tissues. [30] Numerous approaches have been evaluated for their ability to overcome the barrier function of the stratum corneum and enhance drug delivery into the skin. Specifically, penetration enhancers may operate through one or more of three potential mechanisms according to the lipid-protein-partitioning theory: they can modify the intercellular lipid arrangement among the corneocytes to increase diffusivity; alter intracellular protein regions within the stratum corneum and potentially enhance drug partitioning into the skin tissue. [31] Over the past decade, niosomes have been extensively studied for transdermal drug delivery and are emerging as promising carriers for active substances targeted at the skin layer. Niosomes are gaining popularity in the field of dermal drug delivery due to their unique characteristics and properties induced by their presence in a formulation, such as enhanced drug penetration, local depot for sustained drug release, and a rate-limiting barrier for modulation of systemic drug absorption through the skin. [32]

MECHANISM OF ACTION OF NIOSOMES AS PERMEATION ENHANCERS:

There is no singular mechanism that can adequately elucidate the ability of niosomes to enhance drug penetration through the skin, and several mechanisms have been proposed, including: modulation of the barrier function of the stratum corneum, through reversible perturbation of lipid organization.[33] Reduction of transepidermal water loss, leading to increased hydration of the stratum corneum and disruption of its densely packed cell structure. [34] Additionally, adsorption and/or fusion of niosomes on the skin surface, as revealed by freeze-fracture electron microscopy and small-angle X-ray scattering, resulting in a high thermodynamic activity gradient of drug at the interface, which drives drug saturation.[35] Adsorption of niosomes onto the cell surface occurs with minimal concealment of either aqueous or lipid components; this may happen due to attractive physical forces or binding by specific receptors to ligands on the vesicle membrane and direct transfer of drug from vesicles to the skin. Alternatively, niosomes may fuse with the cellular membrane, leading to complete mixing of the niosomal contents with the cytoplasm. Finally, niosomes may be engulfed by the cell (endocytosis), with lysosomes present in the cytoplasm degrading or digesting the membranous structure of the niosome, thereby releasing the encapsulated material into the medium. [36, 37]

CONCLUSION:

Niosomal drug delivery system represents a significant advancement in the pharmaceutical field, demonstrating a noteworthy evolution in drug delivery technologies and nanotechnology. It stands out as the preferred dosage form due to its cost-effectiveness and inherent stability. The utilization of niosomes offers promising opportunities for delivering encapsulated toxic anticancer drugs, anti-infective agents, and anti-AIDS medications. Niosomes are favored for their ability to enhance bioavailability and targeting features, ultimately aiding in minimizing drug toxicity and adverse effects. The strategic integration of niosomes into dosage forms enables precise targeting of specific tissues within the body.

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