academicJournals

Vol. 7(48), pp. 3034-3059, 29 December, 2013
DOI: 10.5897/AJPPX2013.0004
ISSN 1996-0816 © 2013 Academic Journals
http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Review

Lipid-based drug delivery systems (LDDS): Recent advances and applications of lipids in drug delivery

Salome Amarachi Chime* and Ikechukwu V. Onyishi

Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka 410001, Nigeria.

Accepted 3 December, 2013

Recently, advances in pharmaceutical research is focused on new delivery systems utilizing new devices to achieve modification of delivery time, targeting, as well as improve the *in vivo* solubility and hence bioavailability of poorly soluble drugs. Lipid based drug delivery systems (LDDS) consists of diverse group of formulations, each consisting of varying functional and structural properties that are amenable to modifications achieved by varying the composition of lipid excipients and other additives. LDDS has evolved, overtime, from micro- to nano-scale enhancing the efficacy and therapeutic application of these systems. LDDS are accepted, proven, commercially viable strategies for formulating challenging pharmaceutical molecules and can be tailored to meet a wide range of product requirements. Generally, most lipid drug delivery systems used as drug carriers have high stability, high carrier capacity, feasibility of incorporating both hydrophilic and hydrophobic substances and feasibility of variable routes of administration, including oral, topical, parenteral and pulmonary routes. LDDS can also be designed to allow modified drug release from matrices. LDDS could be broadly grouped into four: solid lipid particulate dosage forms, emulsion based systems, solid lipid tablets, and vesicular systems. Modifications from these four types include: lipospheres, solid lipid nanoparticles (SLNs), nano structured lipid carriers (NLC), lipid drug conjugate nanoparticles (LDC), self emulsifying formulations (SEFs), pickering emulsions, dry emulsions, micro and nano-emulsions, solidified reverse micellar solution (SRMS) based tablets, liposomes, herbosomes, cryptosomes and transferosomes amongst others. This work exhaustively reviewed the advances in LDDS and also drew comparison between the different types based on history, methods of manufacture, applications, advantages and disadvantages.

Key words: Cryptosomes**,** lipospheres, lipoplexes, solid lipid tablets, pharmacosomes, virosomes, vesosomes.

INTRODUCTION

Pharmaceutical research is recently geared towards the development of new delivery systems of existing drugs (Dinesh et al., 2012). These novel delivery systems improve the bioavailability of the drug(s) while at the same time minimize their toxic effects. The oral delivery of lipophilic drugs presents significant challenges to pharmaceutical scientists due to their inherent low aqueous solubility, which generally lead to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality (Jyoti et al., 2012; Stegemanna and Leveillerb, 2007). The advances in combinatorial chemistry have led to tremendous increase

*Corresponding author. E-mail: emmymarachi@yahoo.com, salome.chime@unn.edu.ng. Tel: +2348033763348. Fax: +234-42-771709.

in sparingly soluble drugs, and currently 40 to 70% of new pharmacologically active chemical entities exhibit poor aqueous solubility (Jyoti et al., 2012). Many formulation approaches are presently being employed in tackling the formulation challenges posed by drugs belonging to the biopharmaceutics classification system (BSC) class II and IV, either by pre-dissolving the compound in a suitable solvent and subsequently filling the formulation into capsules (Jyoti et al., 2012; Stegemanna and Leveillerb, 2007) or by formulating as solid solution using water-soluble polymers (Cole et al., 2008). These approaches however, can probably resolve the issue related to initial dissolution of drug molecules in aqueous environment within the gastrointestinal tract (GIT) to a certain extent. However, major limitations like drug precipitation during dispersion of formulation in the GIT or drug crystallization in the polymer matrix may be unresolved. These problems have been effectively resolved by the use of lipid based drug delivery systems (DDS) (Jyoti et al., 2012; Attama and Nkemnele, 2005).

The widening availability of lipid excipients with specific characteristics offers flexibility of application with respect to improving the bioavailability of sparingly soluble drugs and manipulating their release profile (Attama and Nkemnele, 2005). Lipid-based DDS is an accepted, proven, commercially viable strategy in formulation of pharmaceuticals. Lipid formulations can be tailored to meet a wide range of product requirements (Attama et al., 2012). Generally, most lipid drug delivery systems used as drug carriers have high stability, high carrier capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration, including oral, topical, parenteral and pulmonary routes. It can also be designed to allow controlled drug release from matrices (Gelperina et al., 2005; Chime et al., 2013a).

Lipid-based formulations can be used to influence the absorption of active ingredients through different mechanisms. They can affect the intestinal environment, stimulate the lymphatic transport of active ingredients, and interact with enterocyte based transport (Fouad et al., 2011). Lipid formulations in general provide increased drug solubilization for water-insoluble drugs. If the drug is dissolved in the lipid matrix of the DDS, the drug absorption is observed to be better. Drug suspended in the lipid matrix has been shown to get absorbed better than the conventional solid dosage forms (Chime et al., 2013b, c; Umeyor et al., 2012a). This could be due to the ease of wetting of the hydrophobic drug particles in the presence of lipid matrix. The presence of surfactant in the formulation may ease the wetting further. Also, entrapment of drug in the micelles may be enhanced due to the presence of lipidic matrix (Joshi and Shah, 2008). For poorly water soluble drug molecules, whose dissolution in water is likely the rate limiting step to overall oral absorption, the primary role of ingested lipids and their lipolytic products is to impact the drug dissolution step by forming different colloidal particles with bile components, which are able to maintain a larger quantity of hydrophobic drugs in solution via micellar solubilization (Porter et al., 2007). The primary mechanism of action which leads to improved bioavailability is usually avoidance or partial avoidance of slow dissolution process which limits the bioavailability of hydrophobic drugs from conventional solid dosage form (Pouton, 2000).

