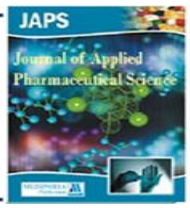
Journal of Applied Pharmaceutical Science
Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 02-06-2012
Revised on: 06-06-2012
Accepted on: 12-06-2012
DOI: 10.7324/JAPS.2012.2625

Recent Trends in Niosome as Vesicular Drug Delivery System

Anchal Sankhyan and Pravin Pawar

ABSTRACT

Over decades researchers are striving to use the drugs in an efficient manner to treat various diseases. The efficient use can be explained as reduced dose, reduced side effects, reduced dosage frequency, greater patient compliance and maximum concentration of the drug at the site of action so as to reduce the undue exposure to the entire body. The article focuses on various advantages of vesicular systems (niosomes) to develop the effective delivery system to achieve maximum effective concentration. Niosomes, nonionic surfactant vesicles with lamellar structure which may be unilamellar and multilamellar serve to be efficient in providing these required advantages. The bilayer structure of niosomes being amphiphillic in nature can be used to deliver hydrophilic drugs in its aqueous core and lipophilic drugs in the bilayer made up of surfactants. Various additives in niosomes include nonionic surfactant as film forming agent, cholesterol as stabilizing and rigidizing agent for the bilayer and various charge inducers which develop a charge on the surface of niosomes and stabilize the prepared formulation by the resulting repulsive forces. This article also comprises of various breakthroughs in niosomal delivery of drugs representing various classes. On the basis of above information, the niosomes have been thoroughly exploited for the drug delivery system and still offer scope for research on various drugs for their maximum therapeutic utilization in management and treatment of various dreadful diseases.

Keywords: Vesicular system, niosomes, nonionic surfactant, cholesterol.

Anchal Sankhyan, Pravin Pawar
Chitkara College of Pharmacy, Chitkara University, Chandigarh-Patiala Highway, Rajpura, Patiala, Punjab-140401, India.

For Correspondence
Pravin Pawar
Email: pkpawar80@yahoo.com

INTRODUCTION

Niosomes are non-ionic surfactant vesicles having a bilayer structure formed by self-assembly of hydrated surfactant monomers. The bilayer is multilamellar or unilamellar which enclose aqueous solution of solutes and lipophilic components are in the bilayer itself. Niosomes are formed by hydration of non-ionic surfactant dried film resulting in imbibing or encapsulating the hydrating solution. Major component of niosomes is non-ionic surfactant which give it an advantage of being more stable when compared to liposomes thus overcoming the problems associated with liposomes i.e. susceptibility to oxidation, high price and the difficulty in procuring high purity levels which influence size, shape and stability (Vyas and Khar, 2011). Niosomes can entrap both hydrophilic and lipophilic drugs in aqueous layer and vesicular membrane respectively. The bilayers of niosomes have both inner and outer surfaces to be hydrophilic with sandwiched lipophilic area in between. Thus a large number of drugs and other materials can be delivered using niosomes (Udupa, 2004).

Salient features

Niosomes serve as drug depots in the body which release the drug in a controlled manner through its bilayer providing sustained release of the enclosed drug. Targeted drug delivery can also be achieved using niosomes the drug is delivered directly to the body part where the therapeutic effect is required. Thereby reducing the dose required to be administered to achieve the desired effect (Mujoriya and Bodla, 2011; Karim *et al*., 2010). The therapeutic efficacy of the drugs is improved by reducing the clearance rate, targeting to the specific site and by protecting the encapsulated drug. Drug targeting reduces the dose which leads to subsequent decrease in the side effects. Niosomes are amphiphillic i.e. both hydrophilic and lipophillic in nature and can accommodate a large number of drugs with a wide range of solubilities. The formulation is in the form of aqueous vehicle based suspension having greater patient compliance when compared to oily dosage forms. Niosomal dispersion being aqueous can be emulsified in a non aqueous phase to regulate the drug release rate and to administer the vesicles in non-aqueous phase. They improve the oral bioavailability of poorly soluble drugs and also enhance the skin permeability of drugs when applied topically. Niosomes provide advantage of usage through various routes viz. oral, parentral, topical, ocular etc. The bilayers of the niosomes protect the enclosed Active pharmaceutical ingredient from the deterogenous factors present both inside and outside the body. So niosomes can be used for the delivery of labile and sensitive drugs. Niosomes are osmotically active and stable and also increase the stability of the entrapped drug. The surfactants used and also the prepared niosomes are biodegradable, biocompatible and non-immunogenic. Handling and storage of surfactants does not require any special conditions. The characteristics and the performance of the prepared niosomes can be controlled by altering the composition, concentration of various additives, size, lamellarity and surface charge of vesicles (Khan *et al*., 2011)

STRUCTURAL COMPONENTS OF NIOSOMES

Surfactants

A wide range of surfactants and their combinations in different molar ratios have been used to entrap many drugs in niosomes of varying features such as size (Giddi *et al.*, 2007).

Ether linked surfactants

These are polyoxyethylene alkyl ethers which have hydrophilic and hydrophobic moieties are linked with ether. The general formula of this group is (CnEOm), where n can be 12-18 and m can be 3-7. Surfactants with polyhydroxyl head and ethylene oxide units are also reported to be used in niosomes formation (Vyas and Khar, 2011). Single alkyl chain surfactant C_{16} mono alkyl glycerol ether with an average of three glycerol units is one of the examples of this class of surfactants used for the preparation of niosomes (Baillie *et al.*, 1985). Polyoxyethelene 4 lauryl ether (Brij30) has an HLB value of 9.7, phase transition temperature $<10^0$C and cannot be used to formulate some drugs and iodides, mercury salts, phenolic substances, salicylates, sulfonamides and tannins as it cause oxidation leading to discoloration of product. Polyoxyethylene cetyl ethers (Brij58) and Polyoxyethylene stearyl ethers (Brij72and76) are also used in preparation of niosomes (Gannu and Pogaku, 2011).

Ester linked surfactants

These surfactants have ester linkage between hydrophilic and hydrophobic groups and have been studied for its use in the preparation and delivery of sodium stibogluconate to the experimental marine visceral leishmaniasis (Hunter *et al.*, 1988).

