IJPSR (2013), Vol. 4, Issue 2 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 October, 2012; received in revised form, 29 November, 2012; accepted, 18 January, 2013

NIOSOMES: A ROLE IN TARGETED DRUG DELIVERY SYSTEM

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Keywords:

Advantages, Applications, Factors governing Niosomes formation, Introduction, Methods, Types

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ABSTRACT

Niosomes are non-ionic surfactant vesicles inclosing an aqueous phase and a wide range of molecules could be encapsulated within aqueous spaces of lipid membrane vesicles. They are microscopic lamellar structures formed on the admixture of a non-ionic surfactant, cholesterol and phosphate with subsequent hydration in aqueous media. Niosomes belongs to novel drug delivery system which offers a large number of advantages over other conventional and vesicular delivery systems. Namely they are the targeted drug delivery system which showing reduction of dose, stability and compatibility of non-ionic surfactants, easy modification, delayed clearance, suitability for a wide range of Active Pharmaceutical Agents.

INTRODUCTION: The basic goal of the drug therapy is to achieve a steady state blood or tissue level that is therapeutically effective and nontoxic for an extended period. The design of proper dosage regimen was an important element in accomplishing the goal. Novel drug delivery systems are aiming to delivery the drug at a rate directed by the needs of the body during the period of treatment and channel the active entity to the site of action.

Targeted drug delivery implied for selective and effective localization of pharmacologically active moiety at pre-identified (preselected) targeted in therapeutic concentration while restricting its access to non-target normal cellular linings thus it minimizing the toxic effect and maximizing therapeutic index. Targeted drug delivery was an event where a drug carrier complex/conjugate delivers drug (s) exclusively to the pre-identified targeted cells in a specific manner. To pursue the optical drug action, functional molecules could be transported by a carrier to the site of action and released for performing their task.

The targeting methods may be classified as chemical methods, by covalent bonding and physical methods. Chemical methods involved chemical modification of the parent compound to a derivative, which was activated only at the target site. Various physical methods made use of the carriers such as liposomes, niosomes, resealed erythrocytes, platelets, magnetic microspheres, nanoparticles, and monoclonal anti-bodies. Recently the niosomal drug delivery system (A particulate colloidal carrier system) is basically drawing attention due to its significant advantages over conventional drug delivery system.

Niosomes are the nonionic surfactant vesicles with lamellar structure which may be unilamellar and multilamellar serve to be efficient in providing the required advantages like: to develop the effective delivery system to achieve maximum effective concentration, to form vesicles that able of entrapping hydrophilic and hydrophobic molecules, modification of the particle composition or surface could adjusted the affinity for the target site and/or the drug release

rate, etc. Niosomes proved to be a promising drug carrier and had potential to reduce the side effects of drugs and enhanced therapeutic effectiveness in various diseases through restricting its action to target cells. The bilayer structure of niosomes being amphiphillic in nature could be used to deliver hydrophilic drugs in its aqueous core and lipophilic drugs in the bilayer which is made up of surfactants. Various additives in niosomes included nonionic surfactant as film forming agent, cholesterol as stabilizing and rigidizing agent for the bilayer and various charge inducers which was developing a charge on the surface of niosomes and stabilized the prepared formulation by the resulting repulsive forces [1-5].

There are different types of Niosomes that are based on the vesicle size then niosomes can be divided into three groups:

- Small Unilamellar Vesicles (SUV, Size = 0.025-0.05µm),
- Multilamellar Vesicles (MLV, Size = >0.05µm),
- Large Unilamellar Vesicles (LUV, Size = >0.10µm) [6].

Some advantages of Niosomes are:

- The vesicle suspension was water–based vehicle. This will 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 could accommodate drug molecules with a wide range of solubilities.
- The characteristics of the vesicle formulation were variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration could control the vesicle characteristics.
- The vesicles may also act as a depot, releasing the drug in a controlled manner [7].

