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Niosomes: A Review

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ABSTRACT -: Development of nanocarriers for drug delivery had received considerable attention due to their potential in achieving targeted delivery to the diseased site while sparing the surrounding healthy tissue. Safe and efficient drug delivery had always been a challenge in medicine.Niosomes are self-assembled vesicular nano-carriers formed by hydration of non-ionic surfactant, cholesterol or other amphiphilic molecules that serve as a versatile drug delivery system with a variety of applications ranging from dermal delivery to brain-targeted delivery Based on their biodegradable, biocompatible, and nonimmunogenic structure, niosomes are promising drug carriers that are formed by self-association of nonionic surfactants and cholesterol in an aqueous phase.The amphiphilic nature of niosomes promotes their efficiency in encapsulating lipophilic or hydrophilicdrugs. Other additives, such as cholesterol, could been used to maintained the rigidity of the niosomes, structure. Several mechanisms had beenproposed to explained the ability of niosomes to increase drug transfer through the skin. Niosomal carriers were suitable for the transdermal delivery of numerous pharmacological agents, including antioxidant, anticancer, anti-inflammatory, antimicrobial, and antibacterial molecules,This narrativereview describes fundamental aspects of niosomes, including their structural components, methods of preparation,limitations, and current applications to various diseases.

Keywords -: Niosomes, Hydration, Cholesterol, Surfactant.

I. INTRODUCTION

Niosomes are composed of non-ionic surfactant vesicles hydrating mixture of cholestrol and nonionic surfactants, with or without incorporation of cholesterol or other lipids. Niosomes are vesicular nanocarriers and have received much attention as potential drug delivery systems in the last 30 years due to their special advantages. They have lamellar (bilayer) structures composed of amphiphilic molecules surrounded by an aqueous compartment. These amphiphilic molecules, known as surfactants, contain both hydrophobic groups (tails) and hydrophilic groups (heads) and show self-assembling properties, aggregating into a variety of shapes like micelles or into a flat lamellar bilayer.[1](Muzzalupo et.al 2015) Modified drug release kinetics with targeted site-specific distribution can be achieved with controlled drug delivery systems, improving patient compliance and therapeutic efficacy as well as adherence to patient regimens. The idea of location-specific Paul Elrich brought drug delivery to the pharmaceutical sector in 1909.In one of his best-known publications, he described using a "magic bullet" to transport a medication to the intended site of action while causing little side effects in nearby tissues or organs. [2](Chen et.al 2019). Reducing the medicine's systemic toxicity and improving selectivity are the two main goals of a site-specific drug delivery system. When formulating a therapeutic active pharmaceutical ingredient, researchers must take into account all possible hazards of systemic exposure and toxicity in order to steer the ingredient to a specific site of action in a regulated manner.Because niosomes are nonionic and less toxic, they offer a promising method of medication administration by limiting the drug's effect to certain target cells. Niosomes, also known as non-ionic surfactant vesicles, are tiny lamellar structures that are created when cholesterol and non-ionic surfactant belonging to the alkyl or dialkyl polyglycerol ether class are mixed together and then hydrated in aqueous conditions.The addition of cholesterol and, on rare occasions, charged molecules stiffens the bilayers and improves system stability. Niosomes and liposomes have a similar structure, and niosomes were developed as a substitute to get around issues with liposome stability, sterilization, and mass production. Like liposomes, niosomes have the ability to encapsulate hydrophilic and hydrophobic medicines in their respective hydrophilic and bi-layer compartments. Additionally, they could enable drug targeting, boost absorption and bioavailability of their loaded drugs, and improve pharmacokinetics and bio-distribution of therapeutics. In addition, niosomes offer a few

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more benefits over alternative micro- and nano-delivery methods, which can be summed up as follows:

- Cost-effectiveness because nonionic surfactants, which are readily available and reasonably priced in comparison to phospholipids needed to make lipid-based vesicles (such liposomes),
- Simple, inexpensive, and low-tech manufacturing; additionally, production can be easily scaled up; and
- Niosomes are more stable and have a longer shelf life than liposomes.