Lipid-based excipients such as glycerides, fatty acids, ionic and non-ionic surfactants are known permeability enhancers (Kuentz, 2010) which may be due to increased membrane fluidity. Permeability enhancement may also be achieved by the interaction of LDDS with efflux transporters. A well-known efflux transporter at the apical membrane of human intestine is the P-glycoprotein (P-gp). Substrates for P-gp can be found in many groups of drugs such as anti-cancer compounds, HIV-protease inhibitors, immune suppressants, hormones, cardiovascular drugs or H2-receptor antagonists (Aungst et al., 1996; Kuentz, 2010; Pang et al., 2007). Substrates are expected to have increased permeability when the efflux pump is inhibited by excipients. Excipients with inhibiting effects on efflux pumps are found in the group of medium chain glycerides, polyethylene glycols, polysorbates and polyethoxylated castor oil or block copolymers of the type pluronic. Surfactants have been shown to inhibit P-gp because of their amphiphilic structure (Aungst et al., 1996; Kuentz, 2010; Bogman et al., 2003; Pang et al., 2007).

Lipid based DDS represent a diverse group of formulations comprising several classes of excipients (for example, triglyceride oils, mixed glycerides, lipophilic surfactants, hydrophilic surfactants, and water soluble co-solvents) with a wide range of properties. An array of lipid systems such as emulsions, micellar solutions, liposomes, lipid nanoparticles, structured lipid carriers, self-emulsifying lipid formulations, solid dispersions, dry emulsions, solid-liquid compacts, and drug lipid conjugates is available to drug formulators as shown in Figure 1 (Attama et al., 2009; Attama et al., 2012). The article reviews the newer lipid-based drug delivery systems utilized in formulating drugs in order to enhance their bioavailability, its applications, merits and demerits as well as comprehensive comparison among the LDDS were exhaustively discussed in order to guide formulation scientists in the choice of lipid based dosage form designs and selection.

RECENT ADVANCES IN LDDS

Lipid-based drug delivery systems are broadly classified into four groups, including the solid lipid particulate dosage forms, emulsion based systems, solid lipid tablets, and vesicular systems.

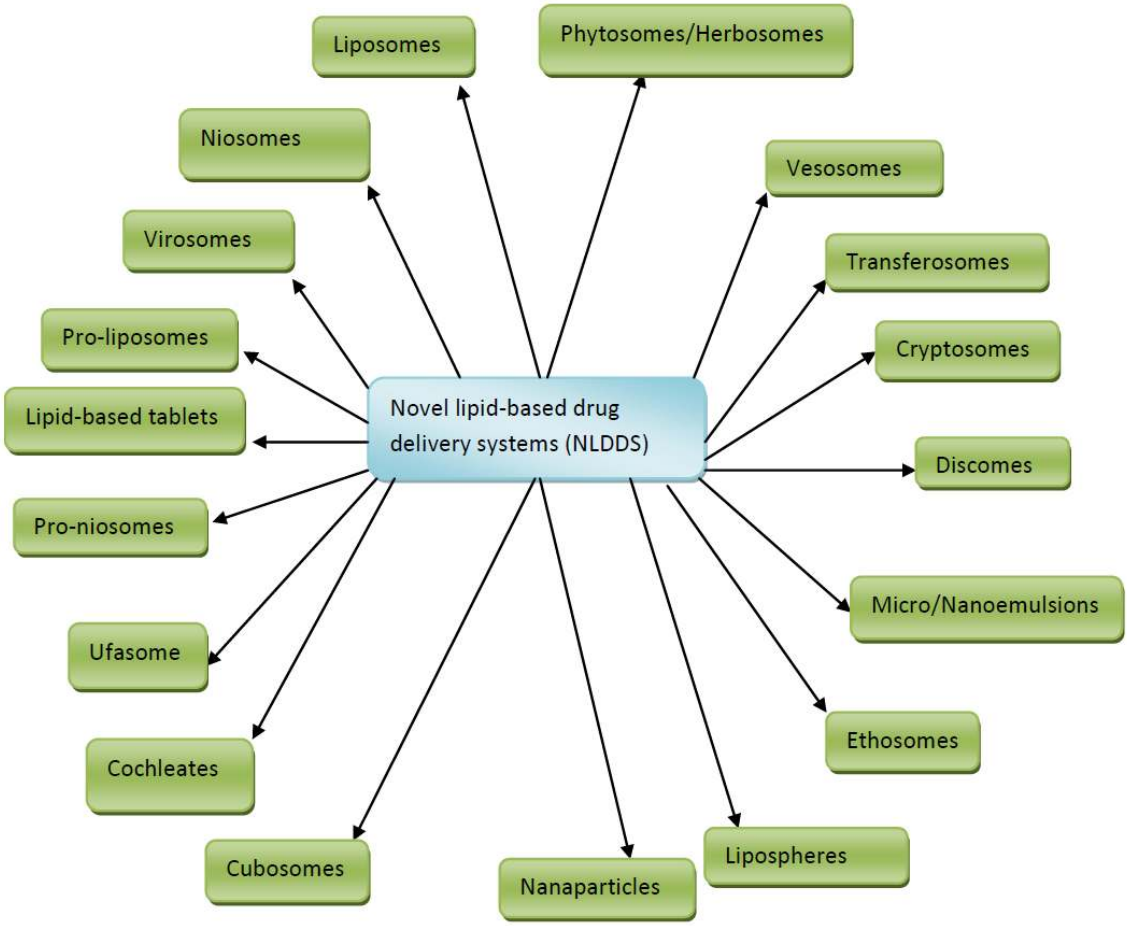

Figure 1. Novel lipid-based drug delivery systems (NLDDS).
Source: Attama et al. (2012).