Sorbitan Esters

These are most widely used ester linked surfactants especially in food industry. The commercial sorbitan esters are mixtures of the partial esters of sorbital and its mono and di-an-hydrides with oleic acid. These have been used to entrap wide range of drugs viz doxorubicin (Uchegbu *et al.*, 1996)

Alkyl Amides

These are alkyl galactosides and glucosides which have incorporated amino acid spacers. The alkyl groups are fully or partially saturated C_{12} to C_{22} hydrocarbons and some novel amide compounds have fluorocarbon chains.

Fatty Acids and Amino Acid Compounds

These are amino acids which are made amphiphilic by addition of hydrophobic alkyl side chains and long chain fatty acids which form “Ufasomes” vesicles formed from fatty acid bilayers.

Cholesterol

Steroids bring about changes in fluidity and permeability of the bilayer and are thus important components. Cholesterol a waxy steroid metabolite is usually added to the non-ionic surfactants to provide rigidity and orientational order. It does not form the bilayer itself and can be incorporated in large molar ratios. Cholesterol is an amphiphilic molecule; it orients its OH group towards aqueous phase and aliphatic chain towards surfactant’s hydrocarbon chain. Rigidization is provided by alternative positioning of rigid steroidal skeleton with surfactant molecules in the bilayer by restricting the movement of carbons of hydrocarbon. Cholesterol is also known to prevent leakage by abolishing gel to liquid phase transition (Dahiya *et al.*, 2011)

Charge Inducers

Charge inducers increase the stability of the vesicles by induction of charge on the surface of the prepared vesicles. It act by preventing the fusion of vesicles due to repulsive forces of the same charge and provide higher values of zeta potential. The commonly used negative charge inducers are dicetyl phosphate, dihexadecyl phosphate and lipoamine acid and positive charge inducers are sterylamine and cetyl pyridinium chloride (Shan *et al.*, 2008; Bandyopadhyay and Johnson, 2007).

METHODS OF PREPARATION

Passive Trapping Techniques

This category include most of the techniques used in preparation of niosomes in which drug is incorporated during the preparation of niosomes i.e. during their formation (Udupa, 2004).

Thin Film Hydration

All vesicles forming Components i.e. surfactant, cholesterol and charge inducers are dissolved in a volatile organic solvent in a round bottom flask. Using rotary evaporator the organic solvent is evaporated at room temperature forming a thin dry film of Dissolved components. The dried thin film is hydrated with aqueous phase with gentle agitation which leads to formation of niosomes. The drug can be added to the aqueous phase if hydrophilic and can be dissolved in organic solvent with other components if hydrophobic (Baillie *et al.*,1986; Palozza *et al.*, 2006)

Ether Injection

Surfactant and other components are dissolved in ether (diethyl ether) and is then slowly injected into aqueous solution maintained at 60°C through a needle. This addition leads to evaporation of ether and formation of single layered vesicles. This method offers advantage of control of size, which can be obtained by controlling size of needle and other conditions. It suffers from disadvantage of limited solubility of materials in ether and difficulty of removal of ether from final formulation (Yasin *et al.*, 2012; Guinedi *et al.*, 2005)

Reverse Phase Evaporation

The ingredients are dissolved in a mixture of volatile organic solvents (ether and chloroform) and drug is dissolved in aqueous phase. Water in oil emulsion is formed of the two phases in a bath sonicator. The basic principle involves evaporation of organic solvent to form niosomes. This emulsion is dried in a rotary evaporator at 40°C to form a semi solid gel of large vesicles. Small quantity of buffer is added and the semi solid form is sonicated at 4-5°C to form small unilamellar vesicles (Guinedi *et al*., 2005)

Multiple Membrane Extrusion

The basic principle involves extrusion that is forced passage of mixture/suspension/emulsion of the components through polycarbonate membranes repeatedly to obtain niosomes of desired size. The organic phase is dried in a rotary evaporator and is hydrated by aqueous phase, the resultant is extruded through the membrane (Khandare *et al.*, 1994)

Microfluidization

The two phases are allowed to interact at ultra high speed in micro channels in an interaction chamber. The high speed impingement and the energy involved leads to formation of uniform and small niosomes. This method has a high degree of reproducibility (Khandare *et al.*, 1994).

Sonication

The mixture of drug solution in buffer, surfactant and cholesterol is sonicated with titanium probe sonicator at 60°C for 3 minutes to yield niosomes. This method is also used to produce small unilemellar vesicles from large multilamellar vesicles prepared by other techniques (Carter *et al*., 1988; Yoshida *et al*., 1992 and Hofland, 1992)

The Bubble Method

This method prepares niosomes in one step without the use of organic solvent. All the components are dispersed in buffer and the dispersion is placed in a round bottom flask immersed in a water bath with controlled temperature. The flask has three necks attached to water cooled reflux, thermometer and nitrogen supply. The dispersion is mixed with a shear homogenizer for 15 seconds and then bubbled with nitrogen in this assembly to form niosomes (Chauhan and Luorence, 1989)

Active Trapping Techniques

This includes the loading of drug after the formation of niosomes. The niosomes are prepared and then drug is loaded by maintaining pH gradient or ion gradient to facilitate uptake of drug into niosomes. It offers various advantages of 100% entrapment, high drug lipid ratios, absence of leakage, cost effective and suitability for labile drugs (Udupa, 2004).

Trans Membrane pH Gradient

The organic phase with dissolved components is evaporated to form a thin layer and hydrated with citric acid, multilamellar vesicles are formed which are freeze thawed 3 times and sonicated. To this niosomal suspension aqueous solution with drug is added, vortexed and pH is raised upto 7.0-7.2 with 1M disodium phosphate. The mixture is later heated at 60 °C for 10 minutes to get drug loaded niosomes (Biju *et al.*, 2006; Mayer *et al.*, 1985)