Other advantages of Niosomes included:

- They are osmotically active and stable, as well as they increased the stability of entrapped drug.
- Handling and storage of surfactants required no special conditions.
- They improved oral bioavailability of poorly absorbed drugs and enhanced skin penetration of drugs.
- They could be made to reach the site of action by oral, parenteral as well as topical routes.
- The surfactants are basically biodegradable, biocompatible and non-immunogenic.
- They improve the therapeutic performance of the drug molecules through delayed clearance from the circulation, protecting drug from biological environment and restricting effects to target cells.[7]

Comparison between Niosomes and Liposomes are:

- Liposomes are expensive and their ingredients like phospholipids were chemically unstable due to their predisposition to oxidative degradation, they required special storage and handling and also purity of natural phospholipids is variable.
- Differences in characteristics exist between liposomes and niosomes, especially where niosomes were prepared from uncharged single-chain surfactant and cholesterol whereas liposomes were prepared from double-chain phospholipids (neutral or charged).
- Niosomes behave *in-vivo* like liposomes, prolonging the circulation of entrapped drugs and modulating its organ distribution and metabolic stability. Encapsulation of various antineoplastic agents the carrier vesicles had been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, enhancing the anti-tumor efficacy. Such as vesicular drug carrier systems altered the plasma clearance kinetics,

tissue distribution, metabolism and cellular interaction of the drug. They could be expected to target the drug to its desired site of action and/or to control its release profile.

- As with liposomes, the properties of niosomes depend on the composition of the bilayer and on method of their formulation.

- The entrapment efficiency enhances with increase in the concentration and lipophilicity of surfactants [7, 8].

There are some factors governing Niosomes formation:

- Amount and type of Surfactant- The mean size of niosomes enhances proportionally with increase in the HLB of surfactants such as Span 85 (HLB 1.8) to Span 20 (HLB 8.6) due to the surface free energy decreases with an enhance in hydrophobicity of surfactant. Niosome formation required the presence of a particular class of amphiphile and aqueous solvent. In some cases cholesterol is required in the formulation and vesicle aggregation. It may be prevented by the inclusion of molecules that stabilize the system against the formation of aggregates by the repulsive steric or electrostatic effects.

  The bilayers of the vesicles were either in the so called liquid state or in gel state depends on the temperature, the type of lipid or surfactant and the presence of other components like cholesterol. In the gel state, alkyl chains are present in a well ordered structure, and in the liquid state, the structure of the bilayers was more disordered. The surfactants and lipids were characterized by the gel-liquid phase transition temperature (TC). Phase transition temperature also affects entrapment efficiency. E.g.: span 60 is the good surfactant because it is having high phase transition temperature and low HLB (Hydrophilic Lipophilic Balance) value so it form vesicle of good size without the micelle formation.

- Cholesterol content and charge- Inclusion of cholesterol in niosomes enhances its hydro-dynamic diameter and entrapment efficiency. Generally, the action of cholesterol was in two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other hand, cholesterol decreases the chain order of the gel state bilayers. At a high cholesterol concentration, the gel state was transformed to a liquid-ordered phase. An increased in cholesterol content of the bilayers results in a decrease in the release rate of encapsulated material and then an increase of the rigidity of the bilayers obtained.

  Presence of the charge tends to increase the interlamellar distance between successive bilayers in the multilamellar vesicle structure and leads to greater overall entrapped volume. The level of surfactant/lipid used to make niosomal dispersions is in general 10-30 mM (1- 2.5% w/w). Altering the surfactant water ratio during the hydration step may affected the system's microstructure and hence the system's properties. However, increasing the surfactant/lipid level will also increases the total amount of drug encapsulated, although highly viscous systems resulted, if the level of the surfactant/lipid is too high.

- Nature of the Encapsulated drug- Entrapment of drug in niosomes increases vesicle size, probably by the interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, by which increasing vesicle size. E.g.: DOX had been shown to alter the electrophoretic mobility of hexadecyl diglycerol ether (C16G2) niosomes in a pH dependent manner, an indication that the amphipathic drug was incorporated in the vesicle membrane.

