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Review Article

Review On Niosomal Gel Based Drug Delivery To Periodontal

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ABSTRACT

Niosomes play an important role in medicine delivery because they can reduce toxins and modify pharmacokinetics and bioavailability. When compared to liposomes, niosomes a non-ionic, spherical surfactant are more affordable, biodegradable, non-toxic, and have a higher durability. Through niosomes delivery of both hydrophilic and lipophilic drug can be achieve very constructively. The components of a niosome are cholesterol and a nonionic surfactant. Niosome diameters range from 10 nm to 100 nm. Niosomes are superior to traditional drug delivery methods in several ways. Niosomes can be prepared using a variety of techniques, some of which are described here. These include ether injection, thin film hydration, reverse phase evaporation, and Sonication. We attempt to include all relevant information about niosomes in this review paper, including an introduction, a structure, composition advantages, disadvantages, types, preparation techniques, influencing factors, evaluation studies, applications of niosomes, and a conclusion

INTRODUCTION

The field of targeted delivery was initiated in 1909 by Paul Ehrlich, who had an idea for a medication delivery method that would directly target injured cells. "Drug targeting" refers to the ability to precisely guide a therapeutic agent to a desired location of action with minimal or no contact with non-target tissue.[1] A nonionic surfactant-based liposome is called a niosome.The main mechanism o niosome formation is cholesterol inclusion as an excipient.It is also possible to use various excipients. Niosomes are more able to penetrate than previous emulsion formulations. Architecturally, niosomes and liposomes are similar in that they both feature a bilayer; but, due to the materials used in their production, niosomes are more stable and, as a result, have certain advantages over liposomes.[2,3] Niosomes are little particles that are in the nanometric range.Particle diameters vary from 10 nm to 100

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nm.The components of a typical niosome vesicle would be an anionic surfactant called dicetyl phosphate and a vesicle forming amphiphile like Span60, which is a nonionic surfactant that is usually stabilised by the addition of cholesterol.[3,4]

COMPOSITION OF NIOSOMES-

In the medication of niosomes two factors is used:

- Cholesterol
- Non-ionic surfactants

A.Cholesterol have steroid like structure that provides stability and proper shape, as well as configuration to the niosome form.

B.For the Manufacturing of niosomes, non-ionic surfactants are commonly used.

Examples:

Tween 40, Tween 20, Tween 60, Tween 80

Span 80, Span 60, Span 40, Span 20, and Span 85

Brij 76, Brij 30, Brij 35, Brij 52, Brij 58, Brij 72[5]

CHARACTERISTICS OF NIOSOME :

- Like liposomes, niosomes are capable of ensnaring solutes.
- Niosomes are a stable, bibulous supporter that is active.
- Niosomes have an internal structure that largely consists of hydrophobic and hydrophilic molecules, allowing them to bind pharmaceutical molecules with a variety of solubility.
- Niosomes are structurally rigid in terms of composition, fluidity, and size, but they can be shaped to fit the required scenario.
- Niosomes may also improve how well the medication motes work.
- Improved permeability to the specific administration site by shielding the medication from the environment.
- The surfactants included in niosomes are biodegradable, immunogenic, and biocompatible.[6]

ADVANTAGES:[7,9,10]

- They exhibit stability and osmoticism.
- They increase the stability of the complicated medication.
- There are no specific guidelines for the handling or storage of surfactants.
- The oral bioavailability of medications may also be improved by niosome carriers
- Niosomal gel can improve medication absorption through the skin.
- Niosomal gel is a topical and optical approach.The surfactants exhibit biodegradability, biocompatibility, and lack immunogenicity.
- The surfactants don't cause allergies and are biodegradable and biocompatible.
- Enhance the medication's therapeutic effects by protecting it from the environment and limiting supplies to the intended cells, which lowers the medication's concurrency.
- To regulate the medication release rate and deliver regular vesicles in an external nonaqueous phase, the niosomal dissipations in a waterless phase can be emulsified in a non-aqueous phase .
- The administration of medication using niosomal gel is beneficial for treating both systemic and superficial fungal infections .
- They have the ability to function as a depot formulation, enabling controlled drug release.
- For poorly soluble medications, they increase their oral bioavailability.
- Even as emulsions, they have a stable structural integrity.
- They are economical for large scale production.
- By blocking enzyme metabolism, they can shield the medication.
- They have the ability to increase a drug's skin penetration.