APPLICATIONS OF NIOSOMES

Antineoplastic Agents

A biggest drawback of cancer chemotherapy is side effects and lesser therapeutic efficiency. Various attempts have been made to overcome these drawbacks including niosomes as a novel drug delivery system. Negatively charged niosomes of Paclitaxel showed slow release being beneficial in storage, administration, reduced toxic side effects and efficient oral delivery (Bayindir and Yuksel, 2010). 5-fluorouracil (5-FU) used for the treatment of actinic keratosis and non melanoma skin cancer shows a poor percutaneous permeation which was enhanced by delivery through niosomes and also showed (Alvi *et al.*, 2011). Further the suitability of niosomes was also studied for 5-FU using different preparation techniques and surfactants which provided promising results (Namdeo and Jain, 1999). Innovative niosomes of alpha, omega-hexadecyl-bis-(1-aza-18-crown-6) (bola) were proved to be delivery systems for the administration of 5-fluorouracil (Cosco *et al*., 2009). Use of immunomodulators

muramyl dipeptide and tuftsin on niosomes showed enhanced delivery of bleomycin by macrophage activation. Thus present greater efficacy of bleomycin in cancer chemotherapy (Raja *et al.,* 1996). Doxorubicin niosomes of span 60 provided prolonged release with double tumoricidal activity, 10 times decreased clearance and increased levels of metabolites in liver (Uchegbu *et al*., 1995). Preparation of niosomes of doxorubicin has also lead to slow release with peak plasma concentration same as the free drug with no pulmonary side effects, reduced IC50 in doxorubicin resistant cell lines and increased activity in ovarian cancer cell line (Uchegbu *et al.*,1994; Uchegbu *et al.,* 1996). Innovative doxorubicin niosomes of dimethylsuberimidate with transferrin covalently bound to the surface showed higher uptake and cytotoxicity as compared to glucose targeted niosomes of N-palmitoyl glucosamine also the effect of cholesterol was studied which resulted in More sustained release and reduced tumor growth in presence of cholesterol (Dufes *et al*., 2004; Rogerson *et al*., 1988).

High degree of chemical purity, high entrapment values and also reduced light induced degradation of adriamycin was observed when encapsulated in niosomes and on further evaluation it showed delayed growth of tumor volume in human lung tumor cells, monolayered and spheroid cultures and in xenografted nude mice (Rogerson *et al*., 1987; Kerr *et al.,* 1988). Metabolic profile and urinary and faecal excretion of methotrexate was altered by niosomes, there is rapid formation of 7-hydroxy methotrexate, prolong levels in blood, large amounts in liver and brain, reduced excretion of drug and its 7-hydroxy metabolite into urine and bile and in vivo protection of drug (Azmin *et al.,* 1985; Azmin *et al*., 1986). Plumbagin niosomes showed better anticancer activity and less toxicity when compared to free drug (Naresh *et al*., 1996). Combination of the stealth action and active targeting function of polyethylene glycol cyanoacrylate-co-hexadecyl cyanoacrylate (PEG-PHDCA) and transferrin (Tf) was used to promote drug delivery to solid tumor of hydroxycamptothecin (Hong *et al*., 2009). Niosomes are also proved to be efficacious in prolonging the action by sustaining the release of cytarabine hydrochloride leading to decreased side effects and toxicities (Ruckmani *et al.,* 2000).

NSAIDS

With a view to prepare stable niosomes with reduced leakage cholesterol and surfactant ratios were optimized using Aceclofenac as model drug. The prepared niosomes showed good entrapment efficiency, which may improve bioavailability of Aceclofenac (Srinivas *et al.,* 2010). Aceclofenac niosomes have also been prepared for topical use after incorporation into carbopol gel. The gel showed improved penetration and therapeutic efficacy of the drug (Solankia *et al.,* 2010). Niosomal gel was compared with plain nimesulide gel in terms of drug delivery. It was concluded that niosomal gel showed prolonged release of nimesulide, thereby enhancing the anti-inflammatory activity (Shahiwala and Misra, 2002). Despite of having high oral bioavailability rofecoxib was withdrawn due to its gastrointestinal adverse effects and cardiac toxicities. So an attempt was made to reduce its side effects and toxicities by encapsulation in niosomes. The niosomal gel showed prolong drug release that is sustaining the action of rofecoxib, thereby reducing its severe adverse effects (Das and Palei, 2011). Niosomes with sustained release of Diclofenac Sodium were prepared to achieve longer duration of action with release upto 72 hours thus providing an effective and improved therapeutic effect to treat rheumatoid arthritis (Raja *et al.,* 1994). Ketoprofen was encapsulated in niosomes of span 60 for topical application which released the drug in slow and sustained manner (Arora and Sharma, 2010).

Pharmacokinetic parameters of flurbiprofen (FBP) were compared of niosomal and non-niosomal formulations in dairy cattle which showed long circulation of FBP niosomes offering a potential application in improving short half-life (Confalonieri *et al.,* 2010). Formulation variables have been optimized for flurbiprofen proniosomes for preparation niosomes using a two-factor, three-level randomized full factorial strategy and were proved to be critical in performance of formulation (Zidan and Mokhtar, 2011).

Stable precursors of niosomes have been developed using different non-ionic surfactants and also cholesterol was proven to be an important ingredient of stable niosomes of flurbiprofen (Mahmoud *et al.,* 2008). Meloxicam was entrapped in niosomal gel which showed decreased side effects and increased pharmacological activity thus proving to be an promising vehicles for transdermal delivery and an alternative to the conventional dosage form as shown by increased permeation through skin (El-Menshawe and Hussein, 2011). Antiplatelet effect of indomethacin have been sustained by incorporation into niosomes, the effect may be shown due to greater quantity of the drug reaching the specific site of inhibition in the interior of the platelets and acting directly on the cyclo-oxygenase system to prevent thromboxane formation (Pillai and Salim, 1999).

Antileishmanial Agents

Niosomal sodium stibogluconate was shown to be more active than free drug against experimental murine visceral leishmaniasis. High levels in liver and low serum levels were obtained with high drug levels in infected reticuloendothelial systelm (Baillie *et al.,* 1986). Paromomycin niosomes showed increased activity when tested in-vitro and in-vivo for activity against Leishmania donovani. They showed increased activity against liver parasites without any significant suppression of bone-marrow parasites (Williams *et al.,* 1998).

Amarogentin, a secoiridoid glycoside has been evaluated for its antileishmanial property using niosomes, liposomes and free drug. The niosomal form was found to be more efficacious than the liposomal form at the same membrane microviscosity level and may have clinical application in the treatment of leishmaniasis (Medda *et al.,* 1999). The appreciable efficacy in destroying intracellular parasites as well as non-hepatotoxic and non-nephrotoxic nature, harmine in niosomes can be considered for clinical application in humans (Lalaa *et al.,* 2004).

