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Review Article

Niosomes in a Nut Shell: A Concise Review

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ABSTRACT

Niosomes represent a promising targeted drug delivery system for hydrophilic and lipophilic drugs. They present a structure similar to liposome and hence they can be an alternative vesicular system with respect to liposomes. Due to the niosome ability to encapsulate different type of drugs within their multi environmental structure they can be exploited for various treatments of various diseases. Niosomes can be a better drug delivery system as compared to liposomes due to various factors like cost, stability. Various routes of drug delivery and drug targeting can be achieved using niosomes.

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INTRODUCTION

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. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. The method of preparation of niosome is based on liposome technology. The basic process of preparation is the same i.e. hydration by aqueous phase of the lipid phase which may be either a pure surfactant or a mixture of surfactants with cholesterol. After preparing niosomal dispersion, unentrapped drug is separated by dialysis centrifugation or gel filtration. A method of in-vitro release rate study includes the use of dialysis tubing. Niosomes are promising vehicles for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. 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.
They have shown promise in the release studies and serve as a better option for drug delivery system.

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Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. This class of vesicles was introduced by Handjani Vila et.al [1] .They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs and can act as targeted delivery system (Fig 1).

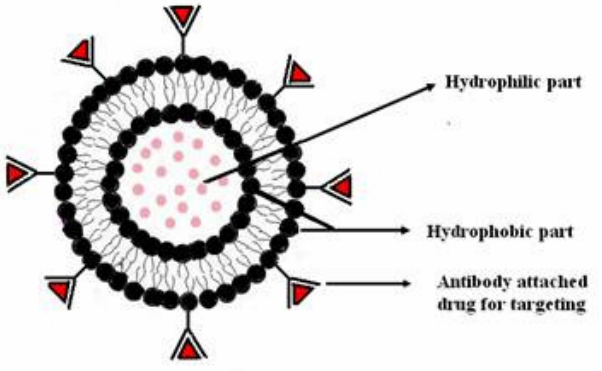


Figure1: Structure of antibody targeted Niosome

One of the reasons for preparing niosomes is the assumed higher chemical stability of the surfactants than that of phopholipids, which are used in the preparation of liposomes. Due to the presence of ester bond, phospholipids are easily hydrolysed [2]. Unreliable reproducibilty arising from the use of lecithins in liposomes leads to additional problems and has led scientist to search for vesicles prepared from other material, such as nonionic surfactants. Niosomes are

promising vehicle for drug delivery and being non-ionic; it is less toxic and improves the therapeutic index of drug by restricting its action to target cells [3]. 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.

Advantages of Niosomes

The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages. 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 nonaqueous phase. Since the vesicle suspension is water based vehicle, this offers high patient compliance in comparison with oily dosage forms. Niosomes 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 are osmotically active and stable, as well as they increase the stability of entrapped drug. 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. Since, the nonionic surfactants used are biodegradable, biocompatible and non-immunogenic, hence can be used safely in preparation of niosomes. They also 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. Also, handling and storage of surfactants requires no special conditions.

Preparation methods for niosomes

The preparation methods should be chosen according to the use of the niosomes, 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 [4].

Ether injection method [5,6]

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether 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 leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle ranges from 50 to 1000 nm. The disadvantage of this method is that a small amount of ether is often still present in the vesicle dispersion and is often difficult to remove.

Hand shaking method (Thin film hydration technique) [6]

The vesicle 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) under reduced pressure using rotary evaporator (Fig 2) leaving a thin layer of solid mixture deposited on the wall of the flask.

Figure 2: Flash evaporator

The dried surfactant film can be rehydrated with aqueous phase at phase transition temperature with gentle agitation. This process forms typical multilamellar niosomes. Thermosensitive niosomes were prepared by Raja Naresh et al [7] by evaporating the organic solvent at 60°C and leaving a thin film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by

sonication. Large multilamellar vesicles are prepared. Similarly, Chandraprakash et al entrapped methotrexate in niosomes prepared by hand shaking method using lipophilic surfactants like span 40, span 60 and span 80, cholesterol and dicetyl phosphate. The tissue distribution of methotrexate was improved after entrapping with niosomes. Rogerson et al [8] prepared doxorubicin entrapped niosomes using pure surfactant or a mixture of surfactants and cholesterol [9]. Azmin modified this method for preparation of methotrexate entrapped niosomes [10].