- Structure of Surfactants- The geometry of vesicle to be formed from surfactants was affected by its structure, which is related to the critical packing parameters. On the basis of critical packing parameters of Surfactants can predicate geometry of vesicle to be formed. Critical packing parameters (CPP) can be:

  1. CPP ≤0.5 micelles form
  2. CPP= 0.5 – 1 spherical vesicles form
  3. CPP = ≥1 inverted vesicles form

Span 60 is the good surfactant because it has CPP value between 0.5-1.

- **Temperature of Hydration**- Hydration temperature influenced the shape and size of the noisome. The hydrating temperatures used to make niosomes and it should usually be above the gel to liquid phase transition temperature of the system [6, 9, 10].

  Niosomes were developed in different dosage forms for different diseases like cancer treatment, pain and inflammation relief, fever treatment and glaucoma treatment etc. It can be prepared by different methods e.g.: Ether injection method, Hand shaking method (Thin film hydration method), Sonication, Microfluidization, Multiple membrane extrusion method, Reverse phase evaporation technique, Trans membrane pH gradient, the Bubble method, formation of Niosomes from Proniosomes, Method of Handjani-Vila, Heating method. Among all of these methods the Microfluidization is the best method because it leads to form uniform vesicles [1-3, 11-13].

1. **Ether injection method**- In this method by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C mainly provides a means of making niosomes. The surfactant mixture in ether was injected by 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to the formation of single layered vesicles which is basically depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm.

2. **Hand Shaking method (Thin Film Hydration Technique)**- The mixture of vesicles forming ingredients like surfactant and cholesterol were basically dissolved in a volatile organic solvent (diethyl either, chloroform or methanol) in a round bottom flask. The organic solvent was then removed at room temperature (20°C) using rotary evaporator leaving a formation of thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film could be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms the typical multilamellar niosomes.

3. **Sonication Method**- A typical method of production of the vesicles was by sonication of solution as described by the Cable. In this method an aliquot of drug solution in buffer was added to the surfactant/cholesterol mixture in a 10ml glass vial. The mixture was probe sonicated at 60°C for 3 minutes using a sonicator with the titanium probe to yield noisome formation.

4. **Micro fluidization Method**- Micro fluidization is a recent technique used in preparing unilamellar vesicles of defined size distribution. This method was based on submerged jet principle in which two fluidized streams interacted at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along with a common front was arranged such that the energy supplied to the system remains within the area of niosomes formation. The result was found as a greater uniformity, smaller size and better reproducibility of niosomes formed.

5. **Multiple membrane extrusion method**- The mixture of surfactant, cholesterol and dicetyl phosphate in chloroform was made in the form of thin film by evaporation. The film was hydrated with aqueous drug polycarbonate membranes, solution and the resultant suspension extruded by which it were placed in series for upto 8 passages. It was a good method for controlling size of niosomes.

6. **Reverse Phase Evaporation Technique (REV)**- Cholesterol and surfactant (1:1) were dissolved in a mixture of ether and chloroform. Then an aqueous phase containing drug was added to this and the resulting two phases were sonicated at 4-5°C. The clear gel formed was further sonicated and after that the addition of a small amount of phosphate buffered saline (PBS) takes place. The organic phase was removed at 40°C under low pressure.

   The resulting viscous niosome suspension was then diluted with PBS and heated on a water bath at 60°C for 10 min to better yield of niosomes.

7. **Trans membranes pH gradient (inside acidic) Drug Uptake Process or Remote Loading Technique**- Surfactant and cholesterol were dissolved in the chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The firm was hydrated with 300mM citric acid (PH 4.00 by vertex mixing. The multilamellar vesicles were frozen and shared 3 times and then later sonicated. Aqueous solution containing 10 mg/ml of drug was added and vortexes. The pH of the sample was then raised to 7.0-7.2 with the help of addition of 1M disodium phosphate. This mixture was later heated at 60°c for 10 minutes so it will provide niosomes.

8. **The Bubble Method**- It was a novel technique for preparation of liposomes and niosomes without the use of organic solvents in the one step. The bubbling unit consisting of round bottom flask with three necks positioned in the water bath for controlling the temperature. Water was cooled refluxed and the thermometer was positioned in the first and the second neck and also nitrogen supply through the third neck. Cholesterol and surfactant were dispersed together in the buffer (PH 7.4) at 70°C; the dispersion was mixed for 15 seconds with the high shear homogenizer and then immediately afterwards “bubbled” at 70°C through nitrogen gas.

