GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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Niosomes: A nanocarrier drug delivery system

Rahiman Mohammed Noor Hazira * and M Sunitha Reddy

Department of pharmaceutics, Centre for pharmaceutical sciences, JNTUH UCEST, JNTUH, Hyderabad, Telangana-500085, India.

GSC Biological and Pharmaceutical Sciences, 2023, 22(02), 120–127

Publication history: Received on 06 January 2023; revised on 15 February 2023; accepted on 17 February 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.22.2.0062

Abstract

Novel approaches in the drug delivery system can be used for drug targeting in which the drug gets distributed in the body in such a manner that drug interacts with the target tissue. Niosomes are a type of novel drug delivery system in which the medication is encapsulated in a vesicle. Niosomes are a non-ionic surfactant based multilamellar or unilamellar vesicles in which a fluid arrangement of solute is completely enclosed by a membrane because of the association of surfactant macromolecules as a bilayer. Niosomes release the drug in a controlled manner through its bilayer. Niosomes can be used to carry both the amphiphilic and lipophilic drugs. Niosomes have a great potential in targeted drug delivery of anticancer and anti-infective agents. Niosomes are used to modify the drug release profile, drug absorption, distribution and elimination for the benefit of improving product efficacy and safety and improving patient convenience and compliance. They are very small and microscopic. Although they are structurally similar to liposomes, they offer several advantages over them. Niosomes are stable, less toxic and less expensive than liposomes. This review article represents the structure of Niosomes, its advantages and disadvantages, applications, method of preparation, and characterization techniques of Niosomes.

Keywords: Niosomes; Novel Drug Delivery System; Thin film hydration method; Non-ionic surfactants; Applications of Niosomes

1. Introduction

Niosomes are a non-ionic surfactant-based vesicle. Niosomes are formed mostly by non-ionic surfactant and cholesterol .They are structurally similar to liposomes as they are both composed of a lipid bilayer. They are more stable when compared to liposomes in case of preparation and storage. They are used for the entrapment of both hydrophilic and lipophilic drugs [1]. Niosomes are microscopic lamellar structures. They are made up of different non-ionic surfactants and cholesterol. The surfactant molecules tend to orient themselves in a way that the hydrophilic ends of the non-ionic surfactant point outwards, while the hydrophobic ends face each other to form the bilayer [1].

The size of Niosomes range between 10 to1000 nm [2]. They consists of biodegradable, non-immunogenic, and biocompatible surfactants [3]. Niosomes are better than liposomes and stable because of usage of non-ionic surfactants which make them chemically stable because they can be easily hydrolyzed due to the ester bond. They are cost effective. Niosomes act as drug depots in the body by releasing the drug in a controlled manner through its bilayer which results in sustained release of the encapsulated drug. Using Niosomes the drug is delivered directly to the part of the body where the therapeutic effect is required. This reduces the dose required to achieve the desired effect. This results in reduction in the clearance rate, drug targeting to the specific site and protection of the drug encapsulated and improvement in therapeutic efficacy of the drugs. Drug targeting reduces the dose which also reduces the side effects. Due to the vesicular system, Niosomes can encapsulate both hydrophilic and lipophilic drugs. Hydrophilic drugs are

*Corresponding author: Rahiman Mohammed Noor Hazira

usually encapsulated in the inner aqueous core and the lipophilic substances are entrapped between the lipophilic bilayer [3].

As they are capable of carrying various types of therapeutic agents, they have been widely used as drug delivery systems. Drug targeting, controlled release, and permeation enhancement can be achieved using Niosomes. They deliver drug in a controlled manner which not only enhances bioavailability, but also produces therapeutic effect for a long period of time. They can be modified by changing their composition, like using different concentrations of various additives, and surface charge of vesicle components and membrane additives.

1.1. Structure of Niosome

A Niosomal vesicle generally consists of a vesicle forming amphiphile i.e. a non-ionic surfactant and cholesterol which is added for stabilizing the vesicle along with a small amount of anionic surfactant such as diacetyl phosphate, also for stabilization of the vesicle [4].