Sonication [6]

A typical method of production of the vesicles is by sonication of the dispersion as described by Cable et al. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes. The resulting vesicles are small and unilamellar. In the case of niosomes, the resulting vesicle size in general is larger than liposomes, niosomes being no smaller than 100 nm in diameter. Baillie et al prepared carboxy fluorescein in entrapped niosomes by sonication method. Carter et al [4] prepared sonicated niosomes by sonication of multilamellar niosomes being prepared by Ether injection method. Yoshida et al [11] modified this method for entrapping 9-desglycinamide 8-arginine vasopressin (DGA VP). Hofland et al [12] prepared niosomes by sonication of transdermal delivery of estradiol by niosomes in vitro [13].

Micro fluidization [14]

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle (Fig. 3) 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 greater uniformity, smaller size and better reproducibility of niosomes.

Multiple membrane extrusion method [14]

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 a good method for controlling niosome size the resultant suspension extruded through which are placed in series for upto passages.

Figure 3: Microfluidiser

Reverse Phase Evaporation Technique (REV) [7]

The novel key in this method is the removal of solvent from an emulsion by evaporation. Water in oil emulsion is formed by bath sonication of a mixture of two phases, and then the emulsion is dried to a semi-solid gel in a rotary evaporator under reduced pressure. The next step is to bring about the collapse of certain portion of water droplets by vigorous mechanical shaking with a vortex mixture. In these circumstances, the lipid monolayer, which encloses the collapse vesicles, is contributed to adjacent intact vesicles to form the outer leaflet in the bilayer of large unilamellar niosomes. Cholesterol and surfactant (1:1) is 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 reduced pressure. The resulting viscous niosome dispersion is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes. The vesicles formed are unilamellar and have a diameter of 0.5 μm. Raja Naresh et al [7] reported preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

Transmembrane pH gradient method (remote loading) [14]

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 dispersion, 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 loaded with the drug.

The "Bubble" Method [15]

It is a novel technique for 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 is then mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

Figure 4: Bubble method

Formation of niosomes from proniosomes [16]

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes" (Fig.5). The niosomes are recognized by the addition of aqueous phase at Temperature (T) > mean phase transition temperature (Tm) with brief agitation. Blazek Walsh A.I. et al [16] reported the formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier.

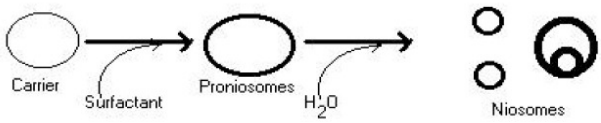


Figure 5: Proniosomal method

Slurry of maltodextrin and surfactant is dried to form a free flowing powder, which could be rehydrated by addition of warm water. The size and number of bilayers of vesicles consisting of polyoxyethylene alkyl ethers and cholestrol can be changed in alternative way. A temperature rise above 600˚C transforms from small unilamellar vesicles to large multilamellar vesicles while vigrous shaking at room temperature results in the opposite effect by changing multilamellar vesicles into unilamellar ones. The transformation from unilamellar to multilamellar vesicles at higher temperature might be characteristics for the polyoxythelene alkylether surfactants since it is known that polyethylene glycol (PEG) and water demixes at higher temperature due to a breakdown of hydrogen bondings between water and PEG moities [17]. Generally free drug is removed from the encapsulated drug by gel permeation chromatography, dialysis methods or by centrifugation. Often weight density differences between niosomes and the external phase are smaller than in the case of liposomes which make separation by centrifugation very difficult. A possibility is to add protamine to the vesicle dispersion in order to facilitate separation during centrifugation.

Characterisation of Niosomes

Entrapment Efficiency

After preparing niosomal dispersion, unentrapped drug is separated by dialysis [18], centrifugation [18,19], or gel filtration [20] and the drug entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug.

Entrapment efficiency (EE) =
(Amount entrapped/total amount) x 100

Entrapment efficacies of hydrophilic and lipophilic compounds depend on the preparation method. Baillie et al [4] concluded that niosomes prepared by ether injection method resulted in entrapment efficacies of carboxy fluorescein that were significantly higher than those of vesicles prepared by hand shaking. Both baillie et al [4]

and hunter at al [21] used glycerol surfactants and reported that the entrapment efficacy decreased as the amount of cholestrol added in the nonionic surfactant vesicle increased.

Vesicle Diameter

Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing [22] of niosomes increases the vesicle diameter, which might be attributed to fusion of vesicles during the cycle.

In-Vitro Release

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 dispersion 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 [18].