STRUCTURE OF NIOSOMES

They have amphiphilic molecules arranged in lamellar (bi-layer) structures with an aqueous compartment encircling them.[1](Muzzalupo et.al 2015) These amphiphilic molecules, sometimes referred to as surfactants, have self-assembling qualities and can aggregate into a range of configurations, such as micelles or a planar lamellar bilayer.[1](Tavano et.al 2015) They include both hydrophobic groups (tails) and hydrophilic groups (heads). The spherical niosomes are made up of microscopic lamellar structures, which can be unilamellar or multilamellar (Figure 1). Nonionic surfactants, with or without cholesterol, and a charge inducer combine to produce the bilayer.[3](Yeo Ling et.al 2017) Niosomes are formed by varying the combinations and molar ratios of several types of surfactants.[3](Yeo Ling et.al 2017)

MERITS AND DEMERITS OF NIOSOMES

Merits of niosomes are following:

- Because their structure is made up of both hydrophilic and hydrophobic components, niosomes can be a unique drug dosage form for drugs with a broad range of solubility.
- Vesicles distinguishing attributes were malleable; desirable niosomes could be created by modifying the vesicle's composition, size, lamellarity, tapping volume, surface charge, and concentration.
- Compared to oil-based dose forms, vesicle suspension offers improved patient compliance because it is a water-based carrier. The therapeutic effectiveness of drug molecules is enhanced by enhancing the oral bioavailability of poorly absorbed pharmaceuticals, delaying their clearance from the circulation, and shielding them from the biological environment.
- They boost the stability of the medication that is entrapped and are stable and osmotically active. It is possible to use topical, parenteral, and oral methods for.
- Niosome production, as well as the handling and storage of surfactants, require the use of biodegradable, biocompatible, and non-immunogenic surfactants. needs no particular circumstances
- The niosomes have a few drawbacks, which are as follows:
- The shelf life of niosome aqueous solutions may be restricted because of drug encapsulation hydrolysis, fusion, aggregation, and leakage.
- Multilamellar vesicle preparation techniques like sonication and extrusion take a lot of time and may need specialised processing equipment.[4] (Lohumi et.al 2012)

TYPES OF NIOSOMES-: The various types of niosomes are as:
i) Multi lamellar vesicles (MLV),
ii) Large unilamellar vesicles (LUV),
iii) Small unilamellar vesicles (SUV). [5](Kumar et.al 2018.)

Small Uni-lamellar vesicle (SUV)-: The small uni-lamellar vesicles are obtained from large uni-lamellar vesicle (LUV) by sonication method and MLV contain number of bilayers surrounding to aqueous lipid compartment separately.[6] (Umbarkar et.al 2021).The average size of MLV is about 0.5-10 μm in diameter. [6](Umbarkar et.al 2021).

Multi-lamellar Vesicle (MUV)-: The formation of SUV, MLV and LUV are depending on which method used for preparation of niosome. [6](Umbarkar et.al 2021).

Large Uni-lamellar Vesicle (LUV)-: The entrapment quantity of drug in this vesicle is more as compare to other types. Average size of Large uni-lamellar vesicle is 100nm. [6](Umbarkar et.al 2021).

FORMULATION COMPONENT AND THEIR EFFECTS: -

The components for niosomes include surfactants (generally non-ionic surfactants), cholesterol and charge inducing agents. [2](Chen et.al 2019).

Surfactants-: Nonionic surfactant vesicles have been prepared using different type of Spans and cholesterol at different ratios.[1](Tavano et.al 2015).

Cholesterol-: Cholesterol is a structural component of cell membranes and serves as a building block

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for synthesizing various steroid hormones, vitamin D, and bile acids. Inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency.[7](Khurana et.al 2011.). Cholesterol is a 27 carbon compound with a unique structure with a hydrocarbon tail, a central sterol nucleus made of four hydrocarbon rings, and a hydroxyl group. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. [7](Khurana et.al 2011.).

Charge Inducing Agent-: Charge inducing agents also play an essential role in stabilizing bilayer membranes by imparting either a negative charge or positive charge to the surface of the niosomes, preventing aggregation by electrostatic repulsion . Negatively charged ionic compounds such as dicetyl phosphate (DCP) and positively charged compounds like stearyl amine (STR) or stearyl pyridinium chloride are commonly used charges inducing agents in the preparation of niosomes. Generally, these charged molecules are added to the formulation in an amount of 2.5 to 5 mol %. However, increasing amount of the charge inducing agents beyond the limit will prevent the formation of niosomes . [2](Falconer et.al 2019.).