SOLID LIPID PARTICULATE DOSAGE FORMS

Lipospheres

Lipospheres were first reported as a particulate dispersion of solid spherical particles of a particle size range 0.2 to 100 µm in diameter consisting of solid hydrophobic fat core such as triglycerides or fatty acids derivatives, stabilized by monolayer of phospholipid (Domb and Manier, 1990). Internal core of liposphere contains the drug dissolved or dispersed in solid fat matrix. Lipospheres represent a new type of fat based encapsulation system developed for parenteral and topical delivery of bioactive compounds (Domb and Manier, 1990). Lipospheres are restricted to the stabilizing material of a phospholipid layer (Rawat and Saraf, 2008). These have been utilized in the delivery of anti-inflammatory compounds, local anesthetics, antibiotics, anticancer agents, insect repellents, vaccines, proteins and peptides (Amselem et al., 1992; Domb et al., 1995; Khopade and Jain, 1997; Masters and Domb, 1998; Rawat and Saraf, 2008). Agents for agricultural application such as herbicides, fungicides and fertilizers can also be incorporated into lipospheres (Domb and Maniar, 1996). The lipospheres are distinct from micro droplets, vesicles or liposomes since the lipospheres have solid inner core at room temperature. The lipospheres are distinct from microspheres of uniformly dispersed material in homogenous polymer since they consist of at least two layers of phospholipid (Domb et al., 1996).

Since lipospheres were introduced in the beginning of the 1990s, they have been used for the delivery of multiple types of drugs by various routes of administration. However, a self-assembling pro-nano lipospheres (PNL) encapsulation system was developed for oral drug delivery (Elgart et al., 2012).

The combination of solid inner core with phospholipid exterior confers several advantages on the lipospheres and PNL compared with conventional microspheres and micro particles, including high dispersibility in an aqueous medium, and a release rate for the entrapped substance that is controlled by phospholipid coating and carrier

(Rawat and Saraf, 2008). There are also many advantages over the dispersion based delivery systems. Lipospheres have increased stability as compared to emulsion based systems, including vesicles and liposomes, and are more effectively dispersed than most suspension based systems. Further, the substance to be delivered does not have to be soluble in the vehicle since it can be dispersed in the solid carrier. Lipospheres also have a lower risk of reaction of substance to be delivered with the vehicle than in emulsion system because the vehicle is a solid material. Moreover, the release rate of substance from the lipospheres can be manipulated by altering either or both the inner solid vesicle or the outer phospholipid layer. Lipospheres are also easier to prepare than vesicles such as liposomes, and are inherently more stable. Stability has become the major problem limiting the use of liposomes, both in terms of shelf life and after *in vivo* administration. Liposomes and vesicles do not remain intact or available *in vivo* after injection for more than a few hours to a couple of days (Rawat and Saraf, 2008). The cost of the reagents for making the lipospheres (food grade) is significantly less than the cost of reagents for making liposomes, which require very pure lipids (Domb and Maniar, 1996).

Advantages of liposphere and PNL drug delivery system

1. High dispersibility in aqueous medium (Domb et al., 1996).
2. Ease of preparation and scale up (Domb et al., 1996).
3. High entrapment of drugs.
4. Liposphere exhibit enhanced physical stability due to avoidance of coalescence.
5. Reduced mobility of incorporated drug molecules responsible for reduction of drug leakage, circumvention of instabilities due to interaction between drug molecules and emulsifier film.
6. Static interface facilitates surface modification of carrier particles after solidification of the lipid matrix (Domb et al., 1996).
7. Low cost of ingredients (Domb et al., 1996).
8. Extended release of entrapped drug after a single injection (Domb et al., 1996).
9. Controlled particle size, the liposphere particle size allows administration at many sites, including perineural, subcutaneous or intramuscular locations. The small particle size of lipospheres (< 20 µm) is hypothesized to be well tolerated by a single cell contact, where large particle size (> 50 µm) are much more reactive due to attractive forces (for example, Van der Waals) (Khopade and Jain, 1997).

Disadvantages of liposphere/PNL DDS

1. Low drug loading capacity for hydrophilic protein (Rawat and Saraf, 2008).
2. Insufficient stability data (Rawat and Saraf, 2008).
3. High pressure induced drug degradation.
4. Variable kinetics of distribution process.
5. Different lipid modifications and colloidal species coexist that may cause differences in solubility and melting point of active and excipients (Rawat and Saraf, 2008).

SOLID LIPID MICROPARTICLES (SLMs)

SLMs is a typical example of lipospheres and combine many advantages of drug carrier systems. The amount of drug encapsulated can vary up to 95% for lipophilic and hydrophilic drugs (Chime et al., 2013b, c; Umeyor et al., 2012a) and because they are made from physiological or physiologically related materials, they are well tolerated in living systems. The solid matrix protects loaded labile substance against degradation and they offer the possibility of controlled drug release and drug targeting (Eradel et al., 2009). Compared to the polymer microparticles, SLMs have the advantage of better biocompatibility, which minimizes the hazards of acute and chronic toxicity; they possess solid cores which reduces the mobility of incorporated drug and drug leakage from the carriers. Therefore, SLMs combine the advantages of many colloidal carriers and also overcome some of their disadvantages (Long et al., 2006). They can be produced on a large industrial scale and allow the control of drug release. SLMs also appear promising as drug carrier systems for topical applications. Occlusion properties as a result of film formation on the skin which can enhance the penetration of drugs through the stratum corneum have been reported (EL- Kamel et al., 2007). They also have the ability to mask the taste of some drugs (Milak et al., 2006).

