CHAPTER – II

REVIEW OF LITERATURE

2.1 INTERNATIONAL STATUS

Majid Tabbakhian et al., 2006 investigated whether topical application of finasteride-containing vesicles (liposomes and niosomes) could enhance drug concentration at the pilosebaceous unit (PSU), as compared to finasteride hydroalcoholic solution (HA). Liposomes consisted of phospholipid (dimyristoyl phosphatidylcholine (DMPC) or egg lecithin): cholesterol: dicetylphosphate (8:2:1 mole ratio). Niosomes were comprising non-ionic surfactant (polyoxyethylene alkyl ethers (Brij® series) or sorbitan monopalmitate): cholesterol: dicetylphosphate (7:3:1 mole ratio). Vesicles were prepared by the film hydration technique and characterized with regard to the size, drug entrapment efficiency and gel–liquid transition temperature (Tc). In vitro permeation of 3H-finasteride through hamster flank skin was faster from hydroalcoholic solution (0.13 g/cm² h) compared to vesicles (0.025–0.058g/cm² h). In vivo deposition of 3H-finasteride vesicles in hamster ear showed that liquid-state vesicle, i.e. those made of DMPC or Brij 97: Brij 76 (1:1), were able to deposit 2.1 or 2.3% of the applied dose to the PSU, respectively. This was significantly higher than drug deposition by gel-state vesicles (0.35–0.51%) or HA (0.76%). Both in vitro permeation and in vivo deposition studies, demonstrated the potentials of liquid-state liposomes and niosomes for successful delivery of finasteride to the PSU.

Tianqing Liu et al., Rong Guo 2007 investigated the microstructure and transformation of the niosome prepared from PEG 6000/Tween 80/Span 80/H₂O lamellar liquid crystal (LLC) by the methods of freeze fracture-TEM, negative-staining TEM, dynamic light scattering technique and micropolarity measurements. The size of the niosome made from the LLC is little larger than that from directly mixing samples. The layer membrane of the former niosome is looser than that of the later niosome. The former niosome is held with the partial behaviors of the LLC and can tend to be transformed into the later niosome.
Abbas Pardakhty et al., 2006 studied niosomes of polyoxyethylene alkyl ethers (BrijTM) prepared for encapsulation of insulin by film hydration method. Without cholesterol, brij 35 and brij 58 did not form niosomes, apparently because of relatively large polar head groups in comparison with their alkyl chains. The size of vesicles depended on the cholesterol content, charge incorporation or hydrophilicity of surfactants. Entrapment of insulin in bilayer structure of niosomes protected it against proteolytic activity of α-chymotrypsin, trypsin and pepsin in vitro. The maximum protection activity was seen in brij 92/cholesterol (7:3 molar ratios) in which only 26.3 ± 3.98 percent of entrapped insulin was released during 24 h in simulated intestinal fluid (SIF). The kinetic of drug release for most formulations could be best described by Baker and Lonsdale equation indicating diffusion based delivery mechanism. These results indicate that niosomes could be developed as sustained release oral dosage forms for delivery of peptides and proteins such as insulin.

Tianqing Liu et al., 2006 investigated the structural behaviors of Hemoglobin (Hb) in detail by the methods of UV–vis and fluorescence spectra, circular dichroism, negative staining-TEM, FF-TEM and electrochemistry techniques in PEG 6000/Tween 80/Span 80/H2O niosome system. The obtained results show that Hb can be adsorbed and outspread on the surface of the niosome membrane. The intensities of the UV–vis and fluorescence spectra of Hb in Hb/niosome system are greater than those in Hb/H2O system. The structure behaviors of Hb are partially stabilized and protected in Hb/niosome system. With the increase of PEG 6000 content in the niosome system, the content of helix structure decreases but the contents of β-sheet and random increase for Hb. The content of β-turn structure is almost independent of PEG 6000 content. The negative zeta potential of Hb and the conductivity of the system all decrease. The zeta potential of the niosome first decreases and then increases.
Agnishwar Girigoswami et al., 2006 investigated that niosomal vesicles are more stable than liposomal vesicles due to higher chemical stability of surfactants compared to phospholipids. Niosomes have been prepared from Span 20, Span 80, Tween 20 and Tween 80. Fluorescence resonance energy transfer studies have been performed in these systems to determine donor–acceptor distances. It has been found that the fluorescence resonance energy transfer efficiency is better in niosomes compared to micelles. The formation of niosomes is guided by the hydrophilic–lipophilic balance value of the nonionic surfactant.

Jain et al., 1995 prepared niosomes (nonionic surfactant-based vesicles) containing rifampicin using various nonionic surfactants of sorbitan ester class and cholesterol in 50:50 percent mol fraction ratio. The drug-entrapped vesicles were characterized for their shape, size, drug entrapment efficiency and in vitro release rate. On the basis of in vitro characterization, the niosomes showing maximum entrapment and minimum release rate were selected for in vivo performance evaluation. Cumulative percent doses of rifampicin recovered in thoracic lymph following intravenous and intraperitoneal administrations of free rifampicin solution and niosome-encapsulated rifampicin were compared. The study revealed that effective compartmentalisation of the drug took place in the lymphatic system following intraperitoneal administration of niosome-encapsulated rifampicin. Thus rifampicin encapsulated in niosomes could successfully be used for treatment of tuberculosis along lymphatic system.

Deepika Aggarwal et al., 2005 formulated Chitosan (REVTMbio1) or Carbopol (REVTMbio2 and 3) coated niosomal timolol maleate (0.25%) formulations by reverse phase evaporation (REV) and compared to timolol solution (TMS; 0.25%) in terms of in vitro release and IOP lowering pharmacodynamic effect. The in vitro release phase of timolol (91% release in 2 h) was extended significantly by its incorporation into niosomes and further by the polymer coating (40–43% release upto 10 h). The developed formulations were evaluated for their pharmacodynamics in albino rabbits, by measuring intraocular pressure (IOP) using a non-contact pneumatonometer, and were compared to a marketed in situ gel forming solution of timolol (Timolet GFS,
0.5%; Sun Pharma). REV TBio 1 formulation showed a more sustained effect of up to 8 h (vis a vis 6 h for carbopol-coated niosomes). TMS in comparison showed effect for only 2 h though the peak effect was slightly more (14%). Lowering of IOP in the contralateral eye (20–40% as compared to 100% in case of TMS), considerably reduces with REV and REVbio formulations indicating lesser systemic side effects. Moreover, the results of REV TBio 1 formulation containing 0.25% of timolol maleate compared well with the 0.5% marketed gel formulation, indicating developed formulation to be significantly better considering that similar effect is obtained at half of the concentration. The latter becomes especially important in context to the cardiovascular side effects associated with ocular timolol maleate therapy.

Rita Muzzalupo et al., 2005 described the formation of two niosomal systems based on synthetic bolaform surfactants (4, 7, 10,13-pentaoxa-16-aza-cyclooctadecane)-hexadecanedioc acid diamide (BD -16) and α, ω-(4, 7, 10, 13-pentaoxa-16-aza-cyclooctadecane)-hexadecane (BC-16). Systems containing BD-16 or BC-16 and different amount of cholesterol were prepared by aqueous dispersion of films, followed by examination of methylene blue entrapment, particle size and morphology. Indeed, they also studied the hydration in the distilled water and physiological solution, in order to investigate the complexing ability on vesicle formation. The results obtained in this study show a high encapsulation capacity and this ability and the size depends on cholesterol content.

