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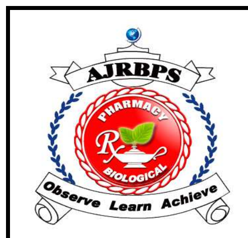

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NIOSOMES AS NOVEL VESICULAR DRUG DELIVERY SYSTEM- A REVIEW

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ABSTRACT

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. Structurally niosomes are similar to liposomes, in that they are also made up of a bilayer. However, the bilayer in the case of niosomes is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Most surface active agents when immersed in water yield micellar structures however some surfactants can yield bilayer vesicles which are niosomes. Niosomes may be unilamellar or multilamellar depending on the method used to prepare them. The niosomes are classified as a function of the number of bilayer or as a function of size or as a function of the method of preparation. Niosomes present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes due to the niosome ability to encapsulate different type of drugs within their multi environmental structure. The technology utilized in niosomes is still greatly in its infancy, and already it is showing promise in the fields of cancer and infectious disease treatments.

KEY WORDS

Niosomes, Phospholipid, anti-cancer, non-ionic surfactant and bilayer.

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INTRODUCTION

At present no available drug delivery system achieves the site specific delivery with controlled release kinetics of drug in predictable manner. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include

immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc. Among different carriers liposomes and niosomes are well documented drug delivery. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with non-target tissue. 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. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span- 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate[1].

Niosomes are the highly ordered vesicular bilayer membrane made up of non-ionic surfactant with or without incorporation of cholesterol and dicetyl phosphate. The closed bilayer vesicular structure of niosome formed by the self-assembling of non-ionic surfactants in the presence of aqueous media[2].

In recent years, niosomes have been extensively studied for their potential to serve as a carrier for the delivery of drugs, antigens, hormones and other bioactive agents. Besides this, niosome has been used to solve the problem of insolubility, instability and rapid degradation of drugs[3].

Factors governing noisome formation

Composition of niosome

Theoretically for the noisome formation the presence of a particular class of amphiphile and aqueous solvent is needed but in certain cases cholesterol is required in the formulation to provide rigidity, proper shape and conformation to the niosomes. Cholesterol also stabilizes the system by prohibiting them formation of aggregates by repulsive steric or electrostatic effects. An example of steric stabilisation is the inclusion of Solulan C24 (a cholesteryl poly-24-oxyethylene ether) in doxorubicin (DOX) sorbitan monostearate (Span 60) niosome formulations**.** An example of electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)- carboxy fluorescein (CF) loaded Span 60 based niosomes[4].

Surfactant and lipid level

To make niosomal dispersions the surfactant/lipid level is generally kept 10-30 mM (1- 2.5% w/w). If the surfactant, water ratio is altered during the hydration step may affect the microstructure of the system and its properties. If we increasing the surfactant/lipid level the total amount of drug encapsulated also increases, but the viscosity level of system also increase[5].

Nature of the encapsulated drug

The nature of encapsulated drug influences the niosomal formation, generally the physico chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The encapsulated drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers and hence vesicle size increases and also cause the aggregation of vesicles, which is prevented by using electrostatic stabilizers like dicetyl phosphate in 5(6)-carboxy fluorescein (CF)[6].

Structure of surfactants

The geometry of vesicle to be formed from surfactants is affected by surfactant's structure, which can be defined by critical packing parameters. Geometry of vesicle to be formed can be predicated on the basis of critical packing parameters of surfactants. Critical packing parameters can be defined using following equation,

CPP (Critical Packing Parameters) = $V / l_c \times a_0$

Where

v = hydrophobic group volume,

l_c = the critical hydrophobic group length,

a_0= the area of hydrophilic head group from the critical packing parameter value type of miceller structure formed can be ascertained as given below,

If CPP < ½ formation of spherical micelles,

If ½ < CPP < 1 formation of bilayer micelles,

If CPP > 1 formation inverted micelles[5-7].