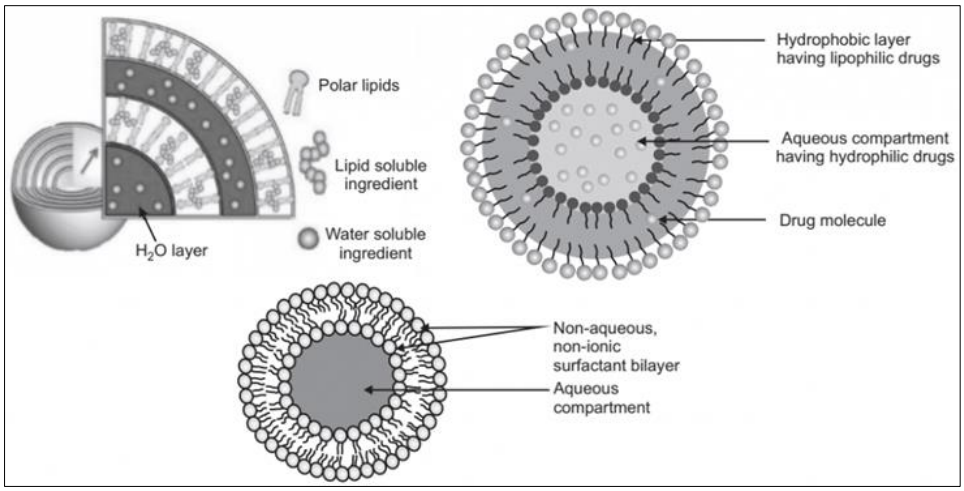

Figure 1 Structure of Niosome

1.2. Advantages

Niosomes has several advantages. The major advantages of Niosomes are:

- Niosomes are water based vehicles, hence they offer high patient compliance over oily vehicles [3].
- They increase stability of drug entrapped and makes them stable [3].
- No special conditions are required for storage and handling of surfactants.
- They enhance penetration of drugs into skin and also improve the bioavailability of poorly absorbed drugs.
- Niosomes protect drug from biological environment, delay the drug clearance and improve the therapeutic performance.
- Niosomes can be used for site targeting through oral, parenteral, and topical routes.
- They have longer shelf life and chemical stability compared to liposomes.
- They do not carry any surface charge. Hence they are less toxic and more compatible.
- They can entrap both hydrophilic and lipophilic drugs.
- They are used as sustained and controlled drug delivery.

1.3. Disadvantages

- Besides several advantages, there are some disadvantages of Niosomes.
- Shelf life of Niosomes is limited because of leakage of drug from the vesicles.
- Aggregation and fusion of vesicles can occur [5].
- There may be small physical and chemical instability problems.
- In aqueous suspensions, the drug may undergo hydrolysis which affects the stability.
- Preparation of Niosomes is a time consuming process.
- They require specialised equipment.

2. Composition of Niosomes

The three main components used in the preparation of Niosomes are

- Non-ionic surfactants
- Cholesterol

2.1. Non-ionic surfactants

Non-ionic surfactants play an important role in the preparation of Niosomes. They are the basic component. They consists of polar head and a hydrophobic tail. They arrange themselves in a bilayer with their hydrophilic head towards aqueous media and hydrophobic or on polar tail facing inside [6]. In order to attain thermal stability they fold inwards to form a vesicle. They are stale because they do not carry any charge. They cause less hemolysis to the tissues. They cause less irritation.

They enhance permeability, improves the solubility and also they are good wetting agents and used as emulsifiers. They enhance absorption and targeting because they inhibit p-glycoprotein. Selection of non-ionic surfactants depends on HLB value liquid transition temperatures and CPP (critical packaging parameter) [5].

High HLB value surfactants are not suitable for preparation of Niosomes. Highest entrapment efficiency is found with HLB value of 8.

Examples:

- Spans like span 60, 40, 20, 85, and 80
- Tweens tween 20, 40, 60, 80[4].

2.2. Cholesterol

Cholesterol also acts as an important part of Niosomes. Cholesterol is not required for the formulation of Niosomes but it provides several properties to the formulation. Cholesterol imparts several characters to the formulation like increase in stability, entrapment efficiency, permeability, rehydration of dried Niosomes etc. [6].