Ahmed S. Guinedi et al., 2005 investigated that niosomes have been reported as a possible approach to improve the low corneal penetration and bioavailability characteristics shown by conventional ophthalmic vehicles. Niosomes formed from Span 40 or Span 60 and cholesterol in the molar ratios of 7:4, 7:6 and 7:7 were prepared using reverse-phase evaporation and thin film hydration methods. The prepared systems were characterized for entrapment efficiency, size, shape and in vitro drug release. Stability studies were carried out to investigate the leaching of drug from niosomes during storage. The intraocular pressure (IOP) lowering activity of acetazolamide niosomal formulations in rabbits
was measured using Shiotz tonometer. Histological examination for the corneal tissues of rabbits receiving niosomal formulations was carried out for assessment of the ocular irritancy of niosomes. The results showed that the type of surfactant, cholesterol content and the method of preparation altered the entrapment efficiency and drug release rate from niosomes. Higher entrapment efficiency was obtained with multilamellar niosomes prepared from Span 60 and cholesterol in a 7:6 molar ratio. Niosomal formulations have shown a fairly high retention of acetazolamide inside the vesicles (approximately 75%) at a refrigerated temperature up to a period of 3 months. Each of the tested acetazolamide niosomes prepared by either method produced a significant decrease in IOP compared to the solution of free drug and plain niosomes. Multilamellar acetazolamide niosomes formulated with Span 60 and cholesterol in a 7:4 molar ratio were found to be the most effective and showed prolonged decrease in IOP. Histological examination of corneal tissues after instillation of niosomal formulation for 40 days showed slight irritation in the substantia propria of the eye which is reversible and no major changes in tissues were observed.

Manconi et al., 2005 studied the recently reported parametrization based on the differential geometry and the thermodynamics of dispersed systems to ascertain the capability of decylpolyglucoside alone or in association with cholesterol to form vesicle structures (niosomes). The theoretical calculation of the energy balance involved in the vesicles formation was carried out using values of the critical concentration of formation (ccf), surface tension and the molar surface area of the non-ionic surfactant. Furthermore, in order to confirm the theoretical results authors prepared and characterized vesicles made with decylpolyglucoside and cholesterol. The vesicles were characterized using transmission electron microscopy and dynamic light scattering.

Behrooz Nasseri, 2005 investigated the mechanical characteristics of non-ionic bilayer membranes composed of sorbitan monostearate, cholesterol and poly-24-oxyethylene cholesteryl were studied by measuring the modulus of surface elasticity ($\mu$), a measure of membrane strength, as a function of cholesterol content and temperature. The modulus of surface elasticity increased
slowly with increasing cholesterol concentration, with a sharp increase around 40 mol% cholesterol (on average an increment of $0.43 \times 10^6 \text{ Nm}^{-2}$ per molar percentage), and displayed a maximum of $6.5 \times 10^6 \text{ Nm}^{-2}$ around 47.5 mol% cholesterol. Further cholesterol resulted in a decrease in $\mu$. Generally the interaction of cholesterol with the sorbitan monostearate should increase the rigidity of the membrane. However, the latter effect may be due to the formation of cholesterol clusters at high cholesterol content where excess amounts of cholesterol cannot interact with the sorbitan monostearate, and deposits on the bilayers compromising their uniformity, strength and permeability. This behaviour was evident when measurements were carried out above and below 25°C.

Suna Erdogan et al., 2005 studied about some accepted imaging techniques in clinic but most of them have several disadvantages limiting their effective use. Because of this, researchers are still performed to develop a rapid, specific means of detecting and/or imaging venous thrombi-based on the changing composition of the thrombus. Urokinase, fibrinolytic enzyme isolated form human urine, is a direct activator of plasminogen. In thrombus formation, plasminogen seems to be trapped in or absorbed onto fibrin matrix thus leading to a localised concentration of plasminogen. This suggests that radiolabelled urokinase would be a suitable compound for the detection of thrombi. The most important disadvantage of this enzyme is short plasma half life. To overcome this problem, it was decided to encapsulate the enzyme in drug delivery systems such as liposomes, niosomes or sphingosomes. In this study, investigators characterized and monitored the biodistribution of three types of vesicular systems containing urokinase. All types of prepared vesicles show in vitro an acceptable encapsulation, stability and release profile. Thrombus uptake was increased by encapsulation of urokinase into vesicles.

Prem N. Gupta et al., 2005 investigated the non-invasive vaccine delivery which is a top priority for public health agencies because conventional immunization practices are unsafe and associated with numerous limitations. Recently, the skin has emerged as a potential alternative route for non-invasive delivery of vaccine. Topical immunization, introduction of antigen through topical application onto the intact skin, has many practical merits compared to injectable routes of administration. One of the possibilities for increasing the penetration of

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Formulation Development and In vivo Evaluation of Zidovudine Niosomes
bioactives through the skin is the use of vesicular systems. Specially designed lipid vesicles are attracting intense attention and can be used for non-invasive antigen delivery. In the present study, elastic vesicle transfersomes, non-ionic surfactant vesicles (niosomes) and liposomes were used to study their relative potential in non-invasive delivery of tetanus toxoid (TT). Transfersomes, niosomes and liposomes were prepared and characterized for shape, size and entrapment efficiency. These vesicles were extruded through polycarbonate filter (50-nm pore size) to assess the elasticity of the vesicles. The immune stimulating activity of transfersomes, niosomes and liposomes were studied by measuring the serum anti-TT IgG titre following topical immunization. The immune response elicited by topical immunization was compared with that elicited by same dose of alum-adsorbed tetanus toxoid given intramuscularly. The results indicate that optimal formulations of transfersomes, niosomes and liposomes could entrap 72.7±3.4, 42.5±2.4 and 41.3±2.2% of antigen and their elasticity values were 124.4±4.2, 29.3±2.4 and 21.7±1.9, respectively. In vivo study revealed that topically given TT containing transfersomes, after secondary immunization, could elicit immune response (anti-TT-IgG) that was equivalent to one that produced following intramuscularly alum-adsorbed TT-based immunization. In comparison to transfersomes, niosomes and liposomes elicited weaker immune response. Thus transfersomes hold promise for effective non-invasive topical delivery of antigen(s).

Dufesa et al., 2004 evaluated the glucose-bearing niosomes as a brain targeted delivery system for the vasoactive intestinal peptide (VIP). To this end, \(^{125}\)I-VIP-loaded glucose-bearing niosomes were intravenously injected to mice. Brain uptake was determined by measuring the radioactivity of \(^{125}\)I-labeled VIP using γ-counting, after intravenous administration of VIP in solution or encapsulated in glucose-bearing niosomes or in control niosomes. VIP integrity was assessed by reverse-phase HPLC analysis of brain extracts. Distribution of \(^{125}\)I-VIP derived radioactivity was examined from serial brain slices. HPLC analysis confirmed the presence of intact VIP in brain after administration of VIP-loaded niosomes, but not after administration of VIP solution. Encapsulation
within glucose-bearing niosomes mainly allowed a significantly higher VIP brain uptake compared to control niosomes (up to 86%, 5 min after treatment). Brain distribution of intact VIP after injection of glucose-bearing niosomes, indicated that radioactivity was preferentially located in the posterior and the anterior parts of the brain, whereas it was homogeneously distributed in the whole brain after the administration of control vesicles.