- Prolonged removal of the medication from circulation can enhance its therapeutic effect.
- They have the ability to shield the active component from biological circulation.

DISADVANTAGES:

- It takes time and specialized equipment to prepare multilamellar vesicles using the extrusion and sonication method.
- Because of drug entrapment fusion, aggregation, and leakage, niosomes in aqueous suspension have a limited shelf life.[8]
- Unstable physical conditions
- Aggregation
- Fusion
- Leaking of a drug that is trapped
- Drugs in capsules undergo hydrolysis, which shortens the dispersion's shelf life.[11]

TYPES OF NIOSOMES :

A. Multilamellar Vesicles (MLV): (MLV, size > 0.05 µm)

These vesicles show increased-trapped volume and equilibrium solute distribution. They can be prepared by hand-shaking method.They show variations in lipid compositions.

B. Small Unilamellar Vesicles (SUV):

(SUV, size 0.025-0.05 µm)These are commonly prepared by sonication and french Press procedures. Ultrasonic electrocapillary emulsification or solvent dilution techniques can also be used to prepare SUV's.

C. Large unilamellar vesicles :

(LUV, size > 0.10 µm)These are prepared by injecting lipids solubilised in an organic solvent into an aqueous buffer, reverse phase evaporation or by detergent solubilisation method

TYPES OF SPECIALISED NIOSOMES :

A. Proniosomes:

A thin layer of non-ionic surfactant is applied to a water-soluble carrier to create proniosomes. When creating proniosomes, water-soluble carriers need to be non-toxic, hygienic, free-flowing, and able to dissolve well in water to facilitate simple hydration. Sorbitol, maltodextrin, glucose monohydrate, mannitol, sucrose stearate, and lactose monohydrate were used to make proteosomes. There are several techniques for creating proniosomes, such as slurry, slow spray coating, and coacervation phase separation. Depending on how they are created, proniosomes can be either liquid-crystalline or dry-granular. [12,13]

B. Elastic Niosomes:

Elastic Niosomes (Ethoniosomes) are composed of nonionic surfactants, ethanol, bile salts, and water. The high flexibility of the vesicular membranes of these ethoniosomes permits them to squeeze through the skin pores, which are much smaller than their diameters. The transport of these elastic vesicles is concentration-independent and driven by trans-epidermal hydration. [14,15]

C. Discomes:

Discomes are disc-shaped, giant (approximately 20 µm in diameter) niosomes that coexist with conventional spherical niosomes. Discomes offer better ocular drug bioavailability than conventional niosomes.[16]

D. Transfersomes :

are deformable vesicular carrier systems that self-assemble into a lipid bilayer in an aqueous environment and fuse together to form vesicles. Lipid bilayer softening agents and lipid bilayer flexibility are added to enhance permeability. Another name for it is an edge activator. A non-ionic single-chain surfactant known as an edge activator causes the lipid bilayer to destabilise, increasing its elasticity and fluidity. Transfersomes can accept a broad range of drug molecules because they contain both hydrophilic and lipophilic moieties. They have the ability to transport both low- and high-molecular-weight drugs. [17,18,19]

MECHANISMS OF NIOSOME PENETRATION THROUGH SKIN DELIVERY [20, 21]

The most difficult tool for dermatological conditions is niosomes. Niosomes have also been utilized in the delivery of peptide medications and cosmetics. Topically applied niosomes can increase the residence time of the drug in the SC and epidermis while reducing the systemic absorption of drugs. It is believed that they enhance smoothness and reconstitute lost skin lipid to improve the properties of the horny layer while also decreasing transepidermal water loss. Thus, niosomes act as penetration enhancers.