Stability of the vesicle is increased if cholesterol is used with low HLB value surfactants and helps in formation of bilayer of vesicles if HLB value is greater than 6[5].

2.3. Charged molecules

They are added to prevent coalescence of Niosomes and increase their stability. Only 2.5-5 mol % concentration is tolerable. If the concentration of charged molecule is high in the formulation it inhibits formation of Niosomes [6].

Niosomes having a composition of cholesterol: Span 20: diacetyl phosphate (10:10:1, 15:15:1 and 20:20:1) were prepared and evaluated for vaccine encapsulation efficiency using HI test. The values obtained of the different ratios were similar and the highest encapsulation was 50% [7].

Examples: dicetyl phosphate and phosphotidic acid [6].

3. Methods of Preparation

Since the preparation methods influence the number of bilayers, size, size distribution, and entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles, the preparation methods should be chosen based on the use of the Niosomes.

3.1. Ether injection method

This process involves slowly introducing solution of surfactant dissolved in diethyl ether into warm water which is maintained at 60°C. The surfactant mixture in ether is injected into aqueous solution through 14 gauge needle. Later the ether is vaporized which results in the formation of single layered vesicles. The diameter of the vesicles may be around 50-1000nm depending on the conditions [6, 8].

3.2. Hand shaking method /thin film hydration method

A mixture of surfactant and cholesterol is dissolved in volatile organic solvent like chloroform or methanol or diethyl ether in a round bottom flask. Organic solvent is removed at room temperature at 20ºC using rotary evaporator which leaves the thin layer of solids deposited on the walls of RBF. This dried surfactant film is rehydrated with aqueous phase at 0-60°C with agitation. This forms multilamellar vesicles [4, 5, 6].

3.3. Sonication method

Drug in the buffer solution is added to the surfactant mixture. This mixture is taken into 10 ml glass vial. This vial containing drug and surfactant mixture is sonicated for 10 minutes at 60ºC using probe sonicator with a titanium probe to produce multilamellar niosomes. Then these Niosomes are ultrasonicated by bath sonicator or probe sonicator to produce unilamellar niosomes [4, 6, 8].

3.4. Reverse phase evaporation method

Surfactant and cholesterol are taken in 1:1 ratio and dissolved in a mixture of chloroform and ether. Drug in aqueous solution is added to the above mixture. As a result, 2 phases are formed. These are sonicated at 5ºC after adding a small amount of phosphate buffered saline. Under low pressure, organic phase is removed at 40ºC. The resulting viscous suspension of Niosomes is diluted using PBS and heated on water bath for 10 minutes at 60ºC to form Niosomes [4,6].

3.5. Transmembrane pH gradient (Inside Acidic) Drug Uptake Process (Remote Loading)

In this method, surfactant and cholesterol are dissolved in chloroform. Under reduced pressure, solvent is evaporated to get thin film on the wall of round bottom flask. This film is hydrated with 300mM citric acid of pH 4. The multilamellar Niosomes formed are sonicated. To this suspension of Niosomes, aqueous solution of 10mg drug is added and vortexed and the pH is raised to 7.0-7.2 with 1 M disodium phosphate. This resulting mixture is heated at 60ºC for 10 min to give Niosomes [4].

3.6. Membrane extrusion method

A mixture of surfactant and cholesterol and diacetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membrane with mean pore size of 0.1µm. the solution and the resultant suspension is extruded which are placed in series for up to 8 passages. This is a good method for controlling the size of niosomal vesicles [4,6,8,2].

3.7. Microfluidization

This is a recent technique which is used to prepare unilamellar vesicles of particular size. This method is based on submerged jet principle.in this method, the two fluidized streams interact with high velocities, in micro channels within the interaction chamber. The solution is then passed through the cooling loop to remove the heat produced during the process. This method produces Niosomes of smaller size with great uniformity, smaller size ad better reproducibility [4, 5, 6].

3.8. Bubble method

This is a novel technique for single step preparation of Niosomes and liposomes without using organic solvents. The bubbling unit consist of a round bottomed flask with 3 necks kept in the water bath to control the temperature. Water cooled reflux and the thermometer are positioned in the first and second neck respectively and nitrogen gas is supplied through 3rd neck. Surfactant and cholesterol are dispersed in the buffer solution of pH 7.4 at 70 ºC. The resultant dispersion is mixed in high shear homogenizer for 15 seconds and immediately bubbled using nitrogen gas at 70 ºC[4, 5, 8, 2].