Gopinath et al., 2004 investigated Ascorbyl Palmitate (ASP) as bilayer vesicle forming material. It formed vesicles (Aspasomes) in combination with cholesterol and a negatively charged lipid (dicetyl phosphate). Aspasomes were prepared by film hydration method followed by sonication in which aqueous azidothymidine (AZT) solution was encapsulated in aqueous regions of bilayer. Aspasomes were obtained with all compositions containing 18–72 mol% cholesterol. Differential scanning calorimetric data of aspasome dispersion and anhydrous mixtures of ascorbyl palmitate, cholesterol and dicetyl phosphate confirm the formation of bilayered vesicles with ascorbyl palmitate. Cholesterol content in aspasome did not exhibit any relation with vesicle size, zeta potential or percent entrapment. A substantial change in release rate of azidothymidine from aspasome was noticed on varying the proportion of cholesterol. Release rate and cholesterol content in Aspasomes did not exhibit any relation. A preparation with 45 mol% of cholesterol showed maximum retardation in release rate, than other compositions. The change in capture volume with time (latency) was studied for 8 h and with such a short duration study it was difficult to predict long term stability of these vesicles. But release experiments do indicate stability upto 18 h. Percent reducing activity of aspasome was estimated by measuring the absorbance of α, α diphenyl-β-picrylhydrazyl (DPPH) at 517 nm after addition of test antioxidant samples. These studies revealed that the antioxidant potency of ascorbyl moiety is retained even after converting ascorbyl palmitate into vesicles (Aspasomes). The antioxidant potency of Aspasomes was assessed by measuring the protection offered by this preparation against quinolinic acid induced lipoperoxidation of whole human blood in vitro, where in the lipoperoxidation was monitored by measuring thiobarbituric acid reactive substances levels. Aspasome rendered much better antioxidant activity than
ascorbic acid. Transdermal permeation of aspasomal AZT, ASP-AZT aqueous dispersion and AZT-solution across excised rat skin was investigated in vitro using Franz diffusion cell. Permeation of aspasomal AZT was much higher than the other two preparations.

Perrie et al., 2004 revealed compared to naked DNA immunisation, entrapment of plasmid-based DNA vaccines into liposomes by the dehydration–rehydration (PRV) method has shown to enhance both humoral and cell-mediated immune responses to encoded antigens administered by a variety of routes. In this paper they have compared the potency of lipid-based and non-ionic surfactant based vesicle carrier systems for DNA vaccines after subcutaneous immunisation. Plasmid pl.18Si/NP containing the nucleoprotein (NP) gene of A/Sichuan/2/87 (H3N2) influenza virus in the pl.18 expression vector was incorporated by the dehydration–rehydration method into various vesicle formulations. The DRV method, entailing mixing of small unilamellar vesicles (SUV) with DNA, followed by dehydration and rehydration, yielded high DNA vaccine incorporation values (85–97% of the DNA used) in all formulations. Studies on vesicle size revealed lipid-based systems formed cationic submicron size vesicles whilst constructs containing a non-ionic surfactant had significantly large z-average diameters (>1500 nm). Subcutaneous vesicle-mediated DNA immunisation employing two DRV(DNA) formulations as well as naked DNA revealed that humoral responses (immunoglobulin total IgG, and subclasses IgG1 and 1gG2a) engendered by the plasmid encoded nucleoprotein were substantially higher after dosing twice, 28 days apart with 10 g DRV-entrapped DNA compared to naked DNA. Comparison between the lipid and non-ionic based vesicle formulations revealed no significant difference in stimulated antibody production. These results suggest that, not only can DNA be effectively entrapped within a range of lipid and non-ionic based vesicle formulations using the DRV method but that such DRV vesicles containing DNA may be a useful system for subcutaneous delivery of DNA vaccines.

Maria Manconi et al., 2002 compared the chemical stability of tretinoin
(TRA) in methanol and in vesicular suspensions exposed both to UV and artificial daylight conditions with the aim of evaluating the potential of niosomes as topical carriers capable of improving the stability of photosensitive drugs. Tretinoin-loaded niosomes were prepared from polyoxyethylene (4) lauryl ether (Brij® 30), sorbitan esters (Span® 40 and Span® 60) and a commercial mixture of octyl/decyl polyglycosides (Triton® CG110). Liposomes made from hydrogenated (P90H) and non-hydrogenated (P90) soy phosphatidylcholines were also prepared and studied. In order to evaluate the influence of vesicle structure on the photostability of tretinoin, TRA-loaded vesicles were prepared by the film hydration method, extrusion technique and sonication. After UV irradiation, TRA dissolved in methanol degraded very quickly while the incorporation in vesicles always led to a reduction of the photodegradation process. The photoprotection offered by vesicles varied depending on the vesicle structure and composition. After fluorescent light irradiation for 21 days, not all the studied vesicular formulations improved TRA stability when compared with the free drug in methanol. Tretinoin incorporated in P90 or Span vesicles presented a half-life shorter or very close to that of the free drug. However, the inclusion of TRA in P90H liposomes and Brij® 30 or Triton® CG110 niosomes retarded the drug photodegradation.

Aranya Manosroi et al., 2003 prepared vesicles (niosomes) with hydrated mixture of various non-ionic surfactants and cholesterol was studied. The bilayer formation was characterized by X-cross formation under light polarization microscope and the ability of the vesicles to entrap water-soluble substance. Membrane rigidity was measured by means of mobility of fluorescence probe as a function of temperatures. The entrapment efficiencies of the vesicles and microviscosities of the vesicular membrane depended on alkyl chain length of non-ionic surfactants and amount of cholesterol used to prepare vesicles. The stearyl chain (C18) non-ionic surfactant vesicles showed higher entrapment efficiency than the lauryl chain (C12) non-ionic surfactant vesicles. Cholesterol was used to complete the hydrophobic moiety of single alkyl chain nonionic surfactants for vesicle formation. Niosome prepared with Tween 61 bearing a long alkyl chain and a large hydrophilic moiety in combination with cholesterol at
1:1 molar ratio was found to have the highest entrapment efficiency of water soluble substances.

Redziniak 2003 investigated various approaches to intra- and percutaneous administration of drugs, e.g. application of patches, ointments, iontophoresis, electroporation, the use of lipid vesicles like liposomes and niosomes presents numerous advantages. They are not toxic or invasive, may deliver hydrophobic and/or hydrophilic molecules, and the size of the transported molecule is not a limiting factor. Liposomes are obtained with natural amphiphilic lipids whereas niosomes are composed of synthetic amphiphilic molecules. These microscopic vesicles contain from one to several concentric lipid bi-layers with intercalated aqueous compartments. Trans-epidermal penetration of the vesicles is proportional to the “fluidity” of their lipids and their negative charge. Several drugs and cosmetics in this galenic form are already commercially available and successfully used, presenting a better dose/effect ratio and provoking less side- effects.