SOLID LIPID NANOPARTICLES (SLNs)

SLNs were developed in the 1990s as an alternative carrier system to the existing traditional carriers, such as emulsions, liposomes and polymeric nanoparticles (Attama et al., 2012). They are a comparatively stable colloidal carrier system in which melted lipid is dispersed in an aqueous surfactant by high-pressure homogenization or micro-emulsification (Müller et al., 2000). They are generally made up of a solid hydrophobic core containing the drug dissolved or dispersed. SLNs exhibit certain potential advantages over polymeric nanoparticles. They are safely taken up by brain and exhibit the least toxicity due to the biodegradable nature of the carrier lipid (Mohammed et al., 2012; Blasi et al., 2007; Kaur et al., 2000). Smaller size (around 10 to 200 nm) and narrow size range (100 to 200 nm) allows them to

cross tight endothelial cells of the blood-brain barrier, escape from the reticuloendothelial system (RES), and bypass the liver (Attama et al., 2012). They have comparatively higher drug entrapment efficiency, render the drug more stable in their lipid matrix, and provide a controlled release. Their production can be scaled up with excellent reproducibility. Surface coating of SLNs with hydrophilic polymers or surfactants, such as poly ethylene glycol (PEG) minimizes their uptake in liver cells and results in improved bioavailability.

Stearic acid–PEG 2000 has been used for their stearic stabilization, whereas the use of complex lipids (mono-, di-, triglycerides of different chain lengths) results in an increased loading efficiency (Pignatello et al., 2013; Mohammed et al., 2012; Blasi et al., 2007; Wissing et al., 2004; Kaur et al., 2000). Also cationic lipid based SLN have been produced for the delivery of proteins and antigens (Cortesi et al., 2013; Vighi et al., 2013). Several anticancer agents have been encapsulated in lipid nanoparticles, and there *in vitro* and *in vivo* efficacy has been evaluated by suitable studies (Attama et al., 2012). SLNs have been shown to improve the efficacy and residence time of cytotoxic drugs with concomitant reduction in the side-effects associated with them (Shenoy et al., 2005). Various drugs such as antipsychotics, anti-Parkinson, anti-ischemic and antibiotics have been encapsulated in lipid nanoparticles with the aim to either modify the biodistribution or for brain targeting (Müller and Keck, 2004; Mohammed et al., 2012).

SLNs can be administered orally as dispersion, SLNs-based tablets, pellets or capsules (Mehnert and Mäder, 2001) or even as lyophilized unit dose powders for reconstitution for oral delivery (Attama et al., 2012). They can easily be nebulized to form an aerosol of liquid droplets containing nanoparticles for inhalation (Almeida and Souto, 2007). For ocularly administered SLNs, increased bioavailability in rabbits has been observed (Cavalli et al., 2002) using tobramycin ion pair as the model drug. Lipid nanoparticles can be incorporated into creams, hydrogel or ointment to obtain semisolid systems for dermal applications. Another possibility is to increase the amount of lipid matrix in the formulation above a critical concentration, resulting in semisolid formulations (Attama et al., 2012). Due to the adhesiveness of small particles, SLNs adhere to the stratum corneum forming a film and these films have been shown to possess occlusive properties (Pardeike et al., 2009).

The use of lipid nanocarriers provides a suitable way for the nasal delivery of antigenic molecules. In this sense, the design of optimized vaccine nanocarriers offers a promising way for nasal mucosal vaccination (Almeida and Souto, 2007). Lipid nanoparticles have been extensively studied for the delivery of proteins and peptides (Almeida and Souto, 2007). For intravenous administration, the small particle size is a prerequisite as passage through the needle and possibility of embolism should be considered. SLNs offer the opportunity of controlled drug release and the possibility to incorporate poorly soluble drugs (Attama et al., 2012).

Demerits of SLNs

1. SLNs dispersions often undergo unpredictable gelation tendency, particle size growth, poor drug loading and relatively high water content (70 to 99.9%) (Soumya et al., 2012).
2. Formation of perfect crystalline structure during storage: Triglycerides crystallize in different polymorphic forms such as α, γ, β', and β- forms. Recrystallization from the melt results in the metastable α-polymorph which subsequently undergoes a polymorphic transition into the stable β-form via a metastable intermediate. The β-polymorph especially consists of a highly ordered, rigid structure with low loading capacity of drugs. Transition to the β-form via a metastable intermediate form leads to drug expulsion and inability to protect or prolong the release of the encapsulated drug (Attama et al., 2012).
3. Gel formation: The change in morphology of lipid nanoparticles from spheres to platelets is responsible for the gelation of solid lipid nanoparticle dispersions (Attama et al., 2012).

NANOSTRUCTURED LIPID CARRIERS (NLC)

NLC are colloidal carriers characterized by a solid lipid core consisting of a mixture of solid and liquid lipids, and having a mean particle size in the nanometer range (Attama et al., 2012). They consist of a lipid matrix with a special nanostructure (Attama et al., 2012; Ravani et al., 2013). This nanostructure improves drug loading and firmly retains the drug during storage. NLC system minimizes some problems associated with SLNs such as low payload for some drugs; drug expulsion on storage and high water content of SLNs dispersions. The conventional method for the production of NLC involves mixing of spatially very different lipid molecules, that is blending solid lipids with liquid lipids (oils). The resulting matrix of the lipid particles shows a melting point depression compared with the original solid lipid but the matrix is still solid at body temperature. Depending on the method of production and the composition of the lipid blend, different types of NLC are obtained (Attama et al., 2012).