4. Characterization Techniques of Niosomes

There are several characterization techniques for Niosomes

4.1. Size, morphology and size distribution

Many techniques like light microscopy, photon correlation spectroscopy, electron microscopic analysis, SEM(scanning electron microscope), TEM(transmission electron microscope), light scattering, zetasizer can be used to study their morphology and determine the size of Niosomes. Particle size measured by the transmission electron microscope is

smaller than the dynamic light scattering (DLS) method because of the different measurement principles used by the two techniques [5].

4.2. Transmission Electron Microscopy (TEM)

TEM is used in the determination of the shape, size and lamellarity of Niosomes. The prepared suspension is mixed with 1% phosphotungstic acid (in required amount) and then a drop of this resultant was then used on carbon coated grid, then the grid was observed after draining off the excess. The images are taken under suitable magnification under TEM after drying completely [6].

4.3. Optical Microscopy Technique

This technique is also used for observation of shape and size of the Niosomes. The particle size is determined by taking nearly 100 niosome are used for particle size determination. The size of the Niosomes is then determined by coinciding stage micrometer and eyepiece micrometer and calculating the measurements [6].

4.4. Entrapment efficiency

Entrapment efficiency can be calculated by subtracting the amount of unloaded drug from the total amount of drug added. The unloaded drug can be determined using techniques such as filtration, exhaustive dialysis, centrifugation or gel chromatography. The concentration of loaded drugs can be calculated by dissolving niosome in 50% n-propanolol or 0.1% Triton X – 100 and the resulting solution can be assayed using any specific method. The following equation can be used to calculate the % entrapment efficiency [5].

$$\%\text{Entrapment Efficiency} = \frac{\text{Quantity of drug} - \text{loaded in the niosome}}{\text{Total quantity of drug in the suspension}} \text{x } 100$$

4.5. Charge on niosome and zeta potential

The charge present on the Niosomes cause them to repel each other. This electrostatic repulsion prevent aggregation and fusion and keeps them stable. The surface charge on Niosomes is determined using zeta potential. Zeta potential is determined by zetasizer, mastersizer, and DLS instrument [5, 6].

The equation used to calculate zeta potential is Henry's equation

$$£ = \mu E \pi \eta / \Sigma$$

Where £ = Zeta potential.
μE = Electrophoretic mobility
η = Viscosity of medium
Σ = Dielectric constant

4.6. Number of lamellae

Various techniques like NMR, small-angle X-ray spectroscopy and electron microscopy can be used for the determination of number lamellae. For the characterization of the thickness of bilayer, small-angle X-ray scattering can be used with the in situ energy-dispersive x-ray diffraction [5].

4.7. Membrane rigidity

Bio distribution and biodegradation of Niosomes is determined by the bilayer's rigidity. In homogeneity, dispersion can occur within niosome frameworks as well as between Niosomes and this can be defined by Differential Calorimetry Scanning (DSC) and FTIR techniques [8].

4.8. Osmotic shock

The change in the vesicle size can be determined by osmotic studies when they are subjected to different tonicity conditions. The formulated Niosomes are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours optical microscopy is used to determine the changes in the size of vesicles in the formulations [8].

4.9. Stability Studies

Niosomes are typically stored at 4±1 °C and 25±2 °C in order to conduct stability tests. One can compare the size, shape, and number of vesicles per cubic millimeter of the formulation before and after 30 days of storage. Residual drug can also be measured after 15 and 30 days. The size of vesicles is determined by Light microscope and the numbers of vesicles per cubic mm is measured by haemocytometer [6].

Number of Niosomes per cubic mm = total number of Niosomes x dilution factor total x 400 / total number of small squares counted

4.10. *In Vitro* Release Study

Generally dialysis membrane method is used in this study. In this method, dialysis bag containing a small amount of Niosomes are tied at both the ends. Then this dialysis bag is kept into a beaker with suitable dissolution media at 37 °C. It and stirred by a magnetic stirrer. At specified time intervals, sample solution is taken from the beaker and replaced with fresh dissolution media. The samples are analyzed for the amount of drug at wave length specified in the monograph of that particular drug [6].