1. The fusion and adsorption of niosomes onto the skin's surface cause a high thermodynamic activity gradient at the interface, which propels the permeation of lipophilic medications.
2. The stratum corneum's barrier qualities are lessened by vesicles' penetration-enhancing effects. Niosomes are made up of surfactants, which improve skin wetting, increase drug distribution, and decrease surface tension to increase transdermal penetration and percutaneous absorption.
3. The lipid bilayers of niosomes act as a rate-limiting barrier for drugs.

AUXILIARY COMPONENTS OF NIOSOMES:

The primary components of niosomes are nonionic surfactants, hydration medium, and lipids such as cholesterol. The list of materials utilised in the planning of niosomes is shown in Table 1.

1. Surfactants:

Surfactants are amphiphilic atoms containing both hydrophilic bunches (their heads) and hydrophobic bunches (their tails). Essentially, niosomes are non-ionic surfactant-based vesicles. Nonionic surfactants are utilised in the planning niosomes due to their benefits with regard to soundness, compatibility, and harmfulness compared to anionic, amphoteric, or cationic surfactants. Nonionic surfactants are by and large less harmful, less hemolytic, and less chafing to cellular surfaces and tend to maintain a close physiological pH. They act as solubilizers, wetting specialists, emulsifiers, and penetrability enhancers. They also upgrade medicated assimilation as they are solid P-glycoprotein inhibitors.

2. Cholesterol:

The expansion of cholesterol in the niosome increases its vesicle estimate, entanglement effectiveness, and inflexibility in the bilayer.

3. Charged particle:

Charged particles increment the steadiness of the vesicles by the expansion of charged bunches into the bilayer of vesicles. They increase surface charge thickness and subsequently avoid vesicle conglomeration. They act by avoiding the combination of vesicles due to the ghastly strengths of the same charge and by giving higher values of zeta potential. [22, 23, 24]

METHOD OF PREPARATION OF NIOSOMES [26, 27, 28]

Various strategies are detailed for the planning of niosomes, such as:

1. Ether injection method:

In this technique, a solution of the surfactant is created by dissolving it in diethyl ether. Subsequently, this solution is injected using a 14-gauge syringe into the warm water and the drug-containing aqueous phase, which is maintained at 60°C. Single-layered vesicles are the product of ether vaporisation. Depending on the conditions, the size of the niosome particle might vary from 50 to 1000 μm. [26]

2. Hand Shaking Method:

Dissolve a combination of vesicle-forming components, including cholesterol and surfactant, in a volatile organic solvent (diethyl ether, chloroform, or methanol) in a round-bottom flask. A rotary evaporator is used to extract the organic

solvent at room temperature (20°C), leaving behind a thin coating of solid mixture on the flask's wall. With moderate stirring and temperatures between 0 and 60°C, the dried surfactant film can be rehydrated with an aqueous phase. Normal multilamellar niosomes are created by this process. Drug addition to the system depends on its type; hydrophilic medications can be mixed with other components in the aqueous phase, whereas hydrophobic drugs can only be dissolved in an organic solvent when combined with other substances.

3. **Sonication:**

This strategy includes putting an aliquot of the medication arrangement in buffer and the surfactant/cholesterol blend into a 10-ml glass vial. The blend is tested and sonicated using a titanium test sonicator for three minutes at 60°C in order to create niosomes.

4. **Reverse Phase Evaporation Technique (Rev):**

Using a combination of ether and chloroform, a 1:1 solution of cholesterol and surfactant is prepared as the first stage in this process. Then, both phases are mixed together with the drug-containing aqueous phase and sonicated at 4-5°C. The process involves adding phosphate-buffered saline (PBS) and sonicating the mixture to generate a clear gel. This eliminates the organic phase by raising the temperature to 40°C and lowering the pressure. In order to obtain niosomes, this results in a viscous niosome suspension that can be diluted with PBS and heated in a water bath for ten minutes at 60°C. [13]

5. **Microfluidization:**

A new technique for producing unilamellar vesicles with a preset size distribution is used here.The submerged jet principle underlies this method, where two fluidized streams come into contact at extremely high velocities in the interaction chamber's precisely designed micro channels.Because niosomes form in the region where a thin liquid sheet impinges along a common front, the energy given to the system remains within that region. As a consequence, more compact, reliable, and repeatable niosomes are created.