The three types of NLC include: The imperfect type, amorphous type and multiple type (Dilip et al., 2003). Drug loading in SLNs is limited due to the formation of the lipid crystal. Drug expulsion is caused by an ongoing crystallization process towards a perfect crystal. Thus, by avoiding crystallization, drug loading is improved and this problem is resolved in the amorphous NLC (Dilip et al.,

2003). The multiple NLC is an oil-in solid lipid-in-water dispersion; the solid lipid matrix contains small liquid oil nano compartments. This NLC type uses the fact that for a number of drugs, the solubility in oils is higher than their solubility in solid lipids (Dilip et al., 2003).

LIPID DRUG CONJUGATES (LDC)

Lipid drug conjugates were developed especially for the hydrophilic drug molecules, wherein an insoluble drug–lipid conjugate bulk is synthetically prepared either by salt formation (for example, with a fatty acid) or by covalent linking (for example, to the esters or ethers). Lipid drug conjugates bulk is then homogenized in the presence of a stabilizer in water using high pressure homogenization (Mohammed et al., 2012). A major problem of SLNs is the low capacity of loading hydrophilic drugs due to partitioning effects during the production process. In order to overcome this limitation, LDC nanoparticles with drug loading capacities of up to 30% have been developed. Such matrices may have potential application in brain targeting of hydrophilic drugs in serious protozoal infections (Müller and Lucks, 1996; Patidar et al., 2010).

EMULSION BASED SYSTEMS

Dry emulsions

Dry emulsions are lipid based powder formulations from which an o/w emulsion can be reconstituted *in vivo* or *in vitro* (Haritha et al., 2013). They are prepared by drying liquid o/w emulsions containing a solid carrier in the aqueous phase. Dry emulsions are of interest because of their stability and sustained release effect. They present a potential oral drug delivery system for lipophilic, sparingly soluble drugs and for drugs that are light sensitive (Corveleyn and Remon, 1998a) or undergo oxidation (Corveleyn and Remon, 1998b). They are prepared using the drug, solid carrier (gelatin, lactose, maltodextrin, mannitol, povidone, sucrose and colloidal silica), aqueous phase and lipophilic solvent. Dry emulsions can be prepared by spray drying, lyophilization and rotary evaporation (Haritha et al., 2013). The solid carrier may undergo partial or complete transformation into an amorphous state. Since the amorphous carrier exhibits a strong tendency to crystallize at a particular elevated temperature and relative humidity, physical stability problems may arise. To avoid stability problems water soluble polymers like hydroxyl propyl methyl cellulose, methyl cellulose and povidone are used as solid carriers. Lipidic solvents like fractionated coconut oil, Miglyol 812, Capmul MCML – 8, sesame oil, lecithin and almond oil can be used for the formulation of dry emulsion (Haritha et al., 2013).

Microemulsions

Microemulsions are defined as isotropic dispersions of oil and water, stabilized by an interfacial film of a surfactant and usually combined with a cosurfactant such as a polyhydroxy compound, a medium-chain alcohol or an another surfactant (Boonme et al., 2011). They are of interest as carriers for many drugs such as dibucaine, lidocaine, tetracaine and their hydrochloride salts (Junyaprasert et al., 2007a, 2008) and clindamycin phosphate (Junyaprasert et al., 2008). In addition, they are of interest as cosmetic and cosmeceutical vehicles for skin, personal and hair products (Boonme et al., 2011). Microemulsions are widely used due to their several advantages that is, aesthetic appearance, thermodynamic stability, high solubilization power, ease of preparation and scale up (Junyaprasert et al., 2007b; Souto et al., 2011).

Nanoemulsions

Nanoemulsions are emulsions with droplet size below 1 µ but usually between 20 and 200 nm (Ochekpe et al., 2009). Unlike microemulsions which are white in colour due to their light scattering ability, nanoemulsions whose nanosize is often smaller than visible wavelength are transparent (Solans et al., 2007; Santos-Magalhães et al., 2000). Nanoemulsions are biodegradable, biocompatible, easy to produce and used as carriers for lipophilic drugs which are prone to hydrolysis. They are employed as a sustained release delivery system for depot formation via subcutaneous injection (Santos-Magalhães et al., 2000). They enhance gastrointestinal absorption and reduce inter- and intra-subject variability for various drugs. Due to their very large interfacial area, they exhibit excellent drug release profile (Chiesa et al., 2008). Nanoemulsions have been studied and developed for parenteral, oral, ocular, pulmonary and dermal deliveries (Solans et al., 2007; Lai et al., 2013a). Stability against sedimentation is attained based on the nano size of their droplets because the sedimentation rate due to gravity is less than Brownian movement and diffusion (Solans et al., 2007). Unlike microemulsions, nanoemulsions are metastable and can be destabilized by Ostwald ripening. Some factors that affects the stability of nanoemulsions and should be controlled include selecting an appropriate composition, controlling the order of addition of components, applying the shear in a manner that will effectively rupture the droplets, and ensuring that the dispersed phase molecules are insoluble in the continuous phase so that Ostwald ripening does not occur rapidly (Solans et al., 2007).

Self emulsifying formulations (SEFs)

Self emulsifying drug delivery systems (SEDDS) are

isotropic mixtures of oil, surfactant, co-surfactant and the drug substance which emulsify under gentle agitation similar to what would be encountered in gastro intestinal (GI) tract and are referred to as the self-emulsifying formulation (SEF) (Jyoti et al., 2012; Khan et al., 2012). Upon mixing with water the system has an ability to form fine colloidal droplets with very high surface area. In many cases, this accelerates the digestion of the lipid formulation, improves absorption, and reduces food effect and inter-subject variability (Chudasama et al., 2011). Self emulsifying formulations distribute readily in the GI tract, the digestive motility of the stomach and the intestines provides sufficient agitation enough for the spontaneous formation of emulsions. In the case of sparingly soluble drugs that exhibit dissolution rate limited absorption, the SEDDS system offers a way to improve the rate and extent of oral absorption and to produce more reproducible blood-time profiles (Jingling et al., 2006).