METHOD OF PREPARATION-:

Hand shaking method (Thin film hydration techniques): In an extremely round-bottom flask, surfactant and cholesterol are dissolved in a volatile organic solvent (such as diethyl either, chloroform, or methanol). Using a rotating evaporator, the natural dissolvable is removed at 20°C, leaving behind a thin layer of strong blend that is retained on the jar's mass.

To produce multilamellar niosomes, the surfactant that is dried in a movie is frequently rehydrated with a watery stage at 0–60°C using gentle fomentation. [8](chandu. et.al 2012)

Preparation steps:

Surfactant + cholesterol + solvent
↓
Remove organic solvent at Room temperature by rotary evaporator
↓
Thin layer formed on the Walls of flask
↓
Film can be rehydrated to form multilamellar Niosomes.

Ether injection method-: Using this technique, niosomes can be created by gradually adding a diethyl ether-dissolved surfactant solution to warm water that is kept at 60°C. A 14-gauge needle is used to inject the surfactant mixture in ether into the material's aqueous solution. Single-layered vesicles are formed when ether vaporises. The vesicle's diameter ranges from 50 to 1000 nm, depending on the conditions utilised.[9](Rai Kumar et.al 2017)

Sonication method-: According to Cable , sonication of a solution is a common technique for producing vesicles. This procedure involves filling a 10-ml glass vial with the surfactant/cholesterol mixture and adding an aliquot of medication solution in buffer. To produce niosomes, the mixture is probe sonicated using a titanium probe-equipped sonicater for three minutes at 60°C.**[9]**(Rai Kumar et.al 2017).

Bubble mthod-: This method produces noisome in a single step without the need for an organic solvent. The bubbling unit features a 0.1% Triton X-100 round-bottomed flask. Next, the necessary disrupted vesicle is examined to determine its drug concentration and, consequently, its entrapment efficiency. The formula for entrapment efficiency (EF) is (amount entrapped / total quantity) x 100. [10](Preethi et.al 2015)

Reverse phase evaporation technique (REV)-: This process forms thin dry films by dissolving a specific ratio of cholesterol and surfactant in organic solvents such as ether or chloroform, then evaporating the mixture under low pressure. By vortex mixing , 300 mm citric acid (pH 4.0) is added to the resulting film to hydrate it. After adding a tiny amount of phosphate buffer solution, the gel is further sonicated, and the organic phase is removed at 40°C to yield highly viscous niosomes. Phosphate buffer saline is used to dilute this viscous niosome and it is kept at 60 °C for ten to fifteen minutes.**[10]**(Preethi et.al 2015)

Multiple Membrane Extrusion Method -: Evaporation creates a thin film from a mixture of surfactant, cholesterol, and dicetyl phosphate in chloroform. Aqueous drug polycarbonate membranes hydrate the film solution and the suspension that is produced after being extruded through, arranged in a sequence of up to eight passages. It is an effective way to regulate niosome size. [11](Makeshwar et.al 2013)

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CHARACTERIZATION OF NIOSOMES

The average size, size distribution, zeta potential, shape, stability, and in vitro and in vivo drug release properties of generated niosomal vesicles are all determined by characterization studies.

Size, Shape, and Morphology: Freeze fracture electron microscopy has been used to visualise the niosomal vesicular structure. Photon correlation spectroscopy was used to estimate the vesicles' mean diameter. Studies of vesicles' morphology are conducted using electron microscopy. [12](Lokeswara Babu et.al 2013)

Drug release rate and entrapment efficiency: An extensive dialysis procedure can be used to measure the entrapment efficiency of niosomes. The determined amount of niosomal suspension wil be placed into a dialysis tube and one side of the membrane (osmosis cellulose) will be fastened firmly. Using a magnetic stirrer, 100 ml of phosphate saline buffer (pH 7.4) will be added to the dialysis tube and swirled. Via an osmotic cellulose membrane, the unentrapped medication can be extracted from the niosomal solution and added to the medium. The entire medium (100 ml) will be changed out every hour for a period of nine to twelve hours, or until the absorbance achieved a consistent reading that showed no drug was present in an unentrapped state. Using propane-1-ol, the niosomal solution in the dialysis tube will be further lysed, and the amount of drug entrapped can be calculated using a UV spectrophotometric technique at (λ_{max})210 nm.[12](Lokeswara Babu et.al 2013)

$$EE\% = (Wi - Wf) / Wi \times 100$$

Surface Charge Of Veicles :- When it comes to vesicular dispersion, surface charge is essential. When vesicles are created without adding a charged molecule to the bilayer, they will aggregate in an isotonic saline solution. The reduction of electrostatic repulsion caused by ions in the solution sheltering the vesicle surface charge is the reason for the vesicle aggregation. A decrease in aggregation formation was noted with the incorporation of a charged molecule such as dicetylphosphate into a bilayer vesicle.Particle electrophoretic mobility measurements can be used to determine the vesicle surface charge, which is then expressed as the zeta potential, which can be computed using Henry's equation.