6. **Multiple Membrane Extrusion Method:**

This method forms a thin film by evaporating a combination of dicetyl phosphate, cholesterol, and surfactant in chloroform. An aqueous drug polycarbonate membrane solution is hydrousted with the film, and the resulting suspension is extruded, allowing for the sequential mounting of up to 8 passageways. It's a clever strategy to control niosome size.

7. **Bubble Method:**

This recently developed technique eliminates the requirement for organic solvents while producing niosomes. To keep the temperature constant, the bubbling machine's three-necked, round-bottom flask is submerged in water. The first and second necks supply a water-cooled reflux and thermometer, while the third neck supplies nitrogen. At 158°F, cholesterol and surfactant are distributed in a pH 7.4 buffer. This dispersion is mixed for 15 seconds using a high-shear homogenizer, and then niosomes are created by bubbling nitrogen gas at 158°F.

POST-PREPARATION PROCESSES [29]

The primary post-preparation forms in the fabrication of niosomes are scaling down and partitioning unentrapped fabric. After planning, measure lessening of niosomes is accomplished utilizing one of the strategies given below:

1. Test sonication comes about in the generation of niosomes in the 100–140 nm measurement range.
2. Expulsion through channels of characterised pore sizes.
3. The combination of sonication and filtration has also been utilised to get niosomes in the 200-nm estimate run (e.g., doxorubicin niosomes).

4. Smaller-scale fluidization yields niosomes in the nanorange.
5. High-pressure homogenization also yields vesicles under 100nm in diameter.

As in most cases, 100% of the bioactive specialist cannot be typified in the niosomal vesicles, the un-entrapped bioactive operator ought to be isolated from the captured ones. This gives an advantage since this medication conveyance framework gives a starting burst to start treatment taken after a maintained upkeep dosage.

RESOURCES AND TECHNIQUES:

The primary constituent of a niosome is a non-ionic surfactant. To manufacture niosomes, a variety of components are used, such as an ionic surfactant or another charge compound that demonstrates niosome molecular repulsion and prevents niosome aggregation. Additionally, cholesterol is supplied to the niosome to keep the vesicle stiff. Niosomes can be prepared using a variety of techniques, including ether injection, sonication, reverse phase evaporation, microfluidization, and transmembrane PH gradient (inside acidic). The drug uptake process involves the following methods: bubble method, hand shaking (thin film hydration technique), multiple membrane extrusion method, and remote loading technique. [30]

SEPARATION OF UNENTRAPPED DRUG:

Various strategies may be utilised to evacuate the unentrapped solute from the vesicles, including:

1. Dialysis:

Dialysis tubing is utilised to dialyze the fluid in niosomal scattering against phosphate buffer, standard saline, or glucose solution.

2. Gel Filtration:

Gel filtration of niosomal scattering through a Sephadex-G-50 column and elution with phosphate-buffered saline or normal saline evacuates the unentrapped drug.

3. Centrifugation:

The supernatant is disconnected from the niosomal suspension after centrifugation. To secure a niosomal suspension free of unentrapped sedate, the pellet is streamed over and, at that point, resuspended.

FACTOR AFFECTING NIOSOME PRESENTATION:

1. Surfactant Nature:

A polar head and a non-polar tail would be the characteristics of the idealised surfactant for niosome planning. One or more alkyl or perfluoroalkyl bunches, or, as it were, one steroidal bunch in particular circumstances, make up the non-polar tail. The polar tail of ether-type surfactants with a single-chain alkyl is more unsafe than the dialkylether chain. The previous is less destructive than the last mentioned since ester-linked surfactants are broken down to triglycerides and greasy acids in vivo by esterases. To define niosomes, surfactants with alkyl chains between C12 and C18 work well.

2. Structure of Surfactants:

A surfactant vesicle's structure, which is related to pivotal pressing parameters, influences its geometry. The geometry of the vesicle to be created can be anticipated utilising the basic pressing parameters of surfactants. The taking-after condition can be utilised to decide the basic pressing parameters:

CPP (Basic Pressing Parameters) =v/lc* a0,

Where v indicates the volume of the hydrophobic bunch,

Lc indicates the basic length of the hydrophobic bunch.