SEDDS are believed to be superior compared with lipid solutions due to the presence of surfactants in the formulations leading to a more uniform and reproducible bioavailability (Chudasama et al., 2011). Advantages of SEDDS include more consistent drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, protection of drug(s) from the gut environment, control of delivery profiles, reduced variability including food effects, enhanced oral bioavailability enabling reduction in dose and high drug loading efficiency (Sachan et al., 2010). Self emulsifying formulations spread readily in the gastrointestinal tract (GIT), and the digestive motility of the stomach and intestine provide the agitation necessary for self emulsification. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. Some marketed SEDDs formulations are shown in Table 1.

SEDDSs typically produce emulsions with turbid appearance, and droplet size between 200 nm to 5 µm while self micro emulsifying drug delivery systems (SMEDDSs) form translucent micro-emulsions with droplet size of less than 200 nm. However, self nano emulsifying drug delivery systems (SNEDDS) produces clear or transparent emulsion with droplets size less than 100 nm (Jyoti et al., 2012; Balakumar et al., 2013). When compared with emulsions, which are sensitive and metastable dispersed forms, SEFs are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles (Patel et al., 2008).SEFs have been transformed into solid dosage forms using techniques such as melt granulation, where the lipid excipient acts as a binder and solid granules are produced on cooling. Solvents or supercritical fluids can be used with semisolid excipients, which are solubilized and then the solvent evaporated to produce a waxy powder. Spraying techniques can be used to produce powder form formulations. These techniques enable the production of granules or powders that can then be compressed into a tablet form or filled into capsules. In all cases, the lipid excipients used must be semi-solid at room temperature (Rajan and Nirav 2011).

Pickering emulsions

Pickering emulsions or solids-stabilized emulsions (Figure 2) are emulsions solely stabilized by solid particles, in contrast to conventional molecular surfactants (Salari, 2011). This emulsion was named after Pickering who described the phenomenon in 1907 (Pickering, 1907), however, there has been no significant interest in this field until 1990 (Salari, 2011). Pickering stabilization regained new interest by the works of Velev et al. (1996a, b) and Velev and Nagayama, (1997) who demonstrated its potential for microencapsulation and the development of advanced materials in general (Salari, 2011). However, Lee and Weitz (2008) and Bon et al. (2007) in the last decade realized the synthesis of capsules from Pickering emulsion with a precise control of size, permeability and mechanical properties (Salari, 2011). Pickering emulsions are lipid-based emulsions with internal nanostructures stabilized by solid particles such as silica, clays, calcium carbonate, titanium dioxide, latex and many others (Soumya et al., 2012). Solid particles added will bind to the surface of the interface and prevent the droplets from coalescing thus making emulsion more stable. The skin absorption of caffeine from silica stabilized Pickering emulsion was three fold higher than emulsifier stabilized emulsion and this was attributed to the higher adhesion potential of Pickering emulsions (Frelichowska et al., 2009; Soumya et al., 2012)

SOLID LIPID TABLETS

Solid lipid tablets have recently been produced by molding (Chime et al., 2013c; Umeyor et al., 2012b). In this method, lipids like triglycerides and phosphoglycerides are utilized. The drug is dissolved or dispersed in the lipid matrix and tablets are produced by molding using tablet mold. Gentamicin tablets have been produced by this method using lipid matrix based on solidified reverse micellar solutions consisting of phospholipid and triglycerides (Umeyor et al., 2012b) and the results show that solidified reverse micellar solution (SRMS)-based tablets containing gentamicin were successfully prepared by fusion melt-solidification method which is simple, reproducible, scalable and cheap (Umeyor et al., 2012b). SRMS-based tablets could be an

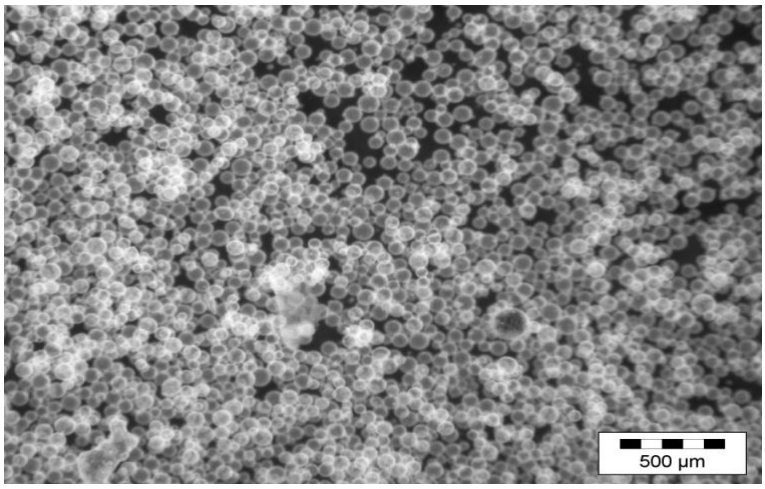

Figure 2. Light microscopy images of inverse Pickering emulsion droplets with a NaCl-concentration of 625 mM. Source: Salari (2011).

Table 1. Examples of marketed pharmaceutical products formulated as SEDDs*.