Yongmei Hao et al., 2002 prepared niosomes which have high encapsulation capacity for soluble drugs, starting from Span 60 and cholesterol, an improved method, evaporation-sonication method, was proposed. The corresponding niosomes show a good stability at least 40 days. Colchicine was chosen as a model drug for examining the capsulation capacity of these niosomes. To obtain the highest encapsulation efficiency, several factors including the structure of surfactant, level of lipid, content of drug and cholesterol were investigated and optimized. The inner cause was also discussed. The results indicate that the Span 60 is the most ideal surfactant among four kinds of Span. Furthermore, the release studies of colchicine and 5-fluorouracil (5-FU) in vitro from niosomes exhibited a prolonged release profile as studied over a period of 24 h. The results demonstrated that niosomes prepared in this way not only have high encapsulation capacity but also is expected that side effects of drugs may be reduced. It still suggests that this method may be used extensively in the field of encapsulation soluble drugs.

Tejas R. Desai et al., 2002 demonstrated the potential of encapsulating
all-trans-retinoic acid (ATRA) in niosomes and delivering it as an inhaled aerosol. Niosomes may provide a means to reduce the toxicity of ATRA and alter the pharmacokinetics in a manner similar to liposomes. In addition, the low cost of the surfactants used for preparing niosomes and their greater stability compared with liposomes makes them an attractive alternative. Various nonionic surfactants were used to achieve optimum encapsulation and nebulization efficiencies, and the best formulations were obtained with combinations of (Span 20+Tween 80) and (Span 60+Tween 80) using an ATRA concentration of 1mg/ml. The aerosol produced with the selected niosomal formulations upon nebulization in PARI LC STAR nebulizers driven by a Pulmo-Aide compressor was subsequently analyzed for the determination of size distribution and entrapment efficiencies on each stage of an Anderson cascade impactor operated in a manner that avoids spurious sizing due to droplet evaporation. Mass median aerodynamic diameters (MMADs) of 3.7± 0.3 and 3.58 ± 0.03 µm, geometric standard deviation (GSD) values of 1.59 ± 0.17 and 1.51± 0.01 and entrapment efficiencies well above 50% were obtained for the optimized formulations. The results are very encouraging and offer an alternative approach to the respiratory delivery of ATRA by aerosolization.

Maria Manconi et al., 2002 prepared Tretinoin-loaded niosomes from polyoxyethylene (4) lauryl ether, sorbitan esters and a commercial mixture of octyl/decyl polyglucosides, in the presence of cholesterol and dicetyl phosphate. Liposomes made of hydrogenated and non-hydrogenated phosphatidylcholine were also prepared as a comparison reference. A study was made of the influence of vesicle composition and preparation method on the vesicle structure (MLV, LUV, SUV), size distribution, entrapment efficiency and \textit{in vitro} release of incorporated tretinoin. Results showed that in the presence of cholesterol all the amphiphiles used were able to form stable vesicle dispersions with or without tretinoin. Vesicle sizes were dependent on the preparation method, bilayer composition and drug load. Multilamellar (MLV) vesicles were larger than extruded (LUV) and sonicated (SUV) vesicles while drug-loaded vesicles were
generally smaller than empty ones. Entrapment efficiencies of tretinoin were always very high especially for multilamellar (91–99%) and extruded (88–98%) vesicles. The in vitro release of tretinoin from the prepared vesicular formulations was studied using the vertical Franz diffusion cells. The rate of drug release through a Silastic membrane from a liposomal and niosomal tretinoin dispersion was generally faster than from a tretinoin solution. Release data showed that tretinoin delivery is mainly affected by the vesicular structure and that tretinoin delivery increased from MLVs to LUVs to SUVs.

Fang et al., 2001 elucidated the skin permeation and partitioning of a fluorinated quinolone antibacterial agent, enoxacin, in liposomes and niosomes, after topical application. In vitro percutaneous absorption experiments were performed on nude mouse skin with Franz diffusion cells. The influence of vesicles on the physicochemical property and stability of the formulations were measured. The enhanced delivery across the skin of liposome and niosome encapsulated enoxacin had been observed after selecting the appropriate formulations. The optimized formulations could also reserve a large amount of enoxacin in the skin. A significant relationship between skin permeation and the cumulative amount of enoxacin in the skin was observed. Both permeation enhancer effect and direct vesicle fusion with stratum corneum may contribute to the permeation of enoxacin across skin. Formulation with niosomes demonstrated a higher stability after 48 h incubation compared to liposomes. The inclusion of cholesterol improved the stability of enoxacin liposomes according to the results from encapsulation and turbidity. However, adding negative charges reduced the stability of niosomes. The ability of liposomes and niosomes to modulate drug delivery without significant toxicity makes the two vesicles useful to formulate topical enoxacin.

Agarwal et al., 2001 studied dithranol in the topical treatment of psoriasis. However, the use of dithranol in psoriatic condition is inconvenient and troublesome, as it has irritating, burning, staining and necrotizing effect on the
normal as well as the diseased skin. The entrapment of drug in vesicles is viewed to help in the localized delivery of the drug and an improved availability of the drug at the site will reduce the dose and in turn, the dose-dependent side effects like irritation and staining. The investigations deal with critical parameters controlling the formulation and stabilization of dithranol loaded liposomes and niosomes. The entrapment efficiency of dithranol in liposomes was optimized by altering the proportion of phosphatidyl choline and cholesterol, and in case of niosomes it was between Span 60 and cholesterol. Hydration and permeation mediums were also established keeping in view the poor solubility and stability of dithranol. The mean liposome and niosomes sizes were 4 ± 1.25 and 5 ± 1.5 µm, respectively. The drug-leakage study carried out at different temperatures of 4–8, 25 ± 2 and 37°C for a period of two months affirms that the drug leakage increased at a higher temperature. The in vitro permeation study using mouse abdominal skin shows significantly enhanced permeation with vesicles as indicated by flux of dithranol from liposomes (23.13µg/cm²/h) and niosomes (7.78µg/cm²/h) as compared with the cream base (4.10µg/cm²/h).

Gopi N. Devaraj et al., 2002 studied the monomers of some amphiphiles organize into bilayers to form liposomes and niosomes. Such bilayers are unstable or leaky and hence cholesterol is a common ingredient included to stabilize them. Cholesterol stabilizes bilayers, prevents leakiness, and retards permeation of solutes enclosed in the aqueous core of these vesicles. Other than cholesterol a material with good bilayer-stabilizing properties is yet to be identified. We have substituted cholesterol with fatty alcohols in niosomes containing polyglyceryl-3-diisostearate (PGDS) and polysorbate-80 (PS-80) to explore their membrane-stabilizing property via permeation studies. Niosomes of polyglyceryl-3-di-isostearate, fatty alcohol/cholesterol, and Polysorbate were prepared by ether injection method. Aqueous solution of ketorolac tromethamine (KT) was entrapped in them. The effects of alkyl chain length of fatty alcohols (C₁₂, C₁₄, C₁₆, C₁₈, and C₁₆+C₁₈), of acyl chain length of polyoxyethylene sorbitan monoester surfactants, and of the molar ratio of lipid mixture on the release rate of ketorolac from niosomes were assessed by employing modified dissolution–
dialysis method. Niosomes with cholesterol or fatty alcohols have exhibited a common release pattern. Niosomes containing fatty alcohol showed a considerably slower release rate of KT than those containing cholesterol. Based on the release rate, fatty alcohols can be ranked as stearyl<myristyl<cetyl<lauryl<cetostearyl. In niosomes containing PGDS, myristyl alcohol (MA), and polysorbate, the fatty acid chain length of polyoxyethylene sorbitan ester-type surfactants has influenced the release rate and encapsulation efficiency. Based on the release rate, polysorbates can be ranked as polysorbate-20 (C₁₂) < polysorbate-60 (C₁₈) < polysorbate-80 (C₉₋₂₀) < polysorbate-40 (C₁₆). In niosome preparation containing polysorbate-20 and dioctyl sodium sulfosuccinate (anionic surfactant), the release rate was slower than niosomes containing polysorbate-20. When MA concentration is kept constant at 50 mole% and the ratio of PGDS and PS-80 was altered, significant changes in entrapment efficiency and the release rate were observed. However, this ratio did not exhibit any relation with encapsulation efficiency or release rate. The release rate and entrapment exhibited an inverse correlation \( r^2 = 0.8774 \) at \( p < 0.02 \) for the data of molar ratios of PGDS: MA: PS 80; \( r^2 = 0.975 \) at \( p < 0.001 \) for the data of acyl chain length variation of polysorbates. It can be concluded that stable niosomes of polyglyceryl-3-di-isostearate could be prepared with fatty alcohols and polysorbates instead of cholesterol and that the release of solutes from these niosomes can be optimized by altering membrane constituents and their concentrations.

