Review Article
CODEN (USA): IJPLCP

ISSN: 0976-7126
Jain *et al.*, 15(10):20-26, 2024

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

An overview Niosomes: Formulation Consideration, Characterization and Applications

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Article info

Received: 19/07/2024

Revised: 22/08/2024

Accepted: 02/09/2024

www.ijplsjournal.com

Abstract

In the past few decades, considerable attention has been focused on the development of novel drug delivery system (NDDS). The NDDS should ideally fulfil two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage forms are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery. In the present review attempt was made to highlight the formulation consideration, characterization and applications of Niosomes.

Key-words: Niosomes, Novel, Applications, Evaluation, Formulation

Introduction

Vesicles act as the vehicle of choice in drug delivery. Lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques, and most recently, genetic engineering. Vesicles can play a major role in modelling biological membranes, and in the transport and targeting of active agents.

Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Niosomes are promising vehicle for drug delivery and being non-ionic, Niosomes are unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. They are very similar to the liposomes. Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Niosomes have shown promise in the release studies and serve as a better option for drug delivery system. The drug is incorporated into niosomes for a better targeting of the drug at appropriate tissue destination. [1-2]

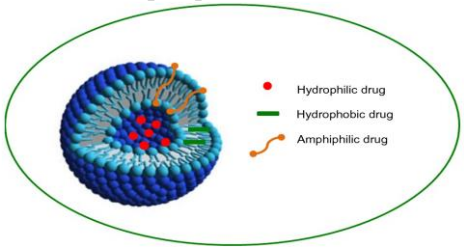

Figure 1: Schematic representation of a niosomal vesicle

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Salient features of niosomes

Niosomes act as alternatives of liposomes. Disadvantages in the liposomes are avoided in this.

Osmotically active and stable.

Niosome increases the stability of entrapped drug.

They can be made to reach the site of action by oral, parenteral as well as topical routes.

Surfactant used in niosome does not require special conditions.

Surfactants used in niosomes are biodegrable, biocompatible and non-immunogenic.

They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation.

Niosome exhibit flexibility in their structural characteristics (composition, fluidity, size) and can be designed to desired situation. [3]

Composition of niosomes

Niosomes contain two major component, Cholesterol and Nonionic surfactants. Cholesterol is used to provide rigidity and proper shape to the niosomes. Surfactants play a major role in the formation of niosomes. The following non-ionic surfactants are generally used for the preparation of niosomes the spans (span60,40,20,85,80), tweens (tween 20,40,60,80) and brijs (brij 30,35,52,58,72,76). The non ionic surfactants possess a hydrophillic head and a hydrophobic tail. [4-5]

Surfactants used in formulation of niosomes

Niosomes are non-ionic surfactant unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. [6]

Types of Niosomes [7-9]

Small unilamellar vesicles (SUV)

SUV are commonly produced by sonication, and French Press procedures. Ultrasonic electro capillary emulsification or solvent dilution techniques can be used to prepare SUVs. (Size - 0.025-0.05 μm)

Multilamellar vesicles (MUV)

Exhibit increased-trapped volume and equilibrium solute distribution, and require hand-shaking method. They show variations in lipid compositions. (size > 0.05 μm)

Large unilamellar vesicles (LUV)

The injections of lipids solubilised in an organic solvent into an aqueous buffer, can result in spontaneous formation of LUV, but the better method of preparation of LUV is Reverse phase evaporation, or by Detergent solubilisation method. (size > 0.10 μm)

Advantages of niosomes

- Niosomal vesicle suspension is water–based vehicle. This offers high patient compliance in comparison with oily dosage forms.
- They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.
- The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
- The vesicles may act as a depot, releasing the drug in a controlled manner.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes
- They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
- Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueos phase**.**

Factors affecting formation of niosomes [7-9]

Nature of surfactants

Surfactants used for preparation of niosomes must contain a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal group. The ether type surfactants with single chain alkyl as hydrophobic tail is more toxic than corresponding dialkylether chain. The ester type surfactants are chemically less stable than ether type surfactants and the former is less

toxic than the latter due to ester-linked surfactant degraded by esterases to triglycerides and fatty acid *in vivo*. The surfactants with alkyl chain length from C_{12}-C_{18} are suitable for preparation of niosome.

Structure of surfactants

The geometry of vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameters. On the basis of critical packing parameters of surfactants can predicate geometry of vesicle to be formed.

Membrane composition

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives.

Nature of encapsulated drug

The physico-chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers and hence increases vesicle size.

Temperature of hydration

Hydration temperature influences the shape and size of the niosome. For ideal condition it should be above the gel to liquid phase transition temperature of system. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation

Method of preparation of niosomes

Various methods are reported for the preparation of niosomes such as:

- ✓ Ether injection method
- ✓ Hand shaking method (Thin film hydration technique)
- ✓ Sonication method
- ✓ Reverse phase evaporation technique (REV)
- ✓ Micro fluidization
- ✓ Multiple membrane extrusion method
- ✓ Trans membrane pH gradient (inside acidic) drug uptake process (remote loading)
- ✓ Bubble method
- ✓ Formation of niosomes from proniosomes

Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether (volatile organic solvent) into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether (volatile organic solvent) leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm

Hand shaking method (Thin film hydration technique)

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes.