Bacopasaponin C, an indigenous glycoside, was tested for antileishmanial properties both in free and in various delivery modes, e.g., niosomes, microspheres, and nanoparticles. Bacopasaponin C was found to be very active in all the vesicular forms analyzed from tissue histology, blood pathology, and specific tests related to normal liver and kidney functions without any side effects (Sinha *et al*., 2002).

Toxicity remains the major obstacle for the most potent drugs known in the therapy of leishmaniasis so an attempt was made to deliver nanocapsulated quercetin to treat experimental leishmaniasis in the hamster model so as to increase its efficacy as well as to reduce the toxicity. It showed reduced parasite burden in the spleen as well as reduced hepatotoxcity and renal toxicity as compared to free drug so may be considered for clinical trials (Sarkar *et al*., 2002). 14-deoxy-11-oxo-andrographolide, an antileishmanial compound reduced the spleen parasite load by 39% with subcutaneous injection of free drug and 78%, 91% and 59% in liposomes, niosomes and microspheres respectively. The niosomal formulation showed greater efficacy and lesser toxicity so might have clinical application to combat visceral Leishmaniasis (Lala *et al*., 2003).

Gene Delivery

Antisense oligonucleotides (OND) were delivered effectively using cationic niosomes of sorbitan monoesters which showed positive cellular uptake of the antisense oligonucleotides from the prepared niosomes (Huang *et al*., 2005). Surface of cationic liposomes was modified by auto-coacervation through electrostatic effect to develop a new gene carrier for antisense-oligonucleotides. The efficacy was shown by facilitated cellular uptake by COS-7 cells and HeLa cells and positive effect on gene expression (Huang *et al.*, 2006). Polysorbate cationic niosomes exhibited the binding capacity and the gene transfer study showed high efficiency in mediating cellular uptake and transferred gene expression (Huang *et al.*, 2011).

Elastic cationic niosomes were used to enhance transdermal absorption of luciferase plasmid (pLuc) by application of iontophoresis or stratum corneum stripping method. The prepared nanovesicles showed high degree of flux thus, presenting niosomes as suitable carriers for luciferase plasmid transdermal delivery (Manosroi *et al.*, 2009). Niosomes of N-palmitoylglucosamine bearing glucose or transferrin ligands were prepared for drug targeting. It was shown that glucose units were accessible on vesicle surface which may be available for glucose receptors in vivo. Over expression of GLUT receptors in cancer cells may lead to targetting of these niosomes. Thus presenting them as gene targetting agents to the cancer cells (Dufes *et al.*, 2000). PEGylated niosomes when compared to cationic niosomes showed enhanced cellular uptake of oligonucleotide in serum by providing protection against serum nucleases and preventing serum proteins from approaching the encapsulated oligonucleotide (Huang *et al.*, 2008). Niosomes have also served to be an alternative carrier of Herring sperm DNA with added a dvantages over the conventional liposomes (Yang *et al*., 2008).

Cosmetic

Niosomes of N-acetyl glucosamine are prepared due to its potential in the delivery of hydrophilic and hydrophobic drugs in topical form and improved penetration into the skin. N-acetyl glucosamine (NAG) has been considered in the treatment of hyperpigmentation disorders due to its inhibitory effect on thyrosinase enzymes in melanocytes. Prepared formulations improved the extent of drug localized in the skin, as needed in hyperpigmentation disorders (Shatalebi *et al.*, 2010). Elastic and non elastic niosomes of gallic acid were prepared and non elastic niosomes showed a slight increase in entrapment efficiency. But the elastic niosomes showed increased permeation through the skin which will be beneficial for topical antiaging application (Manosroi *et al.*,2011). The advantages of niosomes in aqueous dispersions were shown in comparison with classical formulations such as emulsions. These systems exhibit lower toxicity and permit closer control of the availability of active substances at the stratum corneum suitable for skin moisturising and tanning products (Handjani *et al*., 1979). Niosomes were prepared as possible approach to improve the low skin penetration and bioavailability shown by conventional topical vehicle for minoxidil. The results suggest that niosomal formulations could constitute a promising approach for the topical delivery of minoxidil in hair loss treatment (Mura *et al.*, 2007). Finasteride niosomes have been formulated for effective treatment of androgenetic alopecia and the in vitro permeation and in vivo deposition studies, demonstrated the potentials of niosomes for successful delivery of finasteride to the pilosebaceous unit (PSU) (Tabbakhian *et al*., 2006). Ellagic acid (EA) is a potent antioxidant phytochemical substance which has limited use due to poor biopharmaceutical properties, low solubility and low permeability. Niosomes with added solubilizers enhanced the permeation of ellagic acid into the skin with increased efficacy of ellagic acid (Junyaprasert *et al.*, 2012).

Proteins

Elastic anionic niosomes of n-terminal tat-GFP fusion protein were prepared with various concentrations of ethanol and edge activators sodium cholate and sodium deoxycholate compared with nonelastic anionic niosomes. Elastic anionic niosomes showed larger vesicular size, higher negative zeta potential, elasticity (deformability index), entrapment efficiency and flux through rat skin in a transdermal study (Manosroi *et al.*, 2010). Further the Tat-GFP fusion protein has also been loaded in elastic niosomes which enhanced the cellular uptake and chemical stability of the peptide. Thus presenting to be an useful tool for efficient delivery of many therapeutic proteins (Manosoroi *et al.*, 2011). Insulin was entrapped in the niosomes prepared with different lipid composition and doses. Significant decrease in blood glucose levels were observed for longer duration thereby increasing the therapeutic value of entrapped insulin (Khaksa *et al.*, 2000) Niosomes have also shown high protection of insulin against proteolytic enzymes and good stability in the presence of sodium desoxycholate and storage temperatures (Varshosaz *et al.*, 2003). Enhancement of the entrapment of various charged peptide drugs

viz. bacitracin (BCT), insulin and bovine serum albumin (BSA) in niosomes have been achieved by modifying the vesicular charge compositions. The resulted formulation was found to be appropriate to entrap the peptides with different charges and polarity for pharmaceutical application as shown by entrapment efficiency of the peptides in niosomes determined by gel electrophoresis and gel documentation (Mansoroi *et al.,* 2010). Peroral vaccine delivery system was developed by encapsulating ovalbumin in non-ionic surfactant vesicles which were evaluated using BALB/c mice. Encapsulation of ovalbumin into Wasag7 (70% stearate sucrose ester, 30% palmitate sucrose ester (40% mono-, 60% di/tri-ester)) niosomes resulted in a significant increase in antibody titres (Rentel *et al.,* 1999).