9. **Formation of Niosomes from Proniosomes**- There is another method of producing niosomes by coating a water-soluble carrier such as sorbitol with the suitable surfactant. The result of the coating process was found as a dry formulation in which each water-soluble particle was covered with a thin film of dry surfactant. This preparation was termed “Proniosomes”. The niosomes were recognized by the adding aqueous phase at T > Tm and also by brief agitation. T is the Temperature and Tm is the mean phase transition temperature. The formulation of niosomes from the maltodextrin based on the production of proniosomes. This provides quick reconstitution of niosomes with the minimal residual carrier. Slurry of the maltodextrin and the surfactant was dried to form a free flowing powder that could be rehydrated by adding warm water.

10. **Method of Handjani-Vila**- The equivalent amounts of synthetic non-ionic lipids were mixed with the aqueous solution of active substance that was encapsulated and a homogenous lamellar film was formed through shaking. The resultant mixture was then homogenized employing ultra-centrifugation and agitation was done at a controlled temperature.

11. **Heating Method**- This was a non-toxic, scalable and one-stepped method and also based on the patented procedure. Mixtures of non-ionic surfactants, cholesterol and/or charge inducing molecules that are added to an aqueous medium (e.g. buffer, distilled H_2O, etc.) in the presence of the polyol like as glycerol. The mixture was heated while stirring (at low shear forces) until vesicles were formed.

There are some examples in which these all above methods are used in the production of Niosomes:

- Niosomes carrying Cisplatin were prepared by Ether injection method using spans and tweens showing maximum entrapment efficiency. Cisplatin can be targeted to liver, lungs or spleen. It is a suitable drug e.g.: Hepato-carcinogenesis or tumors related to lungs and spleen. The targeting efficiency of the drug loaded niosomes was as compared to pure drug cisplatin, which may provide increased therapeutic efficacy.

- Aceclofenac is a drug with narrow therapeutic index and short biological half-life. Aceclofenac belongs to the non steroidal antiinflammatory drugs (NSAIDs). It works by blocking the action of cyclooxygenase. Niosomes containing aceclofenac were prepared by modified ether injection technique using nonionic surfactant (span 60, span 20) and cholesterol. In all the niosomes prepared with spans, as the concentration of surfactant increased drug entrapment efficiency increased.

  The encapsulation efficiency of niosomes is governed by the ability of formulation to retain the drug molecule in aqueous core or in the bilayer membrane of the vesicles.

- Antiinflammatory drug ketoprofen was encapsulated in niosome for topical application. Ketoprofen niosomes were prepared by thin film hydration method technique using surfactant, cholesterol, dicetyl phosphate & drug mixture.

- The niosomes with nimesulide prepared by lipid film hydration method were multilamellar vesicles (MLVS). It would lead to sustained action of the entrapped drug that reduced the side effects associated with frequent administration of the drug and potentiate the therapeutic effects of the drug.

- Niosomes of brimonidine tartrate were prepared by film hydration method. It allowed a significant vesicular carrier system for therapeutic effectiveness in duration of action and reduce in dose frequency. Thus, niosomes offer a promising avenue to fulfill the need for an ophthalmic drug delivery system that not only had the convenience of a drop, but that could localized and maintained drug activity at its site of action for a longer period of time, thus; allowing for a sustained action; minimizing frequency of the drug administration with patient compliance.

  The main objectives of drug delivery system to the eye is to improve existing ocular dosage forms and exploited newer drug delivery system for improving the therapeutic efficiency. Topical application of eye drops is the most common method of administering drugs to the eye in the treatment of ocular diseases. Topical and localized applications are still an acceptable and preferred route by which dosage forms are no longer sufficient to overcome the various ocular diseases like glaucoma due to poor bioavailability by the efficient mechanism protecting the eye from harmful materials and agents. This includes reflex, blinking, lachrymation, tear turnover, and drainage of tear results in the rapid removal of the drug from eye surface. Similarly frequent instillation of concentrated medication is needed at the site of action which was patient incompliance.