Stability and Toxicity Studies

Compared to liposomes, niosomes are relatively stable structures. But some concern has been expressed regarding the stability of niosomes in vitro and their toxicity in vivo. Surfactants are used in the preparation of niosomes may be a cause of toxicity. However, there are virtually no reports available on the in vivo toxicity of niosomes linked with the concentration of ether or esters surfactants used in the preparation of vesicles. Hofland studied the toxicity of CnEOm surfactants with two models. These include the ciliary beat frequency (CNF) of trachea, which is important for intranasal administration and the cell proliferation of kerationocytes which is important for the transdermal application of vesicles. A decrease in CBF is considered to be a measure for the toxicity of the formulation. Azmin et al performed first in vivo experiment on drug delivery by means of synthetic non-ionic surfactant vesicles and reported that no adverse effects were observed [23]. Rogerson et al performed in vivo experiment over 70 male BALB/C mice and reported that no fatalities were encountered that could be attributed to the preparation. The toxic or side effects directly related to drug are reduced [24].

Surfactants Used In Formation of Niosomes

Niosomes are non-ionic surfactant unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. The surfactants that are reported to form niosomes are as follows:

Ether linked surfactant

These are surfactants in which the hydrophilic hydrophobic moieties are ether linked, polyoxyethylene alkyl ethers with the general formula (C_nEO_m), where n is the number of carbon atoms which varies between 12 and 18 and m is the number of oxyethylene unit that varies between 3 and 7. The surfactants used are $C_{12}EO_3$, $C_{12}EO_7$, $C_{18}EO_3$, and C_3EO_7. Single alkyl chain surfactant C_{16} mono alkyl glycerol ether with an average of three glycerol units. It is used for the preparation of Niosomes [4]. The effect of this surfactant is studied on absorption, metabolism and excretion of methotrexate in mice. The drug entrapment, stability and release of drug from adrimycin loaded niosomes based on this surfactant are studied. Based on this, surfactant stilbogluconate bearing niosomes were prepared and evaluated for various parameters for their effect on the in vivo absorption, distribution and elimination of the drug [21].

Di-alkyl chain surfactant

Surfactant being the principal component of niosomal preparation of stilbogluconate and its potential in delivering sodium stilbogluconate in experimental marine visceral leishmaniasis has been explored.

$$C_{16}H_{33}CH\text{-}O[\text{-}CH_2\text{-}CH\text{-}O]_7\text{-}H$$
$$| \quad |$$
$$CH_2 \; CH_2OH$$
$$|$$
$$C_{12}H_{25}\text{-}O$$

(mol. Wt. 972)

Ester linked

These are the surfactants in which hydrophilic and hydrophobic moieties are ester linked. Ester linked surfactant,

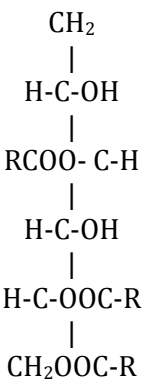
$$C_{15}H_{31}CO[O\text{-}CH_2\text{-}CH\text{-}CH_2]_2\text{-}OH$$
$$|$$
$$OH$$

(mol. Wt. 393)

This surfactant is also studied for its use in the preparation of stibogluconate bearing niosomes and in delivery of sodium stibogluconate to the experimental marine visceral leishmaniasis following administration of niosomal system [21].

Sorbitan Esters

The commercial sorbitan esters are H-C-OH mixtures of the partial esters of sorbital and its mono and di-an- hydrides with oleic acid.

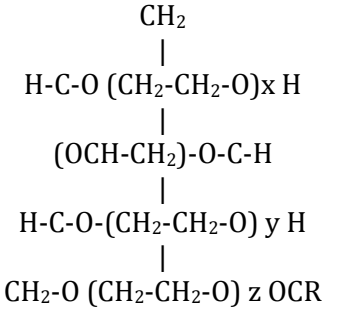


where, R is H or an alkyl chain

The formula of a representative component is shown above. Sorbitan esters based Niosomes bearing methotrexate are prepared and evaluated for pharmacokinetics of the entrapped methotrexate in tumor bearing mice.

Polysorbates

The typical structural formula of polysorbates is as follows;



When n = x + y + z + 2 and R is an alkyl chain this series of surfactants has been used to study the pharmacokinetics of niosomal entrapped methotrexate.