Anti-Fungal Agents

Griseofulvin has a poor and variable oral bioavailability, so niosomes were prepared using different methods of preparation by varying nonionic surfactants, their concentration and cholesterol concentration. It was concluded that span 60 provided highest entrapment efficiency and sustained release so could be one of the promising delivery system for griseofulvin (Jadon *et al.,* 2009). Niosomal encapsulation provided means for parental administration of nystatin, reducing its toxicity and making it a more active antifungal agent. Nystatin niosomes exerted less nephrotoxicity and hepatotoxicity in vivo, showed higher level of drug in vital organs and revealed pronounced efficacy in elimination of the fungal burden in experimental animals compared with those treated with free nystatin (Abdelbary *et al.,* 2011). Clotrimazole is widely used for the treatment of mycotic infections of the genitourinary tract. An alternative formulation was developed for the vaginal administration of clotrimazole to provide sustained and controlled release for local vaginal therapy by formulation in niosomes. The prepared vesicle gel system was evaluated by antifungal activity and tolerability on tissue level in rat which showed sustained and controlled release of the drug, Clotrimazole (Ning *et al.,* 2005).

Fluconazole-loaded niosomes of Span 40, Span 60, and Brij 72 surfactant were prepared and evaluated. The prepared formulation accumulated and formed localized drug depots in the skin, thereby releasing the contents in a sustained manner and is able to greatly enhance cutaneous retention of the drug (Gupta *et al*., 2011). Presence of 50% alcohol in marketed gel of naftifine hydrochloride an antifungal drug has been detrimental to skin after repeated exposure. Non alcoholic niosomal formulation of the drug was prepared and incorporated in the gel to overcome the problem (Barakat *et al.,* 2009).

Anti-Tubercular Drugs

Niosomal formulation of isoniazid was prepared to achieve effective treatment of tuberculosis which showed 61.80% of cellular uptake obtained from the drug-loaded niosomes by macrophage cells. The cellular uptake obtained is sufficient to achieve effective treatment of tuberculosis. The prepared formulations also showed reduced dose, reduced toxicity and frequency and increased patient compliance. The added advantage was macrophage targeting at the sites where tuberculosis bacteria are harbored (Singh *et al*., 2011). Isoniazid was encapsulated as niosomal formulation which showed in vitro release pattern indicating sustained release for 48 hours and lesser toxicity in vivo than free drug (Karki *et al.,* 2008). Encapsulation of rifampicin in niosomes delivered the drug at the target site with reduced toxicity and effective uptake. The prepared formulations showed site specific tagetting by controlling the niosome size and prolonged release, so can be a promising approach in delivery of antitubercular drug Rifampicin (Jain and Vyas, 1995). Pyrazinamide (PZA) plays a unique role in shortening therapy because it kills a population of semilatent tubercle bacilli residing in an acidic environment. Encapsulation in niosomes targeted the maximum concentration of PZA to the affected site (lungs), excluded undesirable side effects, decreased toxicity and may overcome the problem of drug resistance (El-Ridy *et al.,* 2011). Triton X 100 niosomes were used to deliver anti-tubercular drugs whose release patterns were studied. Rifampicin and isoniazid had fickian or diffusional release and pyrazinamide had non-Fickian release mechanism (Mehta *et al.,* 2011).

Antibiotics

The feasibility of using non-ionic surfactant vesicles (niosomes) as carriers for the ophthalmic controlled delivery of a water soluble local antibiotic, gentamicin sulphate was investigated and the results demonstrated niosomes to be promising ophthalmic carriers for the topical application of gentamicin sulphate (Abdelbary and El-Gendy, 2008). Preparation and evaluation of cefpodoxime proxetil niosomes showed controlled release of 65.25% for 24 hours with zero order kinetics, thus reducing the chances of dose dumping during usage (Sambathkumar *et al.,* 2011). The bioavailability of Cefuroxime axetil which is just 25% was improved by preparing niosomes. The prepared niosomes showed good entrapment efficiency and in vitro release and also were stable in bile salts (Sambhakar *et al.,* 2011).

Antibacterial Drugs

The influence of nonionic surfactant vesicles was studied on physicochemical property, stability and in vitro percutaneous absorption of enoxacin and was compared with liposomes. The results showed the ability of niosomes to modulate drug delivery without significant toxicity making them useful to formulate topical enoxacin (Jia-You *et al.,* 2001). A higher and longer-lasting inhibition effect was observed of nisin encapsulated in niosome and EDTA against S. aureus as compared to their free forms. Thus niosomes are offered as an alternative approach to encapsulate nisin in a delivery system better than liposomes (Kopermsuba *et al.,* 2011). Gallidermin was entrapped in niosomes in order to increase its stability and efficiency for pharmaceutical and cosmeceutical uses. The drug was shielded when entrapped in niosomes thereby protecting the drug from the oxidation environments. Gallidermin loaded in anionic niosomes and incorporated in gel is the superior topical antibacterial formulation

because of the high accumulation in the skin with no risk of systemic effect (Manosroia *et al.*, 2010).

Antiviral

Zidovudine (ZDV), an anti-HIV drug was formulated in proniosomes and niosomes and their distributions in lungs, kidney, heart, liver and spleen of mice were studied after intravenous bolus injection. Formulation prepared using Tween 80 was found to be optimized with increased half-life, mean residence time and reduced leakage of drug at 4^0C (Ruckmani *et al.*, 2010). Liver targeting of ribavirin was enhanced upto 6 folds by using niosomes as drug delivery system when compared to free drug solution. Ribavirin niosomes have significant liver targeting property, which is expected to improve the efficacy of low doses of ribavirin and minimize its toxic side-effects at higher doses (Hashim *et al.*, 2010). Drug release was significantly affected by the compositional factors in tenofovir niosomes. The niosomes were prepared using different compositions and were evaluated for vesicular sizing parameters, electrical properties, drug entrapment data and drug release characteristics. The results demonstrated the usefulness of the microfluidization for the production and further scale-up of anti-HIV niosomes with very small mean vesicular sizes (Zidana *et al.*, 2011).