- Niosomes of terbinafine hydrochloride were formulated by thin film hydration method. Anti fungal activities were seen by formulating the drug as niosomal transdermal gel (containing total niosomes) better effect can be obtained through increased penetration.

- Benzoyl peroxide is macrolide antibiotic used commonly for the treatment of acne. Benzoyl peroxide was entrapped into niosomes by thin film hydration technique and it results in enhanced drug retention into skin and improved permeation across the skin after the encapsulation of Benzoyl peroxide into niosomal topical gel.

- Niosomes of rifampicin and gatifloxacin were prepared by lipid hydration technique using rotary flash evaporator. It basically showed that the drugs loaded in niosome vesicles exhibited improved bactericidal activity against the tubercle bacilli[14-29].

Niosomes can encapsulate both lipophilic and hydrophilic drugs and protect against acidic and enzymatic effects *in vivo*. They offered several advantages over liposomes such as higher chemical stability, intrinsic skin penetration increasing properties and lower costs.

However, there may be create problems during the storage, which includes vesicles aggregation, fusion, leaking or hydrolysis of encapsulated drugs. This may affect the shelf life of the niosomes [1, 2].

Different formulations of Niosomes are:

- Discomes.
- Niosomes vesicles in water/oil systems.
- Polymer coated niosomes.
- Niosomal dispersions.
- Proniosomes [6, 30].

There are different applications of niosomes:

- **Transdermal Applications**- It is well-known fact that transdermal applications provide a great benefit of protecting drugs from the hepatic first pass effect. However, stratum corneum layer of skin forms a barrier, resulting in a slow absorption at the application site.

- **Parenteral Applications**- Niosomes in sub-micron size were used for parenteral administration.

- **Peroral Applications**- The oral use of niosomal formulations were first demonstrated in a study involving 100nm methotrexate C16G3 niosomes. Significantly higher levels of methotrexate were found in the serum, liver and brain of PKW mice following oral administration of a niosomal formulation. It thus appears that there is enhanced drug absorption with these niosomal formulations.

- **Radiopharmaceuticals**- The first applications of niosomes as radiopharmaceuticals have been achieved by Erdogan in 1996. They prepared 131-I labeled iopromide niosomes with positive charge.

- **Ophthalmic Drug Delivery**- The biological evaluation of a Niosomal Cyclopentolate drug delivery system for ophthalmic preparation was considered. Polysorbate 20 and cholesterol were used for niosome formulations. It was determined that cyclopentolate penetrated the cornea in a pH dependant manner within these niosomes. Optimum pH for peak permeation values was pH 5.5. Permeation decreased at pH 7.4. However, in vivo data revealed that there was increased mydriatic response with the niosomal formulation irrespective of the pH of the formulation.

- **Targeting of Bioactive Agents**- The cells of RES (Reticulo-Endothelial System) 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.

- To organs other than RES- It had been suggested that carrier system can be directed to specific sites in the body by use of antibodies. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier.

- Niosomes as carriers for Hemoglobin- Niosomes could be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum super imposable onto that of free hemoglobin [27, 31-37].

CONCLUSION: Many drugs, those currently available in the market and those under development, have poor aqueous solubilities that result in variable bioavailabilities. This problem can be overcome by entrapping the drug into niosomes. They are osmotically active, and are stable on their own, while also increasing the stability of the entrapped drugs. Handling and storage of surfactants require no special conditions. Niosomes possess an infrastructure consisting of hydrophilic and hydrophobic moieties together, and as a result, can accommodate drug molecules with a wide range of solubilities.

Although niosomes as drug carriers have shown advantages such as being cheap and chemically stable, they are associated with problems related to physical stability such as fusion, aggregation, sedimentation and leakage on storage. All methods traditionally used for preparation of niosomes are time consuming and many involve specialized equipments. Most of these methods allow only for a predetermined lot size so material is often wasted if smaller quantities are required for particular dose application.

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How to cite this article:
Singh s: Niosomes: A Role in Targeted Drug Delivery System. *Int J Pharm Sci Res*. 2013; 4(2); 550-557.