Arunothayanun et al., 1999 investigated the effects of processing variables; particularly temperature and sonication, on the physical characteristics and phase transitional behaviour of two niosomal systems based on hexadecyl diglycerol ether (C₁₆G) have been studied. Systems containing C₁₆ G₂, cholesterol and poly-24-oxyethylene cholesteryl ether (Solulan C₂₄) in the molar ratios 91:0:9 and 49:49:2 were prepared by aqueous dispersion of films, followed by examination of 5(6)-carboxyfluorescein entrapment, particle size and morphology. The thermal behaviour was examined using high sensitivity differential scanning calorimetry (HSDSC) and hot stage microscopy, while the effects of sonication were studied in terms of size and morphology, both immediately after preparation.
and on storing for 1 h at room temperature and 60°C. Polyhedral niosomes were formed from systems containing C_{16}G_2 and Solulan C_{24} alone, while cholesterol-containing systems formed spherical vesicles mixed with tubular structures; the polyhedral systems were found to have a larger particle size and higher CF entrapment efficiency. HSDSC studies showed the polyhedral systems to exhibit an endotherm at 45.4°C and a corresponding exotherm at 39.1°C on cooling which were ascribed to a membrane phase transition; no equivalent transition was observed for the cholesterol containing systems. Hot stage microscopy showed the polyhedral vesicles to convert to spherical structures at 48°C, while on cooling the spherical vesicles split into smaller structures and reverted to the polyhedral shape at 49°C. Sonication resulted in the polyhedral vesicles forming spherical structures which underwent a particle size increase on storage at room temperature but not at 60°C. The study suggests that the polyhedral vesicles undergo a reversible transition to spherical vesicles on heating or sonication and that this morphological change may be associated with a membrane phase transition.

Calum J. Drummond et al., 2000 reviewed the new impetus in surfactant self-assembly objects as agents for drug delivery that are an alternative to micellar, lamellar/liposome, niosome and transfersome or microemulsion-based vehicles. The review focus herein is on the application of hexagonal, cubic, ‘intermediate’ (viz. rhombohedral, tetragonal and monoclinic) and L_3 (‘sponge’) mesophases.

Arunothayanun et al., 2000 formulated non-ionic surfactant vesicles (niosomes) using hexadecyl diglycerol ether (C_{16}G_2) and a series of polyoxyethylene alkyl ethers exhibit a variety of shapes dependant on their membrane composition. These surfactants form with an equimolar amount of cholesterol a mixture of largely spherical and tubular niosomes. In the absence of cholesterol, they form faceted polyhedral structures. The physicochemical and biological differences between polyhedral and spherical/tubular niosomes were studied. Polyhedral niosomes undergo a reversible shape transformation into spherical structures on heating above their phase transition temperature (T_m). The viscosity of polyhedral niosomes at room temperature is higher than their
spherical counterparts due to their faceted and relatively rigid shape, and is more dependant on temperature due to shape transformation. At room temperature, polyhedral niosomes possess more rigid gel phase membranes and are less osmotically sensitive; however, they are more permeable because of a lack of or low levels of cholesterol in their membranes.

Vyas et al., 1999 formed nonionic surfactant vesicles using Span 60, cholesterol and dicetyl phosphate. The prepared multilamellar vesicles (MLVs) were coated by interfacial polymerization technique using p-phthaloyl dichloride and L-lysine. The formation of the polymeric coat was confirmed by optical microscopic and transmission electron microscopic studies. The prepared, plain and polymer-coated MLVs were studied for their size, shape, encapsulation efficiency, \textit{in vitro} release profile and effect of osmotic shock on vesicle. The results observed showed that the polymer-coated MLVs were stable under various osmotic conditions. \textit{In vivo} studies were carried out on albino rats. The half-life and area under curve were found to be high in the case of polymer-coated MLVs as compared to plain MLVs and plain drug solution. \textit{In vivo} studies using inflamed rat model also indicated that the polymer-coated MLVs were more stable and could release the drug in a controlled fashion as compared to plain MLVs.

Gopal K. Pillai et al., 1999 prepared indomethacin incorporated in a non-ionic surfactant vesicle (niosome). The objective was to study the effect of niosomal-encapsulated indomethacin on platelet function such as inhibition of aggregation and ATP release induced by a variety of agonists (adenosine 5%-diphosphate (ADP), epinephrine, arachidonic acid, ristocetin) and to explore the feasibility of carrier-mediated drug delivery to the platelets. Multilamellar vesicles (niosomes) were prepared from Tween-60 by the lipid hydration method. Freshly prepared human platelet rich plasma (PRP) was used for aggregation inhibition studies, the extent of which was observed as a change in light transmission measured by the Chronolog Aggregometer. The percent inhibition of aggregation induced by the agonist ADP ranged from 28.21±0.28 at the 2.0 µmol
level to 92.6±1.20 at 12.7 µmol of the encapsulated drug while the same concentrations of the drug inhibited aggregation only to the extent of 13.75±0.13 and 36.82±0.57%, respectively. A 100% inhibition of aggregation induced by arachidonic acid was achieved by niosomal indomethacin while inhibition by the free drug was 41.9% at equimolar concentrations. ATP release study showed that 100% inhibition was achieved by 8 µmol of the encapsulated drug while inhibition by the free drug was 40.00±1.82%. Therefore, at equimolar doses, the niosomal drug proved to be more efficient in inhibiting platelet aggregation than the free drug, probably 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.

Rentel et al., 1999 developed a peroral vaccine delivery system based on non-ionic surfactant vesicles (niosomes) were evaluated using BALB/c mice. Ovalbumin was encapsulated in various lyophilized niosome preparations consisting of sucrose esters, cholesterol and dicetyl phosphate. Two different formulations were compared in this study. The specific antibody titres within serum, saliva and intestinal washings were monitored by ELISA on days 7, 14, 21 and 28 after intragastric administration. Only encapsulation of ovalbumin into Wasag®7 (70% stearate sucrose ester, 30% palmitate sucrose ester (40% mono-, 60% di:tri-ester)) niosomes resulted in a significant increase in antibody titres. Administration of ovalbumin and empty niosomes did not exert a similar effect; neither did administration of any control formulation. In contrast to ovalbumin loaded Wasag®7 niosomes, application of the more hydrophilic Wasag®15 (30% stearate sucrose ester, 70% palmitate sucrose ester (70% mono- 30% di/tri-ester)) niosome preparations did not result in an increase in antibody titres.