A0 indicates the locale of the hydrophilic head bunch.

CPP between 0.5 and 1 surfactant forms vesicles.

CPP<0.5 Spherical micelles

CPP>1Inverted micelles

3. Nature of the Encapsulated Drug:

The charge and rigidity of the niosome bilayer are influenced by the physico-chemical properties of

the encapsulated compound. The drug interacts with surfactant head groups, causing mutual repulsion between surfactant bilayers and thus increasing vesicle size.

4. **Hydration Temperature:**

The shape and measure of the prominent are impacted by the temperature of the hydration. It ought to be over the system's gel-to-fluid stage when the ideal comes about. The get-together of surfactants into vesicles is influenced by temperature changes in the niosomal framework as well as vesicle shape transformation.

5. **Cholesterol Substance:**

The expansion of cholesterol into the niosome bilayer composition causes film adjustment and diminishes layer defectiveness. As a result, including cholesterol in a bilayer makes strides towards entanglement adequacy. The expansion of cholesterol decreases the porousness of the vesicle bilayer to 5,6-carboxyfluorescein (CF) by a factor of ten.

6. **Effect of Drug Concentration:**

The drug entrapment efficiency of the niosome decreases as the drug concentration exceeds 50 mg. [31- 34]

CHARACTERIZATION OF NIOSOMES: [35]

1. **Vesicle structure and shape:**

Vesicle structure and shape can be characterised by different sorts of microscopy, such as optical microscopy, solidify break electron microscopy, surface electron microscopy, checking electron microscopy, negative recoloring transmission electron microscopy, cryo-electron microscopy, fluorescence, and confocal microscopy.

2. **Morphology of niosomes:**

Microscopic methods like transmission electron microscopy (TEM), scanning electron microscopy, and atomic force microscopy can be used to analyse the morphology of niosomal vesicles. For investigating the morphology of niosomes,TEM is frequently utilised. In this method, a drop of the samples (niosomal formulation) is applied to copper grids covered with carbon, dyed with, for instance, 2% phosphotungstic acid (w/v), and then left to dry before imaging. Cholesterol, Span 60, and Tween 40 (2:1:1 M ratio) make up niosomes.

3. **Entrapment efficiency:**

The entrapment efficiency provides information about the amount of medication within niosomes. The amount of free drug in the supernatant after centrifuging the loaded niosomal solution is measured (an indirect measure of entrapment effectiveness), and this can be calculated using equation (1).

Entrapment efficiency (%) = Total amount of initially added drug minus unentrapped drug / Total

Amount of initially added drug × 100 = equation (1)

4. **In vitro release of drug:**

The in-vitro drug release rate can be studied by using dialysis tubing. A dialysis sac is washed and soaked in distilled water. The niosomal dispersion is pipetted into this bag and sealed. The bag containing the vesicles is placed in 200 ml of phosphate-buffered saline of pH 7.4 in a 250 ml beaker with drug content by an appropriate assay method. Constant shaking at 37±1°C. At various time intervals, the buffer is analysed for drug content by an appropriate assay method.

5. **Bilayer formation:**

The bilayer formation of the vesicles is characterised by X-cross formation under light polarisation microscopy. [36]

Tabel 1 : Detail study of drug with their application and method use for formulation of Niosome[37]

Application	Components	Method used	Drug used
For drug targeting	Monostearate(Span60), Cholesterol, glycol, Chitosan	Reverse phase evaporation method	Methotrexate
To reduce toxicity	Span20,Span40, Span60, Cholesterol	Thin film hydration	Cefpodoxime Proxertill
To increase entrapment efficiency	Span60, Cholesterol,DCP	Thin film hydration	Ketoprofen
To prolong the release time	Sorbitan esters	Reverse phase evaporation	Rifampicin

EVALUATION PARAMETERS OF NIOSOMAL GEL [38]

1. **Opacity:**

It was decided by visual assessment beneath a dark and white foundation, and it was evaluated as follows: straightforward, translucent, and opaque.