Temperature of hydration

Hydration temperature influences the shape and size of the niosome, temperature change of niosomal system affects assembly of surfactants into vesicles

by which induces vesicle shape transformation. Ideally the hydration temperature for niosome formation should be above the gel to liquid phase transition temperature of system[8-9].

Salient features of niosomes[10]

1. Niosomes can entrap solutes in a manner analogous to liposomes.
2. Niosomes are osmotically active and stable.
3. Niosomes possess an infra structure consisting of hydrophobic and hydrophilic mostly together and so also accommodate the drug molecules with a wide range of solubility.
4. Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
5. Niosomes can improve the performance of the drug molecules.
6. Better availability to the particular site, just by protecting the drug from biological environment.
7. Niosomes surfactants are biodegradable, biocompatible and non-immunogenic solubility.

Advantages[11]

1. High patient compliance in comparison with oily dosage forms as the vesicle suspension is a water based vehicle.
2. Accommodate drug molecules with a wide range of solubilities.
3. The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, surface charge and concentration can control the vesicle characteristics.
4. The vesicles may act as a depot, releasing the drug in a controlled manner.
5. They are osmotically active and stable, as well as they increase the stability of entrapped drug.
6. Handling and storage of surfactants requires no special conditions.
7. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
8. They can be made to reach the site of action by oral, parenteral as well as topical routes.
9. The surfactants are biodegradable, biocompatible and non-immunogenic.

Disadvantages[6]

1. The aqueous suspensions of niosomes may have limited shelf life due to fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs.
2. The methods of preparation of multilamellar vesicles such as extrusion, sonication, are time consuming and may require specialized equipments for processing.

Method of preparation

Some of the important methods that are used to prepare niosomes are as follows:

Ether injection method

A solution containing a particular ratio of cholesterol and surfactant in ether is slowly injected into the preheated aqueous solution of the drugs maintained at 60 °C through the specified gauze needle. The vaporization of ether leads to the formation of unilameller vesicles of the surfactants containing drug. Alter-natively, fluorinated hydrocarbons have been used as a substitute for ether for thermo labile drugs, as they vaporize at a much lower temperature. The size of niosomes obtained by this method varies between 50-1000 nm, which mainly depends on the formulation variables and experimental conditions[12].

Extrusion method

A mixture of cholesterol and diacetyl phosphate is prepared and then solvent is evaporated using rotary vacuum evaporator to leave a thin film. The film is then hydrated with aqueous drug solution and the suspension thus obtained is extruded through the polycarbonate membrane (mean pore size 0.1 nm) and then placed in series up to eight passages to obtain uniform size niosomes[13].

Hand shaking method

The Cholesterol and surfactant are dissolved in some organic solvents such as ether, chloroform, benzene etc. Then, the solvent is evaporated under reduced pressure in a vacuum evaporator in a round bottom flask which then leaves the mixture of solid surfactant and cholesterol on the walls of round bottom flask. This layer was then rehydrated with aqueous solution containing drug with continuous

shaking which results in swelling of surfactant layer. Swelled amphiphiles eventually folds and form vesicles which entrap the drugs[14].

Sonication method

A mixture consists of surfactant and cholesterol, is dispersed primarily in the aqueous phase. This dispersion is then probe sonicated for 10 min at 60 °C, which leads to the formation of multilameller vesicles (MLV). These MLVs are further ultrasonicated either by probe sonicator or bath sonicator, which in turn leads to the formation of unilameller vesicles[14].

Reverse phase evaporation method

The solution of cholesterol and surfactant is prepared in a mixture of ether and chloroform (1: 1). To this, the aqueous solution of drug is added and sonicated at temperature 4 - 5 °C. The solution thus obtained is further sonicated after addition of phosphate buffer saline (PBS) resulting in the formation of gel. Thereafter temperature is raised to 40 °C and pressure is reduced for the removal of solvent. The PBS is added again and heated on water bath at 60 °C for 10 min to yield niosomes[15].

Micro fluidization method

Two fluidized streams (one containing drug and the other surfactant) interact at ultra high velocity, in precisely defined micro channels within the interaction chamber in such a way that the energy supplied to the system remains in the area of niosomes formations. This is called submerged jet principle. It results in better uniformity, smaller size and reproducibility in the formulation of niosomes[16].