4.11. Tissue Distribution/*In Vivo* Study

Animal models are used for studying tissue drug distribution. *In- vivo* studies for Niosomes depends on the route of delivery, concentration of drug, effect and residence time of the drug in tissues such as liver, lung, spleen and bone marrow. To study the distribution pattern, tissues of sacrificed animals like liver, kidney, heart, lungs, and spleen are removed. These tissues are washed with buffer. These tissues are then homogenized and centrifuged. The drug content is analyzed from the supernatant [5].

5. Applications

5.1. Ophthalmic Drug Delivery

Niosomes formulated for ophthalmic drug delivery show prolonged drug release

The most effective gentamicin Niosomes for extending drug release from the ocular delivery system were those made of Tween 60, cholesterol, and DCP, according to an in-vitro comparison of gentamicin Niosomes and gentamicin solution [6, 11].

5.2. Transdermal Delivery of Drugs

Drugs like Lidocaine and estrogen derivatives like estradiol, cyclosporine etc. are used for topical application and transdermal drug delivery system by formulating them as Niosomes [6].

5.3. Antiviral drug delivery

Niosomes are used in the delivery of many antiviral drugs. Ruckmani and Sankar prepared Niosomes containing zidovudine and found the entrapment efficiency and sustainability of drug release. The Niosomes were made up of Tween 80, Span 60, and cholesterol in various proportions. Niosomes which are prepared using Tween 80 exhibited greater entrapment of the drug zidovudine. The addition of dicetyl phosphate to Niosomes improved the drug release for a longer duration [10, 12].

5.4. Anticancer Drug Delivery

Chemotherapy is the current treatment for cancer. Poor penetration into tissues and side effects on other healthy cells limits the therapeutic efficacy of many anti-cancer drugs. The utilization of Niosomes as a novel drug delivery system is one of the numerous approaches that have been taken to overcome these limitations [10].

5.5. To improve oral bioavailability

It has been reported that, the oral bioavailability of niosomal formulation of acyclovir and griseofulvin was increased than the drug alone [6].

5.6. To Modify the Physicochemical Properties of Drugs

Studies showed that the physicochemical properties of free drug were improved by using non-ionic surfactants [6].

5.7. Improvement of stability of peptide drugs

Stability of peptide drugs was found to be increased after formulating as Niosomes.

The Niosomes prepared using span 60-prepared are resistant to proteolytic enzymes well and stable at storage temperature [6, 13].

5.8. Other applications include

- Targeted drug delivery
- Improve anti-inflammatory activity
- Prolonged release of drug from formulation
- Used as carrier for haemoglobin
- For treatment of localizes psoriasis
- In diagnostic imaging
- For studying immune response

6. Marketed formulations of Niosomes

Numerous anti-aging products based on Niosomes Formulations have been released by Lancôme. Additionally, L'Oreal is conducting research on anti-aging cosmetics. The market's preparation of Niosomes is –Lancome[4]

7. Conclusion

Niosomal drug delivery system is an efficient approach towards novel drug delivery. They mainly consists of non-ionic surfactants and cholesterol. Niosomes can be prepared by different methods like ether injection method, hand shaking method, sonication, reverse phase evaporation, remote loading method, extrusion method and microfluidization method. The properties of niosomes are affected by different excipients in different concentrations, methods of preparation, properties of drugs, structure and type of surfactant used, amount of cholesterol used. Niosomes are stable compared to liposomes. Niosomes provide several advantages over other types of drug delivery. They have many applications in pharmaceutical field. It was thus concluded that niosomes is a very effective drug delivery for incorporating many types of drugs and tagertting various tissues with reduced side effects to other tissues.

Compliance with ethical standards

Acknowledgments

We would like to thank Dr. M. Sunitha Reddy and K Anie Vijetha for proper guidance and support at *Department of pharmaceutics, Centre for pharmaceutical sciences, JNTUH UCEST, JNTUH*, Hyderabad.

Disclosure of conflict of interest

All authors declare no conflict of interest of regarding the publication of this paper.

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