Sudaxshina Murdan et al., 1999 investigated multi-component organogels formed using the non-ionic surfactant sorbitan monostearate as gelator has been formulated to contain niosomes. The purpose of this study was to evaluate the potential of these vesicle-in-water-in-oil (v/w/o) gels as delivery vehicles for
vaccines. Bovine serum albumin (BSA) and haemagglutinin (HA) were used as model antigens in depot and immunogenicity studies respectively. The complex gels were prepared by the addition of a hot (60°C) aqueous niosome suspension (v/w) to the sol phase (o, an organic solution of the gelator); a vesicle-in-water-in-oil (v/w/o) emulsion was produced which cools to an opaque, semi-solid, thermoreversible v/w/o gel. Light microscopy of the organogel revealed that the microstructure consists of a tubular network of surfactant aggregates in the organic medium, the niosome suspension being dispersed in these surfactant tubules. Therefore, in such gels, the vaccine is thought to be entrapped in the niosomes, themselves located within the sorbitan monostearate tubular network in the organic medium. In vivo, a depot effect was observed following intramuscular administration of the gel containing the entrapped bovine serum albumin, cleared from the injection site over a period of days. The relatively short-lived nature of the depot was thought to arise due to interactions between the gel and the local interstitial fluid which results in gel disintegration in situ. Thus, the niosomes containing antigens are believed to be released from the organic gel. Immunogenicity studies showed that the v/w/o gel as well as one of the controls, the water-in-oil (w/o) gel, possess immunoadjuvant properties and enhance the primary and secondary antibody titres (of total IgG, IgG1, IgG2a and IgG2b) to haemagglutinin antigen. As far as humoral immunity is concerned, the w/o gel showed stronger immunoadjuvant properties compared to the v/w/o gel, being effective at a lower antigen dose i.e 0.1µg HA.

Ijeoma F. Uchegbu et al., 1998 reviewed the self assembly of non-ionic surfactants into vesicles was first reported in the seventies by researchers in the cosmetic industry. Since then a number of groups world wide have studied non-ionic surfactant vesicles (niosomes) with a view to evaluating their potential as drug carriers. This article presents a summary of the achievements in the field to date. Niosomes may be formed from a diverse array of amphiphiles bearing sugar, polyoxyethylene, polyglycerol, crown ether and amino acid hydrophilic head groups and these amphiphiles typically possess one to two hydrophobic
alkyl, perfluoroalkyl or steroidal groups. The self assembly of surfactants into niosomes is governed not only by the nature of the surfactant but by the presence of membrane additives, the nature of the drug encapsulated and the actual method of preparation. Methods of niosome preparation and the number of different morphologies that have been identified are detailed. The influence of formulation factors on niosome stability is also examined as the \textit{In vivo} these systems have been evaluated as immunological adjuvants, anti-cancer, anti-infective drug targeting agents and carriers of anti-inflammatory drugs. Niosomes have also been used in diagnostic imaging. Efforts to achieve transdermal and ophthalmic drug delivery with some formulations are also discussed.

Ijeoma F. Uchegbu \textit{et al.}, 1995 investigated that PK\textsubscript{1} is an \textit{N}-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-doxorubicin conjugate currently in early clinical development. Niosome encapsulation is a means to increase PK\textsubscript{1} blood residence time, potentially promote tumour uptake and produce a slow, sustained release of active drug. Factors effecting encapsulation efficiency and size of PK\textsubscript{1}-niosome formulations were studied. Five surfactants were used to prepare PK\textsubscript{1}-niosomes; hexadecyl poly-5-oxyethylene ether (C\textsubscript{16}EO\textsubscript{5}); octadecyl poly-5-oxyethylene ether (C\textsubscript{18}EO\textsubscript{5}); hexadecyl diglycerol ether (C\textsubscript{16}G\textsubscript{2}); sorbitan monopalmitate (Span 40) and sorbitan monostearate (Span 60). All were mixed in equimolar ratio with cholesterol and varying amounts of Solulan C\textsubscript{24} (a cholesteryl poly-24-oxyethylene ether) (9–39 mol %). Dicetylphosphate (DCP) was also added (2 mol %). Passive association of PK\textsubscript{1} with preformed C\textsubscript{16} G\textsubscript{2} and Span 60 vesicles was low (3–4%) while subsequent dehydration (freeze drying) followed by rehydration of the formulation increased the entrapment to 61\% in the C\textsubscript{16}G\textsubscript{2} formulation. Transmission electron microscopy revealed that these niosomes had an electron dense core, evidence of intravesicular concentration of PK\textsubscript{1}. Increasing Solulan C\textsubscript{24} content resulted in decreased PK\textsubscript{1} entrapment after freeze drying, and the vesicle size was also decreased. SolulanC\textsubscript{24} (39 mol \%) caused pronounced vesicle aggregation on freeze drying, whereas at lower levels (9 mol \%), PK\textsubscript{1} appeared to act as a
cryoprotectant and the mean size of C16G2 niosomes was 235 nm. A PK<sub>1</sub>-surfactant: lipid ratio of 0.3 (11.2 mg ml<sup>-1</sup> doxorubicin) was achieved with Span 60 niosomes. This formulation, and the C<sub>16</sub> G<sub>2</sub> niosomes, did not induce red blood cell lysis at the proposed dose for in vivo use. Preliminary in vivo biodistribution studies showed PK1-C<sub>16</sub>G<sub>2</sub> niosomes to be mainly taken up by the liver and spleen. After 24 h, 25 and 3% of dose administered was present as free doxorubicin in these organs respectively.

Jain et al., 1995 investigated niosomes (non-ionic, surfactant-based vesicles) containing rifampicin of 8-15 microns in diameter were prepared using Span-85 and cholesterol in various molar fractions. The process variables that could affect the physical characteristics of niosomes and in vitro release of the drug from the niosomes were studied and optimized. In vivo distribution studies of the prepared niosomes found that 65% of the drug could be localized in the lungs by controlling the niosome size.

Toshimitsu Yoshioka et al., 1994 studied formation of multilamellar vesicles (niosomes) of a series of sorbitan monoesters (span 20, 40, 60 and 80) and a sorbitan trioleate (Span 85) has been studied using a mechanical shaking technique without sonication. 5(6)-carboxyfluorescein (CF) was used as a model solute to investigate entrapment efficacy and release. For Span 80, cholesterol and dicetyl phosphate (DCP) in the molar ratio 47.5:47.5:5.0, entrapment efficacy increased linearly with increasing concentration of lipid. Entrapment efficacy per mmol lipid, however, was constant at about 34%, independent of the lipid concentration. Entrapment efficacy increased with increasing cholesterol content when vesicles were prepared by changing the molar ratio of non-ionic surfactant to cholesterol. Most efficient entrapment of CF occurred with Span 60 (HLB 4.7). Mean size of the non-sonicated niosomes showed a regular increase with increasing HLB from Span 85 (HLB 1.8). the release rate of CF from vesicles depended on the surfactant used in the preparation of the vesicles.