Transmembrane pH gradient Drug uptake process

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 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[17].

The "Bubble" Method

It is novel technique for the one step preparation of 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 afterward "bubbled" at 70°C using nitrogen gas[18].

Evaluation

Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation and gel filtration. The drug remain entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzed resultant solution by appropriate assay method using following equation[18,19].

% EE=Amount of entrapped drug/Total amount added×100

Size, Shape and Morphology

Structure of surfactant based vesicles has been visualized and established using freeze fracture microscopy while photon correlation spectroscopy used to determine mean diameter of the vesicles. Electron microscopy used for morphological studies of vesicles while laser beam is generally used to determine size distribution, mean surface diameter and mass distribution of niosomes[19-20].

***In-vitro* release study**

A method of *in-vitro* release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method[21-22].

Stability study

Stability studies can be carried out by storing niosome at two different conditions, usually 4 ± 1 °C and 25 ± 2 °C. Formulation size, shape and number of vesicles per cubic mm can be assessed before and after storing for 30 days. After 15 and 30 days, residual drug can also be measured[23].

Applications[1]

Anti-infective agents

Sodium stibogluconate is a choice drug for treatment of visceral leshmaniasis is a protozoan infection of reticuloendothelial 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 anti-tubercular activity as compared to plain drug.

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. The 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.

Niosomes as Drug Carriers[10]

Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for X-ray imaging. Topical niosomes may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

Targeting of bioactive agents[23]

a. Targeting to reticulo-endothelial System (RES): The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins, which mark them for clearance.

b. Targeting to organs other than RES: It has been suggested that carrier system (antibodies) are attached to direct niosomes to specific sites in the body. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier.

Pulmonary delivery[24]

Niosomes are used in asthmatic patients but drug is poorly permeable through hydrophilic mucus. Terzanom developed polysorbate 20 niosomes containing beclomethasone dipropionate for pulmonary delivery to patients with chronic obstructive pulmonary disease. They reported that the niosomes provided targeted and sustained delivery, improved mucus permeation and amplified therapeutic effect .The non-ionic surfactant vesicles remarkably increases the permeation rate through the model mucosal barrier and hence offering a better targeting of corticosteroids in the treatment of COPD.

Protein and peptide delivery[25]

Oral administration of proteins and peptides is hindered by numerous barriers including proteolytic enzymes, pH gradients and low epithelial permeability. So the entrapment of insulin in the bilayer structure of niosomes was shown to protect it against proteolytic activity of a chymotrypsin, trypsin and pepsin in vitro. Likewise, vasoactive intestinal peptide (VIP) has been tested in the treatment of Alzheimer’s disease but failed to cross the blood–brain barrier (BBB) and by its rapid elimination after intravenous administration. Dufes reported glucose-bearing niosomes encapsulating VIP for delivery to specific brain areas and concluded that glucose bearing vesicles represent a novel tool to deliver drugs across the BBB.

Neoplasia[26]

Doxorubicin, the anthracyclic antibiotic with broad spectrum anti-tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma. Niosomal entrapment

increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination.

Anti-inflammatory agents

Niosomal formulation of Diclofenac sodium with 70% cholesterol exhibits greter anti-inflammatory activity as compare to free drug. Niosomal formulation of Nimesulide and Flurbiprofen also exhibits greter anti-inflammatory activity as compared to free drug.

Ophthalmic drug delivery

It is difficulty 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 tendencies for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide).

Leishmaniasis

Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticulo-endothelial system. Leishmaniasis is such a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney. The study of antimony distribution in mice, showed high liver level after intravenous administration of the carriers forms of the drug.

CONCLUSION

Niosomes present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. The technology utilized in niosomes is still greatly in its infancy, and already it is showing promise in the fields of cancer and infectious disease treatments. The system is already in use for various cosmetic products. Niosomes represent a promising drug delivery technology various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, etc.

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