Brand name	Generic name	Dosage form	Manufacturer
Agenerase®	Amprenavir	Soft gelatin capsule	Glaxosmithkline
Solufen®	Ibuprofen	Hard gelatin capsule	Sanofi- Aventis
lipirex®	Fenofibrate	Hard gelatin capsule	Sanofi- Aventis
Neoral®	Cyclosprorine	Soft gelatin capsule	Novartis
Norvir®	Ritonavir	Soft gelatin capsule	Abbott laboratories
Fortovase®	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche Inc.

Source: *Rajan and Nirav (2011).

alternative to the conventional parenteral dosage form of gentamicin (Umeyor et al., 2012b). Some non-steroidal anti-inflammatory drugs (NSAIDs) based on SRMS have also been produced (Chime et al., 2013c). Diclofenac potassium (Figure 3) and indomethacin solid lipid tablets have been produced and results showed that the tablets had sustained release properties for once daily administration in addition to ulcer inhibition potentials. Diclofenac potassium tablets based on SRMS showed good hardness and friability profiles, sustained release properties and possessed good anti-inflammatory and anti-nociceptive/analgesic effects. The formulations also exhibited good gastro-protective properties, as it inhibited the ulcerogenic potentials of diclofenac potassium by about 85% (Chime et al., 2013c). The *in vitro* release profile of diclofenac potassium tablet based on SRMS was comparable to the release profile of a market brand, coated diclofenac potassium. Advantages of lipid based tablets include: low cost of ingredients, low cost of technologies (equipment and labour requirement for the production of lipid dosage forms are minimal, unlike the conventional tablets) and improved oral bioavailability and and reduced side effects of drugs (Chime et al., 2013c).

VESICULAR SYSTEMS

Liposomes

Liposomes were discovered in 1965 by Bangham et al. and consist of one or more concentric lipid bilayers which enclose an internal aqueous volume(s) (Saurabh et al., 2012). They are microscopic (unilamellar or multilamellar) vesicles that are formed as a result of self-assembly of phospholipids in an aqueous medium resulting in closed bilayered structures (Figure 4) (Bangham and Horne, 1964; Ravi et al., 2011). The assembly into closed bi-layered structures is a spontaneous process and usually needs some input of energy in the form of physical agitation, sonication or heat (Saurabh et al., 2012). There are a number of components present in liposomes, with phospholipid and cholesterol being the main ingredients. The type of phospholipids includes phosphoglycerides and sphingolipids, and together with their hydrolysis products (Kanika, 2012). These amphiphilic phospholipid molecules form a closed bilayer sphere, shielding the hydrophobic groups from the aqueous environment, while maintaining contact with the aqueous phase through the hydrophilic head groups (Makino and Shibata, 2006;

Figure 3. Diclofenac potassium tablets formulated with lipid matrix ratio 1:1 (Softisan® 154: Phospholipon® 90H).
Source: Chime et al. (2013c).

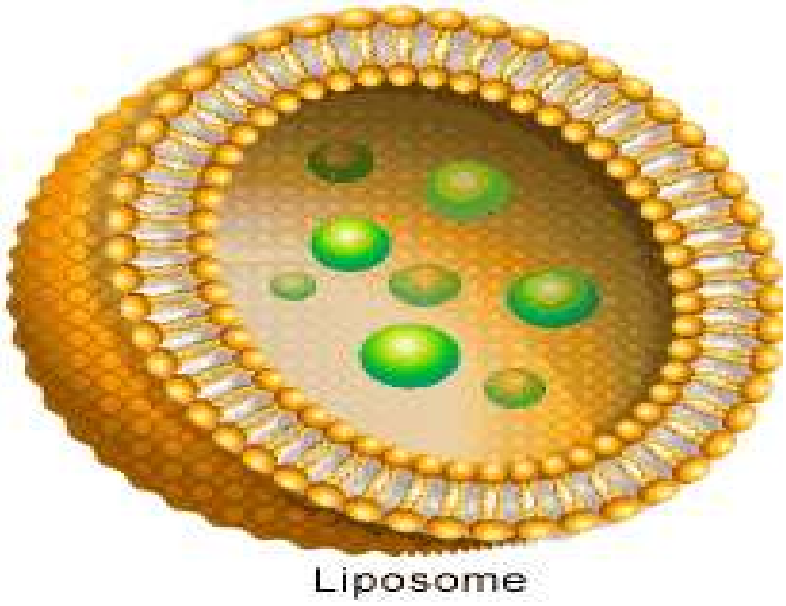

Figure 4. Schematic representation of a liposome. Source: My Vision Test (2009).

Semete et al., 2012). Liposomes are classified into three basic types based on their size and number of bilayers. Multilamellar vesicles (MLVs) consist of several lipid bilayers separated from one another by aqueous spaces. These entities are heterogeneous in size, often ranging from a few hundred to thousands of nanometers in diameter. On the other hand, both small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs) consist of a single bilayer surrounding the entrapped aqueous space. SUVs are less than 100 nm in size whereas LUVs have diameters larger than 100 nm (Lasic and Papahadjopoulos, 1998; New et al., 2003). The

predominant physical and chemical properties of a liposome are based on the net properties of the constituent phospholipids, including permeability, charge density and stearic hindrance. Drug loading into liposomes can be achieved through:

1. Liposome formation in an aqueous solution saturated with soluble drug.
2. The use of organic solvents and solvent exchange mechanisms.
3. The use of lipophilic drugs.
4. pH gradient methods (Malam et al., 2009).