$$\zeta = \frac{\mu E \, 4\pi \, \eta}{\varepsilon}$$

In this case, μ stands for Zeta potential, μE for Electrophoretic mobility, η for Media Viscosity, and ε for Dielectric constant.[12](Lokeswara Babu et.al 2013)

In Vitro Release: Different release kinetics, including zero order, first order, Higuchi's model, and Korsmeyer and Peppas model, can be observed in drug release mechanisms derived from niosomal systems. The cumulative percentage release against time is represented by the zero order model (Equation (2)), whereas the first order model . The logarithmic percentage release against time is shown in (Equation (3)). Equation (4) of Higuchi's model shows the cumulative percentage release against the square root of time, while Equation (5) of Korsmeyer and Peppas's model shows the logarithmic amount of medicine released against the logarithmic time.
The following equations can be used to meet the in vitro release research data with different release kinetics in order to characterise drug release kinetics:

Release Kinetics

Zero order:

$Wt = W0 - K0t$, …… (2)

Where W0 is the starting drug concentration in solution, K0 is the zero order constant, and Wt is the amount of drug released in time t;

First order:

$\ln Wt = \ln W0 - K1t$, ……(3)

where W0 is the starting drug concentration in solution, K1 is the first order constant, and Wt is the amount of drug released in time t;

Higuchi's model:

$Wt = Kh\sqrt{t}$, ……(4)

Where Kh is the Higuchi release constant and Wt is the amount of medication released in time t;

Applications of niosomes:

- It is commonly used to research drug targeting.
- It has been used to study the immune response triggered by antigen.
- It can be used as an anti-neoplastic treatment to treat cancer.

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- Niosomes can be employed as haemoglobin carriers. Currently, they can also be used to deliver peptide drugs.
- It has a good therapeutic effect on the administration of opthalmic drugs. It is also an extensively utilised diagnostic agent.
- Since peptide medications typically have stability issues, parenteral formulation in the form of tablets is challenging. Consequently, the stability of peptide medications can be increased by employing niosomes as drug carriers.
- Transdermal medication administration is being researched these days due to the many drawbacks of the oral drug delivery technique, and the results have been encouraging. Niosomes have a high penetration capacity when used as medication carriers. Niosome can therefore be used to deliver different medications transdermally.
- Niosomal suspension can be utilised as a carrier of haemoglobin since it exhibits a visible spectrum that can be superimposed onto that of free haemoglobin.
- Drugs with low therapeutic index and low water solubility can be encapsulated by the niosomal system and kept in the circulation demonstrating a prolonged release of tension.
- Additionally, the niosomal system is used in diagnostic products. Moreover, it can transport radiopharmaceutics.[13](Vilas et.al 2023)

MARKETED FORMULATIONS OF NIOSOMES -:

Sr.No.	Brand name	Name of the Product
1.	Lancome- Foundation and complexation	Flash Retouch Brush on Concealer
2.	Britney Spears – Curious	Curious Coffret: Edp Spray 100ml +Dualended Parfum & Pink Lipgloss + Body soufflé 100 ml
3.	Loris Azzaro – Chrome	Chrome Eau De Toilette Spray 200 ml
4.	Orlane – Lipcolor and Lipstick	Lip Gloss

[14](Kaur et.al 2018)

II. CONCLUSION-:

In this review article, we have provided the conclusion about the specific vesicular delivery system, niosomal formulation with highlighting several sub-topics like - niosomes, structure of niosomes, merits and demerits of niosomes, types of niosomes, formulation component and their effects, method of preparation, characterization of niosomes , marketed formulations of niosomes. Therefore niosomes present a promising drug delivery system. There is a vast scope to encapsulate a wide variety of drugs such as anti cancer drugs, anti HIV drugs ,anti viraldrugs etc, and to use them as promising and efficient drug carrier to achieve better bioavailability and better tissue targeting with reduced toxicity to non target organs.

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CONFLICT OF INTEREST
The authors have no conflict of interest.

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