Sonication

In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

Reverse phase evaporation technique

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.

Micro fluidization

It is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged

such that the energy supplied to the system remains within the area of niosomes formation. The result is a smaller size, greater uniformity and better reproducibility of niosomes formed.

Multiple membrane extrusion method

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, solution and the resultant suspension extruded through which are placed in series for up to 8 passages. Multiple membrane extrusion method is better for the controlling of niosome size.

Trans membrane pH gradient (inside acidic) drug uptake process (remote loading)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes.

Bubble method

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards bubbled at 70°C using nitrogen gas.

Applications [7-9]

Therapeutic application

There are very less marketed niosomal formulations found in market. But some experimentally evaluated application of niosomal formulation identified in literature listed below.

Anti-cancer drug

Daunorubicin HCl

Niosomal daunorubicin hydrochloride exhibited an enhanced anti-tumor efficacy when compared to free drug. The niosomal formulation was able to destroy the Dalton's ascitic lymphoma cells in the peritoneum within the third day of treatment, while free drug took around six days and the process was incomplete. The hematological studies also prove that the niosomal formulation was superior to free drug treatment. An enhanced mean survival time was achieved by the niosomal formulation that finally substantiates the overall efficacy of the niosomal formulation.

Doxorubicin

Rogerson et al., studied distribution of niosomal doxorubicin prepared from C16 monoalkyl glycerol ether with or without cholesterol. Niosomal formulation exhibited an increased level of doxorubicin in tumor cells, serum and lungs, but not in liver and spleen. Doxorubicin loaded cholesterol-free niosomes decreased the rate of proliferation of tumor and increased life span of tumorbearing mice. The cardio toxicity effect of doxorubicin was reduced by niosomal formulation. Niosomal formulation changes the general metabolic pathway of doxorubicin.

Methotrexate

Azmin et al., quoted in their research article that niosomal formulation of methotrexate exhibits higher AUC as compared to methotrexate solution, administered either intravenously or orally. Tumoricidal activity of niosomally-formulated methotreaxate is higher as compared to plain drug solution.

Bleomycin

Niosomal formulation of bleomycin containing 47.5% cholesterol exhibits higher level drug in the lever, spleen and tumour as compared to plan drug solution in tumorbearing mice . There is no significant difference in drug concentration with niosomal formulation in lung as compared to plan drug solution. Also, there is less accumulation of drug in gut and kidney in case of niosomal formulation.

Vincristine

Niosomal formulation of vincristine exhibits higher tumoricidal efficacy as compared to plain drug formulation Also, niosomal formulation of carboplatin exhibits higher tumoricidal efficacy in S-180 lung carcinoma-bearing mice as compared to plan drug solution and also less bone marrow toxic effect.

Anti-infective agents

Sodium stibogluconate is a choice drug for treatment of visceral leshmaniasis is a protozoan infection ofreticuloendothelial system. Niosomal or liposomal formulation of sodium stibogluconate exhibits higher levels of antimony as compared to free drug solution in liver. Antimony level is same in both formation i.e. niosome and liposome. Niosomal formulation of rifampicin exhibits better antitubercular activity as compared to plain drug.

Anti-inflammatory agents

Niosomal formulation of diclofenac sodium with 70% cholesterol exhibits greater anti-inflammation activity as compared to free drug. Niosomal formulation of nimesulide and flurbiprofen also exhibits greater anti-inflammation activity as compared to free drug.

Diagnostic imaging with niosomes

Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglcemine with [N-palmitoyl-glucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.

Transdermal drug delivery

Administration of drugs by the transdermal route has advantages such as avoiding the first pass effect, but it has one important drawback, the slow penetration rate of drugs through the skin. Various approaches are made to overcome slow penetration rate, one approach for it is niosomal formulation. Studied transdermal delivery pro-niosomal formulation of ketorolac prepared from span 60 exhibits a higher ketorolac flux across the skin than those proniosome prepared from tween20. It is also identified in literature that the bioavailability and therapeutic efficacy of drug like diclofenac , flurbiprofen and nimesulide are increased with niosomal formulation .

Ophthalmic drug delivery

It is difficult to achieve excellent bioavailability of drug from ocular dosage form like ophthalmic solution, suspension and ointment due to the tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But to achieve good bioavailability of drug various vesicular systems are proposed to be use, in experimental level, like niosomes, liposomes. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendency for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide). The chitosan-coated niosomal formulation timolol maleate (0.25%) exhibits more effect for reduction intraocular pressure as compared to a marketed formulation with less chance of cardiovascular side effects**.**

Characterization of Niosomes

The characterization of niosome is essential for the clinical applications. Characterization parameters have a direct impact on the stability of niosomes and a significant effect on their in vivo performance. Therefore these parameters such as morphology, size, polydispersity index (PI), number of lamellae, zeta potential, encapsulation efficiency, and stability must be evaluated.