Chandraprakash et al., 1990 prepared methotrexate encapsulated in niosomes. The entrapment efficacy increased in lipophilicity of surfactant.
Unilamellar vesicles prepared with span 60 showed maximum entrapment and its pharmacokinetics in mice transplanted with S-180 tumor was marketedly different in comparison to unentrapped Methotrexate.

2.2 NATIONAL STATUS

Bhaskaran et al., 2001 formulated niosomes containing salbutamol sulphate using different non-ionic surfactants like Tween 20, 40, 60, 80, Span 20, 40, 60, 80 and Brij 35 by transmembrane pH gradient method. The drug encapsulation efficiency varied from 28 percent to 79 percent. The vesicles have been characterized by infrared spectroscopy. In vitro drug release studies were carried out using dialysis bag and phosphate buffer, pH 7.4 as a dissolution medium for 24 h. The formulation exhibited retarded release for 24 h and Span 60 was found to be the most satisfactory surfactant which released 78.4 percent of drug in 24h. Particle size distribution studies were carried out by optical microscopy technique. Most of the niosomes were found to be spherical in shape. Thermal stability studies were carried out at 4, 25 and 50 for one month. The product was lyophilized. Tissue distribution studies were carried out on rabbits. The maximum concentration was seen in lungs.

Himanshu et al., 2007 designed and characterized verapamil hydrochloride niosomes in varied polymer: drug ratios and optimizing formulation variables and release kinetics with a view to enhance bioavailability, reduce dosing frequency and achieve release in a controlled fashion. Verapamil hydrochloride niosomes were prepared by thin film hydration technique using span-40, span-60 as surfactants and cholesterol as lipids, in different ratios. Amidst non-ionic surfactants, span-60 gave ecstatic results with high drug entrapment efficiency and in vitro drug release.

Jain et al., 2006 prepared niosomes (non-ionic surfactant-based vesicles) containing rifampicin using various non-ionic surfactants of sorbitan ester class and cholesterol in 50:50 percent mol fraction ratios. The drug-entrapped vesicles were characterized for their shape, size drug entrapment efficiency and in vitro release rate. On the basis of in vitro characterization, the niosomes showing
maximum entrapment and minimum release rate were selected for in vivo performance evaluation. Cumulative percent dose of rifampicin recovered in thoracic lymph following intravenous and intraperitoneal administrations of free rifampicin solution and niosome encapsulated rifampicin were compared. The study revealed that effective compartmentalization of the drug took place in the lymphatic system following intraperitoneal administration of niosome encapsulated rifampicin. Thus rifampicin encapsulated in niosomes could successfully be used for treatment of tuberculosis along lymphatic system.

Biju et al., 2006 reviewed about development of novel drug delivery system. Novel drug delivery system aims to deliver drugs 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. At present, no available drug delivery system behaves ideally achieving all the lofty goals, but sincere have been made to achieve them through novel approaches in drug delivery. A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structures is one such system, which can be predicted to prolong the existence of the drug in systemic circulation and reduce the toxicity, if selective uptake can be achieved. Consequently a number of vesicular drug delivery system such as liposomes, niosomes, transferosomes, and pharmacosomes were developed. Advances have since been made in the area of vesicular drug delivery, loading to the development of systems that follow drug targeting, and the sustained or controlled release of conventional medicines. The focus of this review is to bring out the application, advantages and drawbacks of vesicular systems.

Kusum et al., 2006 reveals Human Immunodeficiency Virus (HIV) is a retrovirus that causes irreversible destruction of the immune system, leading to the occurrence of opportunistic infections and malignancies. During the last decades, even though attempts were being made to eradicate HIV, it was found that eradication of HIV is highly unlikely, and effective antiretroviral therapy is
required on a long term basis to maintain viral suppression and reduce disease progression. During this decade, effective therapies aimed at continued suppression of HIV replication and targeted at resting HIV reservoirs such as brain, lymphatic systems will be critical to prolong survival and renewing hopes for a cure. Currently available anti-HIV drugs can be classified into three categories: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Most of these drugs bear some significant drawbacks such as relatively short half-life, low bioavailability, poor permeability and undesirable side effects. Efforts have been made to design drug delivery systems for anti-HIV agents to reduce the dosing frequency, increase the bioavailability and decrease the degradation/metabolism in the gastrointestinal tract, improve the CNS penetration and inhibit the CNS efflux, and deliver them to the target cells selectively with minimal side effects. This article is an attempt to compile all major research work towards drug delivery for AIDS therapy and channel future attempts in the area of more effective controlled delivery of anti-HIV agents.

Mullaicharam et al., 2004 developed rifampicin (first-line anti-tuberculosis drug) niosomes using factorial design and the formulation procedure along with drug entrapment efficiency of the niosomes were optimized. The effects of alteration of process variables like volume of solvent, hydration time, volume of hydrating medium and sonication time were studied. The prepared niosomes were characterized for size, shape and lamellarity. The stability of niosomes in terms of retention of drug was measured at refrigerated temperature (5°C) and ambient temperature (25-35°C) for the period of 60 days. The developed formulation may be useful in the treatment of pulmonary tuberculosis.

Manivannan Rangasamy et al., 2008 formulated acyclovir entrapped niosomes by hand shaking and ether injection process with different ratios of (1:1, 1:2 and 1:3) cholesterol (CHOH) and span-80 (Non-ionic surfactant). The
niosomes prepared were in the size range of 0.5-5 microns in the case of hand shaking process and 0.5-2.5 microns in the case of ether injection process. The order of encapsulation efficiency increases when span-80 concentration was increased. In-vivo release study on Acyclovir niosomes indicates 76.64% release for formulation prepared with CHOH: span-80 (1:1) and it takes an extended period of 1 day and 16 h for release.

2.3 PRONIOSOMES

International Status

Yi-Hung Tsai et al., 2001 investigated the estradiol skin permeation from various pronosome gel formulations across excised rat skin in in-vitro studies. The encapsulation efficiency and size of niosomal vesicles formed from proniosomes upon hydration were also characterized. The encapsulation (%) of proniosomes with Span surfactants showed a very high value of 100%. Proniosomes with Span 40 and Span 60 increased the permeation of estradiol across skin. Both penetration enhancer effect of non-ionic surfactant and vesicle-skin interaction may contribute to the mechanisms for proniosomes to enhance estradiol permeation. Niosome suspension (diluted proniosomal formulations) and proniosome gel showed different behavior in modulating transdermal delivery of estradiol across skin. Presence or absence of cholesterol in the lipid bilayers of vesicles did not reveal difference in encapsulation and permeation of the associated estradiol. The types and contents of non-ionic surfactant in proniosomes are important factors affecting the efficiency of transdermal estradiol delivery.

Ankur Gupta et al., 2007 studied on development of a proniosomal carrier system for captopril for the treatment of hypertension that is capable of efficiently delivering entrapped drug over an extended period of time. The potential of proniosomes as a transdermal drug delivery system for captopril was investigated by encapsulating the drug in various formulations of proniosomal gel composed of various ratios of sorbitan fatty acid esters, cholesterol, lecithin prepared by
coacervation-phase separation method. The formulated systems were characterized \textit{in vitro} for size, vesicle count, drug entrapment, drug release profiles and vesicular stability at different storage conditions. Stability studies for proniosomal gel were carried out for 4 weeks. The method of proniosome loading resulted in an encapsulation yield of 66.7 - 78.7%. Proniosomes were characterised by transmission electron microscopy. \textit{In vitro} studies showed prolonged release of entrapped captopril. At refrigerated conditions, higher drug retention was observed. It is evident from this study that proniosomes are a promising prolonged delivery system for captopril and have reasonably good stability characteristics.