Immunization

The topical immunization with cholera toxin B is potential adjuvant for cutaneous immune responses when coadministered with the HBsAg encapsulated niosomes. Thus the niosomes for topical delivery of vaccines using hepatitis B surface protein as an antigen and cholera toxin B as an adjuvant can be effective as topical delivery of vaccines (Maheshwari *et al.*, 2011). Mannosylated niosomes were formulated as a topical vaccine delivery carrier and adjuvant for the induction of both humoral and cellular immunity.

The proposed system would be simple, stable, and cost effective and might be clinically acceptable (Jain and Vyas, 2005). Mannosylated niosomes as oral DNA vaccine carriers for the induction of humoral, cellular and mucosal immunity were prepared. It was concluded that niosomes produced both humoral (both systemic and mucosal) and cellular immune response upon oral administration and serve as DNA, vaccine carrier and adjuvant for effective oral immunization (Jain *et al.*, 2005). The ability of non-ionic surfactant vesicles (NISV) to stimulate humoral responses to bovine serum albumin were studied and results suggest that adjuvants cannot only circumvent antigen-specific non-responsiveness or low responsiveness, but also can induce antibody isotype switching independent of major histocompatibility complex controls (Brewer and Alexander, 1994).

Vitamins

Tretinoin cutaneous delivery is strongly affected by vesicle composition and thermodynamic activity of the drug. In particular, small, negatively charged niosomal formulations, which are saturated with tretinoin, have shown to give higher cutaneous drug retention (Manconi *et al.*, 2006). A-tocopherol showed improve efficacy, reduce toxicity and enhance therapeutic index when enclosed in nonionic surfactant vesicles. The prepared vesicles had 1-5μm diameter, entrapment efficiency between 61.17%-79.63% and cumulative release 75.92%-96.01% (Desai *et al.*, 2010). Tretinoin-loaded niosomes as multilamellar vesicles (MLV), large unilamellar vesicles (LUV) and sonicated unilamellar vesicles (SUV) were prepared and evaluated. The in vitro release of tretinoin niosomes was found to be greater than tretinoin solution by using Franz diffusion cells. Release data showed that tretinoin delivery is mainly affected by the vesicular structure and that tretinoin delivery increased from MLVs to LUVs to SUVs (Manconi *et al.*, 2002).

Anti-Inflammatory

Niosomes have been immune-targeted to the inflammation areas by conjugation with a purified monoclonal antibody to CD44 (IM7) through a cyanuric chloride (CC) linkage on the polyoxyethylene group of the Tween 61 molecule (Hood *et al.*, 2007). Non-ionic surfactant vesicles (NSVs) were proposed for the pulmonary delivery of glucocorticoids such as beclomethasone dipropionate (BDP) for the treatment of inflammatory lung diseases, e.g. asthma, chronic obstructive pulmonary disease and various type of pulmonary fibrosis. The obtained data indicated that the investigated non-ionic surfactant vesicles (NSVs) represent a promising tool as a pulmonary drug delivery system (Marianeccia *et al.*, 2010). A natural compound with an efficacious anti-inflammatory activity, ammonium glycyrrhizinate was loaded into Bola-niosomes. These loaded niosomes depicted noticeable improvement of the in vivo anti-inflammatory activity of the drug (Paolino *et al.*, 2007).

Anti-Glaucoma Agents

Chitosan or Carbopol coated niosomal formulations of timolol maleate were prepared which showed a sustained effect upto 8 hours. The study concluded that the prepared formulations were significantly better considering that half the concentration is required indicating lesser systemic side effects, which include cardiovascular side effects associated with ocular timolol maleate therapy (Aggarwal and Kaur, 2005). Timolol maleate is conventionally applied in form of eye solutions which results in almost 80% of the instilled dose being lost and results in systemic side-effects especially in patients suffering from heart diseases or bronchial asthma thus limiting its usefulness for the control of glaucoma. Bioadhesive niosomal formulation showed a sustained and controlled effect to eliminate the side effects (Kaur *et al.*, 2010).

Diagnosis

Non-ionic surfactant vesicles (niosomes) are considered as carriers of iobitridol, a diagnostic agent used for X-ray imaging. Increase of the rate of encapsulation and the stability of the vesicles were found to be satisfactory and in addition the physico-

chemical and morphological properties of the vesicles have been studied (muller *et al.*, 2000)

Hormones

Luteinizing hormone releasing hormone (LHRH) was formulated in niosomes of Hexadecyl diglycerol ether (C16G2), cholesterol, and poly-24-oxyethylene cholesteryl ether (Solulan C24) in the ratio 91:0:9 which resulted in polyhedral niosomes. The prepared niosomes were stable in both muscle homogenate and plasma and had clearance of about 49 hours with sustained release (Arunothayanun *et al*., 1999).

Muscle Relaxants

Niosomes of baclofen a centrally acting muscle relaxant have been prepared to improve the low skin penetration and bioavailability characteristics shown by conventional topical vehicle. The prepared niosomes revealed advantages in vesicle surface morphology, entrapment efficiency, in vitro drug release, Osmotic fragility, stability studies and showed improved muscle relaxation activity (Keservani *et al*., 2010).

Anaesthetics

Interest in new delivery systems for local anaesthetics led to non-ionic surfactant vesicles of lidocaine.

The performance of niosomes containing lidocaine hydrochloride is remarkably better than that observed with classical liposomes and Tween 20 micelles. The neutral vesicles, prepared with Tween 20 and cholesterol, entrap a higher lidocaine amount presenting it as novel delivery system for lidocaine hydrochrolide (Carafa *et al.*, 2002).

Anti-Diabetic

Oral bioavailability of Gliclazide an oral antidiabetic drug was improved by entrapment in nonionic surfactant vesicles, also the release was sustained over a period of 24 hours for better therapeutic efficacy. The high values of zeta potential indicate stabilization of niosomes by electrostatic repulsive forces (Tamizharasi *et al*., 2009).