Size and Morphology

Dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), freeze fracture replicationelectron microscopy (FF-TEM), and cryotransmission electron microscopy (cryo-TEM) are the most used methods for the determination of niosome sizes andmorphology. DLS provides simultaneously cumulative information of particle size and valuable information on the homogeneity of the solution. A single sharp peak in the DLS profile implies existence of a single population of scatterers. The PI is helpful in this respect. It less than 0.3 corresponds to a homogenous population for colloidal systems. The microscopic approaches are generally used to characterize the morphology of the Niosomes**.**

Zeta Potential

Surface zeta potential of niosomes can be determined using zetasizer and DLS instruments.The surface charge of niosome plays an important role in the behavior of niosomes. In general, charged niosomes are more stable against aggregation than uncharged vesicles. Bayindir and Yuksel prepared paclitaxel loaded niosomes and investigated the physicochemical properties such as zeta potential of niosomes. They found that negative zeta potential values ranging between −41.7 and −58.4 mV are sufficiently high for electrostatic stabilization of niosomes

Bilayer Characterization

Bilayer characteristics of niosomes have an importance on drug entrapment efficiency. The number of lamellae can be determined by AFM, NMR, and small angle X-ray scattering (SAXS) for multilamellar vesicles. Membrane rigidity of niosomal formulations can be measured by means of the mobility of fluorescence probe as a function of temperature. DPH (1,6 diphenyl1,3,5-hexatriene) is most used fluorescent probe and added to niosomal dispersion. DPH normally exists in hydrophobic region in the bilayer membrane. The microviscosity of niosomal membrane is determined by fluorescence polarization. High fluorescence polarization means high microviscosity of the membrane. Moreover, the bilayer thickness can be characterized using the latter method, together with the in situ energy-dispersive X-ray diffraction (EDXD).

Entrapment Efficiency

Entrapment efficiency (EE%) is defined as the portion of the applied drug which is entrapped by the niosomes. Unencapsulated free drug can be removed from the niosomal solution using centrifugation, dialysis, or gel chromatography. After this step the loaded drug can be released from niosomes by destruction of vesicles. Niosomes can be destroyed with the addition of 0.1% Triton X-100 or methanol to niosomal suspension. The loaded and free drug concentration can be determined by a spectrophotometer or high-performance liquid chromatography (HPLC) .

Stability

The stability of niosomes can be evaluated by determining mean vesicle size, size distribution, and entrapment efficiency over several month storage periods at different temperatures. During storage the niosomes are sampled at regular intervals of time and the percentage of drug which is retained into the niosomes is analyzed by UV spectroscopy or HPLC methods**.**

In Vitro Release

One often applied method to study in vitro release is based on using of dialysis tubing. A dialysis bag is washed and soaked in distilled water. After 30 mins, the drug loaded niosomal suspension is transferred, into this bag. The bag containing the vesicles is immersed in buffer solution with constant shaking at 25◦ C or 37◦ C. At specific time intervals, samples were removed from the outer buffer (release medium) and replaced with the same volume of fresh buffer. The samples are analyzed for the drug content by an appropriate assay method.

Superficial infections and antifungal therapy

The delivery of drugs on the skin is recognized as an effective means of therapy for local dermatological diseases. But skin is widely recognized for its barrier properties compared with other biological membranes. The low permeability of skin for drug entry makes it a difficult port for absorption. Superficial fungal infections affect millions of people throughout the world. Dermatophytosis is a superficial fungal infection on the skin, hair and nails. It is one of the most common diseases caused by dermatophyte fungal species of *Epidermophyton, Trichophyton and Microsporum*. It is estimated that about 10% to 20% of the world population is affected by mycological infections and sites and severity of infection vary according to geographical location, the organism involved, and environmental and cultural differences. There is a rampant increase in opportunistic fungal infections globally due to long term antimicrobial therapy, organ transplants, immunity compromised HIV cases and cancer chemotherapy. Fungi are eukaryotic and exhibit biochemical resemblance to human hosts. This similarity makes antifungal development process a cumbersome process, as drug should be effective against invading fungus and at the same time safe for the host. It has been estimated that over US $ 500 million per year is spent worldwide on drugs to treat dermatophytosis . It is BCS class II -4 drug having very poor solubility, causing its poor and variable absorption from oral solution and more commonly, oral capsules. The treatment spans from one day (*e.g.,* for Vulvovaginal candidiasis) to several weeks *(e.g.,* for Tinea pedis and Tinea corporis), depending on the type and site of infection. Also, the commonest minor side effects of oral ITR therapy are constipation, nausea, flatulence, abdominal pain; headache and diarrhoea (in case of cyclodextrin solutions) are frequently observed. Also severe adverse effects like serious hepatotoxicity, including liver failure and also effects on the nervous system,

gastrointestinal tract, hematologic, and renal insufficiency have been reported

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Cite this article as:
Jain R., Ali. Z. Md. And Tiwari H. (2024). An overview Niosomes: Formulation Consideration, Characterization and Applications. *Int. J. of Pharm. & Life Sci*., 15(10): 20-26.

Source of Support: Nil
Conflict of Interest: Not declared
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