Bhavana Vora \textit{et al.}, 1998 formulated proniosome based transdermal drug delivery system of levonorgestrel (LN) and extensively characterized both \textit{in vitro} and \textit{in vivo}. The proniosomal structure was liquid crystalline-compact niosomes hybrid which could be converted into niosomes upon hydration. The system was evaluated \textit{in vitro} for drug loading, rate of hydration (spontaneity), vesicle size, polydispersity, entrapment efficiency and drug diffusion across rat skin. The effect of composition of formulation, amount of drug, type of Spans, alcohols and sonication time on transdermal permeation profile was observed. The stability studies were performed at 48°C and at room temperature. The biological assay for progestational activity included endometrial assay and inhibition with the formation of corpora lutea. The study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrel for effective contraception.

Alsarra \textit{et al.}, 2005 investigated the permeation of a potent nonsteroidal anti-inflammatory, ketorolac, across excised rabbit skin from various proniosome gel formulations was investigated using Franz diffusion cells. Each of the prepared proniosomes significantly improved drug permeation and reduced the lag time (p <0.05). Proniosomes prepared with Span 60 provided a higher ketorolac flux across the skin than those prepared with Tween 20 (7- and 4-fold the control, respectively). A change in the cholesterol content did not affect the efficiency of the proniosomes, and the reduction in the lecithin content did not
significantly decrease the flux ($p < 0.05$). The encapsulation efficiency and size of niosomal vesicles formed by proniosome hydration were also characterized by specific high performance liquid chromatography method and scanning electron microscopy. Each of the prepared niosomes achieved about 99% drug encapsulation. Vesicle size was markedly dependent on the composition of the proniosomal formulations. Proniosomes may be a promising carrier for ketorolac and other drugs, especially due to their simple production and facile up.

Almira et al., 2001 investigated maltodextrin Proniosomes. The niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. Investigators developed Proniosomes, a dry formulation using a sorbitol carrier coated with nonionic surfactant, which can be used to produce niosomes within minutes by the addition of hot water followed by agitation. The sorbitol carrier in the original proniosomes was soluble in the solvent used to deposit surfactant, so preparation was tedious and the dissolved sorbitol interfered with the encapsulation of one model drug. A novel method is reported here for rapid preparation of proniosomes with a wide range of surfactant loading. A slurry method has been developed to produce proniosomes using maltodextrin as the carrier. The time required to produce proniosomes by this simple method is independent of the ratio of surfactant solution to carrier material and appears to be scalable. The flexibility of the proniosome preparation method would allow for the optimization of drug encapsulation in the final formulation based on the type and amount of maltodextrin. This formulation of proniosomes is a practical and simple.
Ajay B. Solanki *et al.*, 2007 investigated the combined influence of 3 independent variables in the preparation of piroxicam proniosomes by the slurry method. A 3-factor, 3-level Box-Behnken design was used to derive a second order polynomial equation and construct contour plots to predict responses. The independent variables selected were molar ratio of Span 60: cholesterol ($X_1$), surfactant loading ($X_2$) and amount of drug ($X_3$). Fifteen batches were prepared by the slurry method and evaluated for percentage drug entrapment (PDE) and vesicle size. The transformed values of the independent variables and the PDE (dependent variable) were subjected to multiple regressions to establish a full-model second-order polynomial equation. F was calculated to confirm the omission of insignificant terms from the full-model equation to derive a reduced-model polynomial equation to predict the PDE of proniosome-derived niosomes. Contour plots were constructed to show the effects of $X_1$, $X_2$ and $X_3$ on the PDE. A model was validated for accurate prediction of the PDE by performing checkpoint analysis. The computer optimization process and contour plots predicted the levels of independent variables $X_1$, $X_2$, and $X_3$ (0, -0.158 and –0.158 respectively), for maximized response of PDE with constraints on vesicle size. The Box-Behnken design demonstrated the role of the derived equation and contour plots in predicting the values of dependent variables for the preparation and optimization of piroxicam proniosomes.

El-laithy *et al.*, 2008 investigated on development of Novel approach for the preparation of controlled release proniosome-derived niosomes, using sucrose stearate as non-ionic biocompatible surfactants for the nebulisable delivery of cromolyn sodium. Conventional niosomes were prepared by a reverse phase evaporation method followed by the preparation of proniosomes by spraying the optimized surfactant–lipid mixture of sucrose stearate, cholesterol and stearylamine in 7:3:0.3 molar ratios onto the surface of spray dried lactose powder. Proniosome-derived niosomes were obtained by hydrating proniosomes with 0.9% saline at 50°C and mixing for approximately 2 min. All vesicles were evaluated for their particle size, morphological characteristics, entrapment...
efficiency, \textit{in vitro} drug release, nebulisation efficiency and physical stability at 2–8\textdegree{} C. In addition, coating carrier surface with the surfactant–lipid mixture, during preparation of proniosomes, resulted in smaller, free flowing, homogenous and smooth vesicles with high drug entrapment efficiency. Compared to a standard drug solution, a successful retardation of the drug release rate was achieved with the proniosome-derived niosomes, where the t 50\% value of the release profile was 18.1 h compared to 1.8 h. Moreover, high nebulisation efficiency percentage and good physical stability were also achieved. The results are very encouraging and offer an alternative approach to minimize the problems associated with conventional niosomes like degradation, sedimentation, aggregation and fusion.

David G. Rhodes \textit{et al.}, 1999 study described a procedure for producing a dry product which may be hydrated immediately before use to yield aqueous niosome dispersions similar to those produced by more cumbersome conventional methods. These proniosomes minimize problems of niosome physical stability such as aggregation, fusion and leaking, and provide additional convenience in transportation, distribution, storage and dosing. This report describes the preparation of dispersions of proniosome-derived niosomes, comparison of these niosomes to conventional niosomes, and optimization of proniosome formulations. In addition, conventional and proniosome-derived niosomes are compared in terms of their morphology, particle size, particle size distribution and drug release performance in synthetic gastric or intestinal fluid. In all comparisons, proniosome-derived niosomes are as good as or better than conventional niosomes.

Literature survey carried out for the present work includes reports on all previous work done by other workers in the field of niosomes. The level of interest in niosomes was increased substantially as is evident by the number of research activities done on this subject. From the foregoing literature niosome formulation and \textit{in vivo} evaluation for the antiretroviral drug, zidovudine has not been investigated in detail. This lacuna is noticed and the present work is attempted to address these issues.

\section{2.4 \textsc{Patent Search Status for Niosomes}}
Research leading to patent was carried out. From the literature information it was found that a United States patent (4830857) was awarded to Handjani Rose M. (Paris, FR), Ribier Alain (Paris, FR), Vanlerberghe Guy (Villevaude, FR), Zabotto Arlette (Paris, FR), Griat Jacqueline (Ablon, FR) for their invention related to a cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide, and a process for preparing these compositions in the year 05/16/1989. The invention claims it can be usable in cosmetics or pharmaceuticals.

**Marketed Niosomes**

Lancome has come out with a variety of anti-ageing products which are based on niosome formulations.