Contraceptive

The anti-fertility effect of cantchroman was enhanced by incorporation into niosomes. The prepared formulation showed 48.73% release in 8 hours and in vivo anti-fertility studies showed 83.3% protection against pregnancy. Histopathological studies showed no side effects and no other toxic effects. So the study presents the niosomes as suitable delivery system for contraceptives (Shenoy *et al*., 1997).

Miscellaneous

Niosomes with enclosed hemoglobin showed a visible spectrum superimposable to that of free hemoglobin. Vesicles are permeable to oxygen, hemoglobin dissociation curve can be modified similar to free hemoglobin, have some deformability and are more viscous than red blood cells but have similar rheological behavior (Moser *et al.*, 1989). Topical and systemic application of naltrexone markedly improves the characteristic signs of diabetic keratopathy like impaired corneal sensation and delayed wound repair. Niosomes of naltrexone for ocular delivery had high entrapment efficiency and thermoresponsive properties desirable for ocular delivery (Abdelkader *et al.*, 2010). Non-ionic surfactant vesicles (niosomes) appended with a polysaccharide cap were prepared using hydrophobized polysaccharides, O-palmitoyl pullulan (OPPu) and cholesteroyl pullulan (CHPu) anchored onto propranolol hydrochloride containing preformed niosomes. No significant difference was observed in percent encapsulation of polysaccharide coated and uncoated vesicles. The influence of the hydrophobized polysaccharide cap on niosomal membrane integrity and stabilization against harsh bio-environment conditions was also investigated using detergent and bile, freeze-thaw cycling, osmotic stress, and long term and shelf stability studies (Sihorkar and Vyas, 2000). Niosomes of capsaicin were prepared to improve performance of its variety of pharmacological actions on the cardiovascular, respiratory and nervous systems. The prepared formulations were compared to microemulsions prepared from the same surfactants in the same ratio and better promote the transdermal delivery of Capsaicin, with respect to microemulsions for topical delivery of this drug (Tavano *et al.*, 2011).

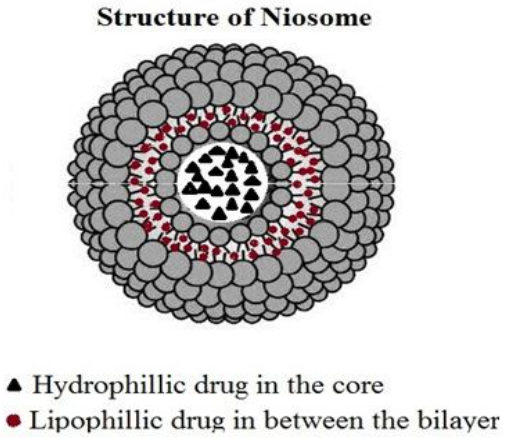


Fig. 1: Entrapment of drugs in the structure of niosome according to its nature (Patel and Patel, 2010).

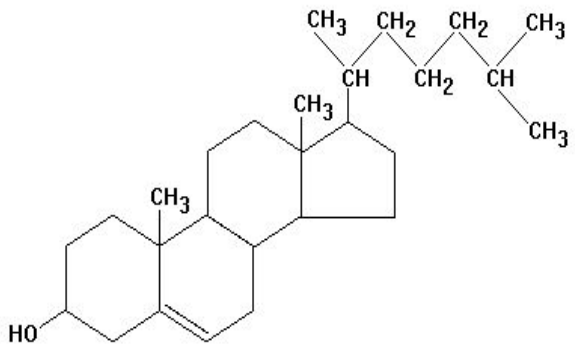


Fig. 2: Cholesterol (Zhang and Kataoka, 2009).

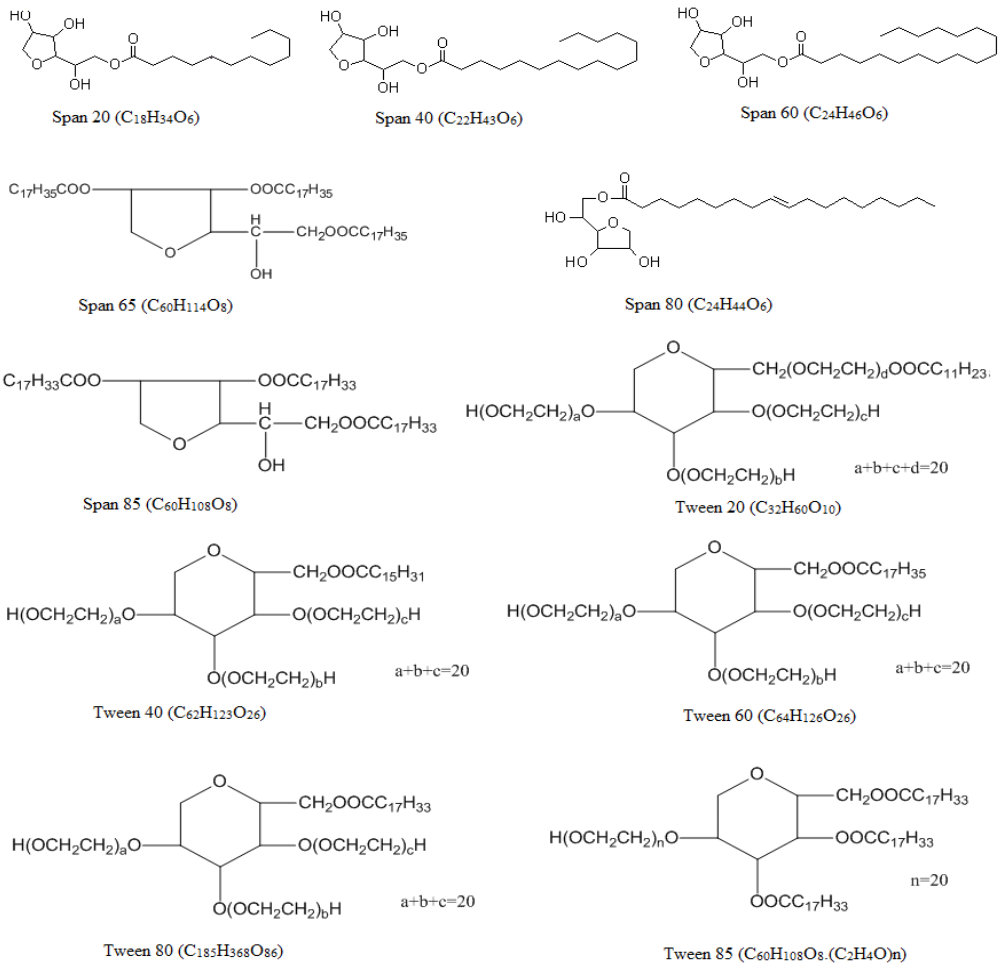


Fig. 3: Structures of commonly used non-ionic surfactants for the preparation of niosomes.