Factors Affecting Formation of Niosomes

Drug

Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size [19]. In polyoxyethylene glycol (PEG) coated vesicles; some drug is entrapped in the long PEG chains, thus reducing the tendency to increase the size [20]. The hydrophilic lipophilic balance of the drug affects degree of entrapment.

Amount and Type of Surfactant

The mean size of niosomes increases proportionally with increase in the HLB of surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant [18]. The bilayers of the vesicles are either in the so called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are present in a well-ordered structure, and in the liquid state, the structure of the bilayers is more disordered. The surfactants and lipids are characterized by the gel-liquid phase transition temperature (TC) [18]. Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment.

Structure of Surfactant

The geometry of vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameter. On the basis of critical packing parameter of surfactant, one can predicate the geometry of vesicle to be formed. Critical packing parameter is calculated using following equation;

Critical Packing Parameter (CPP) = v/lc × a0

v = hydrophobic group volume, lc = the critical hydrophobic group length, a0= 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 then formation of spherical micelles, If ½ < CPP < 1 formation of bilayer micelles and If CPP > 1 then formation inverted micelles.

Cholesterol Content and Charge

Inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency [18]. In general, the action of cholesterol is two folds. On one hand, cholesterol increases the chain order of liquid state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid-ordered phase. An increase in cholesterol content of the bilayers results in a decrease in the release rate of encapsulated material and therefore an increase of the rigidity of the bilayers obtained [12, 26]. Presence of charge tends to increase the interlamellar distance between

successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

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. In case of polyhedral niosomes formed from $C_{16}G_2$, the shape of these polyhedral niosome remains unaffected by adding low amount of solulan C_{24} (cholesteryl poly-24- oxyethylene ether), which prevents aggregation due to development of steric hindrance. In contrast spherical niosomes are formed by $C_{16}G_2$: cholesterol:solulan (49:49:2). The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by $C_{16}G_2$: solulan C_{24} in ratio (91:9) having bigger size (8.0 ± 0.03mm) than spherical/tubular niosomes formed by $C_{16}G_2$: cholesterol:solulan C_{24} in ratio (49:49:2) (6.6±0.2mm). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from niosome [24].

Method of Preparation

Methods of preparation of niosomes such as hand shaking, ether injection and sonication have been reviewed by Khandare et al [14]. Hand shaking method forms vesicles with greater diameter (0.35-13nm) compared to the ether injection method (50-1000nm) [14]. Small sized niosomes can be produced by Reverse Phase Evaporation (REV) method [9,37]. Microfluidization [14] method gives greater uniformity and small sized vesicles. Parthasarthi et al [27] prepared niosomes by trans membrane pH gradient method. Niosomes obtained by this method showed greater entrapment efficiency and better retention of drug.

Temperature of Hydration

Hydration temperature influences the shape and size of the noisome. Ideally, it should be above the gel to liquid phase transition temperature of the system. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation [27,28] Arunothayanun et al reported that a polyhedral vesicle formed by $C_{16}G_2$: solulan C_{24} (91:9) at 25°C which on heating transformed into spherical vesicle at 48°C, but on cooling from 55°C, the vesicle produced a cluster of smaller spherical niosomes at 49°C before changing to the polyhedral structures at 35°C. In contrast vesicle formed by $C_{16}G_2$: cholesterol: solulanC_{24} (49:49:2) shows no shape transformation on heating or cooling [28]. Along with the above mentioned factors, volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection of these factors may result in formation of fragile niosomes or creation of drug leakage problems.

Resistance to Osmotic Stress

Addition of a hypertonic salt solution to a dispersion of niosomes brings about reduction in diameter. In hypotonic salt solution, there is initial slow release with slight swelling of vesicles probably due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress [3].

Niosomes as Drug Carrier

A number of workers have reported the preparation, characterization and use of niosomes as drug carriers. Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug. Doxorubicin niosomes possessing muramic acid and triglycerol surfaces are not taken up significantly by liver. The triglycerol niosomes accumulated in the tumor and muramic acid vesicles accumulated in the spleen. Those vesicles with polyoxyethylene surface are rapidly taken up by the liver and accumulated to a lesser extent in tumor. Baillie et al [6] investigated the encapsulation and retention of entrapped solute 5,6-carboxy fluorescence (CF) in niosomes. They observed that stable vesicles could not be formed in the absence of cholesterol but were more permeable to entrapped solute. The physical characteristics of the vesicles are found to be dependent on the method of production. Carter et al [29] reported that multiple dosing with sodium stibogluconate loaded niosomes is found to be effective against parasites in the liver, spleen and bone marrow as compared to simple solution of sodium stibogluconate. Azmin et al [10] reported the preparation and oral as well as intravenous administration of Methotrexate