2. **Spreadability:**

A spreadability test was conducted by squeezing 0.5 g of gel between two glass slides with the help of a 20 g weight and taking it off for around 5 minutes until no more spreading was observed. The breadth of the formed circle was measured and used as the value for spreadability.

3. **Extrudability:**

A 5 g amount of gel was filled in a clean 10 ml syringe suspended using an answer stand; 0.5 kg of weight was put on the free end of the plunger, and the amount of gel expelled in 5 minutes was noted.

4. **pH:**

A 1 g amount of gel was scattered consistently in 100 ml of refined water using an attractive stirrer. The pH of the 1% w/v scattering of the niosomal gel was measured by utilising a computerised pH meter.

5. **Viscosity:**

The consistency of 1% w/v scattering was decided by the use of a rotational viscometer (NDJ-1, China) utilising a spindle.

6. **Homogeneity:**

It was determined by a visual assessment for the appearance of protuberance and the nearness of any aggregate.

7. **Molecule measure:**

the niosomal anticipation determined by optic microscopy. A drop of niosomal tension was put on a glass slide. A cover slip is put over the niosomes to suspend and appraise the normal vesicle estimate by a conventional optic magnifying instrument utilising a recalibrated optical eyepiece micrometre.

NIOSOME APPLICATION: [39, 40]

Many pharmacological medicines may be able to combat a variety of ailments through the use of niosomal drug delivery. The next section discusses a few of their therapeutic uses.

1. **Drug delivery via niosomes:**

Iobitridol, a diagnostic drug used in X-ray imaging, has also been transported by niosomes. Topical niosomes have multiple functions, such as acting as a solubilization matrix, a local depot for the continuous release of dermally active substances, improving penetration, or acting as a

rate-limiting membrane barrier to control the systemic absorption of medications.

2. **Transdermal medication delivery:**

This method's primary flaw is its slowness. Drug delivery via niosome-based transdermal delivery has increased drug penetration through the skin and its rate of penetration.

3. **Treatment against cancer:**

The majority of anti-cancer medications have serious negative effects. In order to reduce a drug's negative effects, niosomes have the ability to change the drug's metabolism and extend its half-life and circulation. Niosomes reduce the pace at which tumours proliferate and raise plasma levels, which are then followed by a delayed clearance.

4. **Delivering peptide medications:**

Ignoring the enzymes that would break down the peptide has long been a problem for oral peptide medication delivery processes. It's being researched if using niosomes may effectively shield the peptides from degradation by the gastrointestinal tract. A vasopressin derivative entrapped in niosomes was administered orally in an in-vitro investigation, which revealed that the drug's entrapment greatly boosted the peptide's stability.

5. **Application in immune response research:**

Niosomes are employed in the investigation of the kind of immune response elicited by antigens because of their immunological selectivity, reduced toxicity, and increased stability. The ability of non-ionic surfactant vesicles to act as adjuvants after parenteral delivery of various antigens and peptides has been well demonstrated

6. **Niosomes for oral medication delivery:**

Oral drug delivery Niosomal formulations exhibit improved absorption of the drug in the gastrointestinal tract, defence against proteolytic enzymes, and good stability. In studying immune responses.

CONCLUSION

The structure of niosomes, a moderately unused sedate conveyance strategy, is two layers of nonionic surfactants. Different drugs can be put in niosomes by changing the experiment's parameters and the proportion of surfactant and cholesterol utilized. Furthermore, hydrophobic and hydrophilic solutions can be stacked into niosomes due to their amphipathic nature. Also, niosomes move forward medicine steadiness, delay sedate discharge, and lower medicate harmfulness. In differentiate to other sedate conveyance strategies, niosomes do not require to be arranged or put away beneath certain circumstances. In conclusion, it shows up that extra investigate will lead to an hopeful advertise for niosomes in pharmaceutical biotechnology in the future. Niosomes can be utilized for focused on, visual, topical, parenteral, and other sedate conveyance strategies. More think about is required to completely investigate the conceivable outcomes of this imaginative medicate conveyance system.Niosomal medicate carriers are more secure than ionic ones, which are more perilous and inappropriate. Furthermore, handling and putting away niosomes don't call for any interesting circumstances .

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