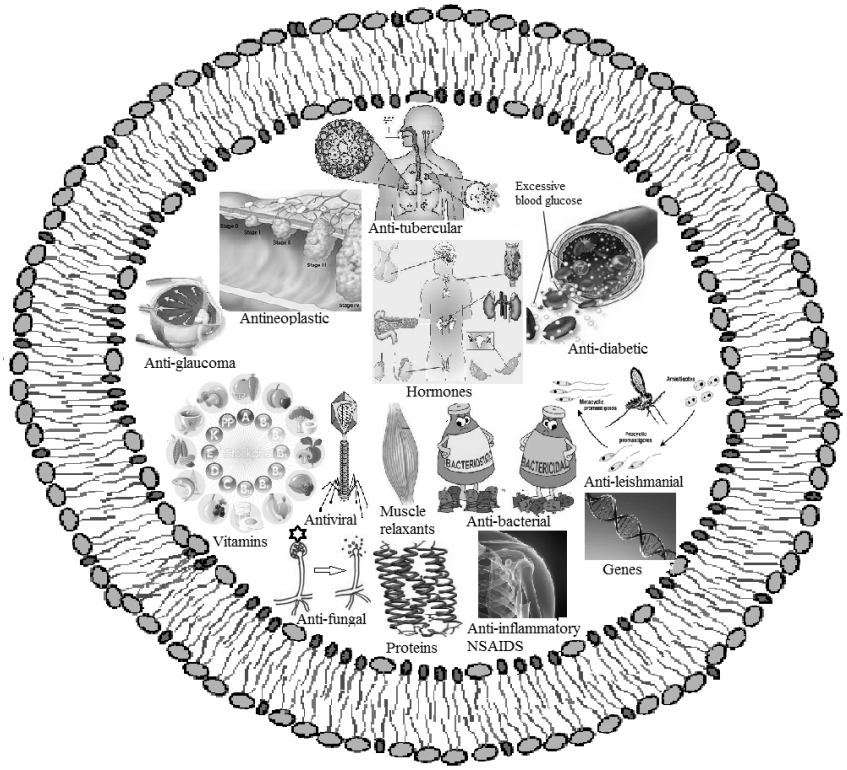


Fig.4: Niosomal delivery of number of drugs falling under various categories of drugs.

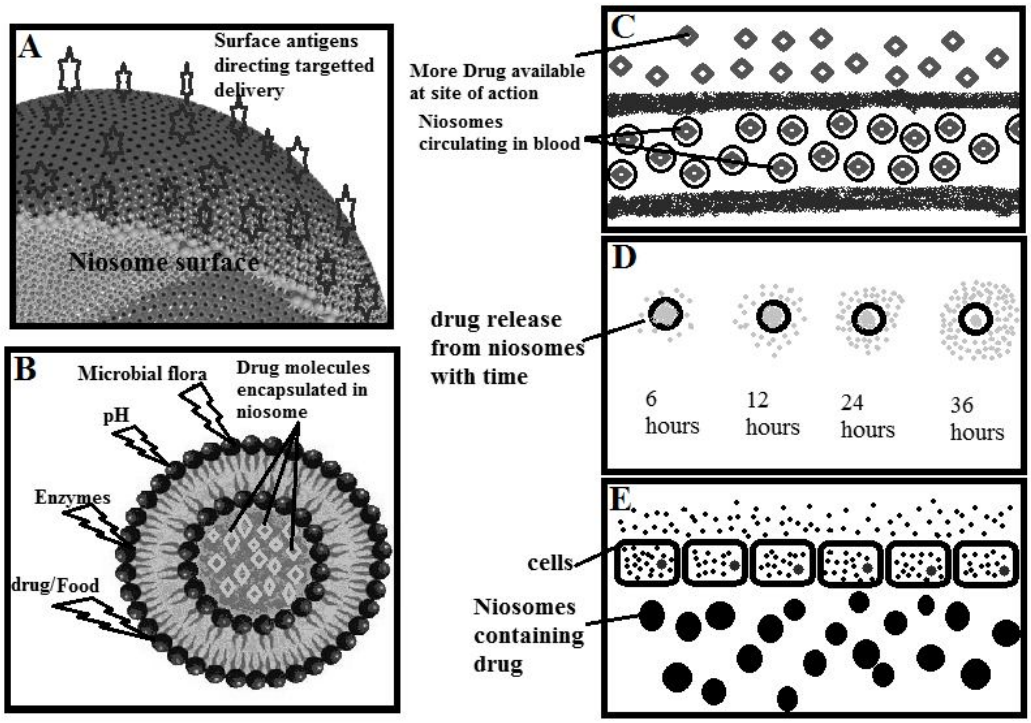


Fig. 5: Advantages offered by niosomes A: Targeted drug delivery (Hashim *et al*., 2010) B: Protection of Drug (Huang et al., 2009) C: Increased bioavailability (Jadon *et al.*, 2009) D: Sustained release (Kaur *et al.*, 2010) E: Enhanced cellular uptake (Huang *et al*.,2005).

CONCLUSION

Niosomes are novel drug delivery system which offers a large number of advantages over other conventional and vesicular delivery systems. Namely targeted delivery, reduction of dose, stability and compatibility of non-ionic surfactants, easy modification, delayed clearance, suitability for a wide range of Active Pharmaceutical Agents etc. From the above compilation of work it can be concluded that niosomes have suitability for encapsulating a varied variety of drugs and also the benefits offered by niosomes are also widely exploited. Niosomes have evolved for treatment of many dreadful diseases efficiently with reduced side effects and better patient compliance. Thus niosomes present itself as a versatile tool in therapeutics.

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