loaded niosomes in mice. They observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution. Chandraprakash et al [30] reported the formation and pharmacokinetic evaluation of Methotrexate niosomes in tumor bearing mice. Cable et al modified the surface of niosomes by incorporating polyethylene alkyl ether in the bilayered structure. They compared the release pattern and plasma level of Doxorubucin in niosomes and Doxorubucin mixed with empty niosomes and observed a sustained and higher plasma level of doxorubicin from niosomes in mice. D'Souza et al [31] studied absorption of Ciprofloxacin and Norfloxacin when administered as niosome encapsulated inclusion complexes. Namdeo et al [32] reported the formulation and evaluation of Indomethacin loaded niosomes and showed that therapeutic effectiveness increased and simultaneously toxic side effect reduced as compared with free Indomethacin in paw oedema bearing rats. Parthasarthi et al [27] prepared niosomes of vincristine sulfate which had lesser toxicity and improved anticancer activity. Jagtap and Inamdar [33] prepared niosomes of Pentoxifylline and studied the in-vivo bronchodilatory activity in guinea pigs. The entrapment efficiency is found to be 9.26 ± 1.93% giving a sustained release of drug over a period of 24 hrs. Raja Naresh et al [7] reported the anti-inflammatory activity of niosome encapsulated Diclofenac sodium in arthritic rats. It is found that the niosomal formulation prepared by employing Tween 85 elicited a better consistent anti-inflammatory activity for more that 72 hrs after administration of single dose

Proniosomes

Proniosomes are dry formulations of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. [34] The resulting niosomes are very similar to conventional niosomes and more uniform in size. The proniosome approach [35] minimizes elated to physical stability, such as fusion, aggregation, sedimentation, and leakage on storage problems by using dry, free-flowing product, which is more stable during sterilization and storage. Ease of transfer, distribution, measuring, and storage make proniosomes a versatile delivery system with potential for use with a wide range of active compounds [34]. Proniosomes in dry powder form makes the possibility of convenient unit dosing as the proniosome powder can further be processed to make beads, tablets or capsules. The findings of the studies on proniosomes till date, opens the door for the future use of different carrier materials with biocompatibility and suitability for the preparation of proniosomes.

Applications

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Some of their therapeutic applications are discussed below.

Targeting of bioactive agents

To reticulo-endothelial system (RES)

The cells of RES preferentially take up the vesicles. The uptake of niosomes is by circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver [3].

To organs other than RES

It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies [36]. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier [37]. Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

Neoplasia

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 [38]. 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 tumour bearing mice resulted in total regression of tumor and alsohigher plasma level and slower elimination [30, 39].

Leishmaniasis

Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting

organism resides in the organ of reticuloendothelial 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 performed by Hunter et al [21] showed high liver level after intravenous administration of the carrier forms of the drug.

Delivery of peptide drugs

Yoshida et al [12] investigated oral delivery of 9-desglycinamide, 8- arginine vasopressin entrapped in niosomes in an in-vitro intestinal loop model and reported that stability of peptide.

Immunological application of niosomes

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander [40] have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

Niosomes as carriers for Hemoglobin

Niosomes can be used as a carrier for hemoglobin. Niosomal dispersion shows a visible spectrum superimposable onto that of free hemoglobin. Vesicles are permeable to oxygen and so hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin [41].

Transdermal delivery of drugs by niosomes

Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Jayraman et al [42] has studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse. From the studies, and confocal microscopy, it is seen that non-ionic vesicles could be formulated to target pilosebaceous glands.

Other Applications

Sustained Release

Azmin et al [10] suggested the role of liver as a depot for methotrexate after niosomes are taken up by the liver cells. Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation.

Localized Drug Action

Drug delivery through niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects e.g. Antimonials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity [15,21] .The evolution of niosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.

CONCLUSION

Drug incorporation in niosomes to target the niosomes to the specific site is a promising drug delivery model. They 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. Niosomes are considered to be better candidates for drug delivery as compared to liposomes due to various factors like cost, stability. Niosomes are promising vehicles at least for lipophilic drugs. These advantages over the liposomes make it a better targeting agent. Ophthalmic, topical, parentral and various other routes are used for targeting the drug to the site of action for better efficacy.

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