Liposomes can be used for oral, ocular, pulmonary and transdermal delivery of drugs. Anti-tumor and antimicrobial agents, chelating agents, peptide hormones, enzymes, other proteins, vaccines and genetic materials have been incorporated into the aqueous or lipid phases of liposomes. Liposomes have evolved from mere experimental tools of research to industrially manufactured products for clinical and veterinary use (My Vision Test, 2012; Anuhya, 2012). Liposomes have been widely reported to be used for drug delivery and drug targeting (Kanika, 2012; Nastruzzi et al., 2000; Welz et al., 2000; Mader et al., 2000). It has also been reported by Allison and Gregonadis, (1974) and Alving and Richards (1990) to be used as immunological adjuvants in vaccination.

Liposomes as a potential delivery system for the oral administration of insulin have been extensively studied (Chono et al., 2009; Mengmeng et al., 2011). Liposomes with a specifically modified design, that is long-circulating and especially actively targeting liposomes, stand a better chance in becoming truly tumoritropic carriers of photosensitizers, and hence have been used successfully in photodynamic therapy (Kanika, 2012). Liposomes have also been used for drug delivery to the brain (Lai et al., 2013b). Anti-malarial drugs such as chloroquine, quinine, primaquine, artesunate, artemether, arteether and very recently, a combination of artemisinin and curcumin have been encapsulated in neutral conventional or long-circulating liposomes using different preparation techniques (Madden et al., 1990; Arica et al., 1995; Cullis et al., 1997; Bayomi et al., 1998; Stensrud et al., 2000; Chimanuka et al., 2002; Gabriels and Plaizier-Vercammen, 2003; Sharma et al., 2010; Isacchi et al., 2012). Some market brands of liposome formulations are shown in Table 2.

Advantages of liposome (Saurabh et al., 2012; Ravi et al., 2011)

1. Liposomes supply both lipophilic environment and aqueous “milieu interne” in the system and are therefore suitable for delivery of hydrophobic, amphipathic and hydrophilic drugs.
2. Liposomes could encapsulate not only small molecules but also macromolecules like superoxide dismutase, hemoglobin, erythropoietin, interleukin-2 and interferon-g.
3. Reduce exposure of sensitive tissues to toxic drugs.
4. Alter the pharmacokinetic and pharmacodynamic property of drugs (reduced elimination and increased circulation life time).
5. Liposomes may increase the solubility of insoluble drugs between one hundred to ten thousand fold.
6. In the small intestine, liposomes are digested in the presence of bile and enzymes. The solubilized compound is liberated and further solubilized in bile and digested lipids.
7. They provide ideal models for biological membranes as well as efficient carriers for drugs, diagnostics, vaccines, nutrients and other bioactive agents.

Disadvantages (Ravi et al., 2011)

1. Low stability
2. Leakage and fusion of encapsulated drug molecules.
3. Sometimes phospholipid undergoes oxidation and hydrolysis
4. Short half-life
5. Low solubility
6. High production cost.

PRO-LIPOSOMES

Pro-liposomes (PLs) are alternative forms to conventional liposomal formulation composed of water soluble porous powder as a carrier, phospholipids and drugs dissolved in organic solvent. Lipid and drug are coated onto a soluble carrier to form free-flowing granular material (Kim, 1993). They show controlled release, better stability, ease of handling and increased solubility (Saurabh et al., 2012). For liposomes to enter the market, they must be stable during the storage period and remain intact before reaching their targeted tissues to produce action. Various approaches have been used to overcome these problems, some of which include, control of particle size and lamellarity, altering the lipid composition, lyophilization and electrosteric stabilization (Jessy, 2003; Yadav et al., 2011). One such approach which helped overcome the stability issue associated with liposome and led to the development of a new drug delivery system is the pro-liposomes (PLs). Discovered by Payne et al. (1986), they are dry, free-flowing granular products composed of drug(s) and phospholipid(s) which, upon addition of water, disperse to form a multi-lamellar liposomal suspension. It is one of the most cost-effective and widely used methods for producing commercial liposome products. It is based upon the intrinsic property of hydrated membrane lipids to form vesicles on contact with water. Being available in dry powder form, they are easy to distribute, transfer, measure and store, making it a versatile system (Janga et al., 2012). Liposomes can either be formed *in vivo* under the influence of physiological

Table 2. Marketed formulation of Liposome.

Brand name	Active constituent	Manufacturer
Intelectol®	Vinpocetine	Menory Secret Inc., USA
Efudex®	N3-o-toluyl-Fluorouracil	Valeant Pharma. Intl, USA
Amphocil®	Amphotericin B	Sequus Pharmaceuticals, Inc., C.A
Abelcet®	Amphotericin B	Liposome Company NJ,USA
MiKasome®	Amikacin	NeXstar Pharmceuticals, Inc., Co
Ambisome®	Amphotericin B	NeXstar Pharmceuticals, Inc., Co
DaunoXome®	Daunorubicin	NeXstar Pharmceuticals, Inc., Co
ELA-MAX®	Lidocaine	Biozone Labs, CA, USA
Epaxel®	Hepatitis A Vaccine	Swiss SerumInstitute, Switzerland
Lipofen®	Fenofibrate	Kowa Pharma Inc., USA
DC99®	Doxorubicin	Liposome Company NJ, USA
Doxil®	Doxorubicin	Sequus Pharmaceuticals, Inc., C.A
Ambisome®	Amphotericin B	Astellas Pharma Inc., USA

Source: Ravi et al. (2011) and Sharma et al. (2010).

fluids or can be formed *in vitro* prior to administration using a suitable hydrating fluid. The liposomes formed on reconstitution are similar to conventional liposomes and more uniform in size (Janga et al., 2012). Some of the commonly used methods employed in the preparation of PLs include film deposition on carrier method, spray drying method and fluidized bed method (Jessy, 2003).

SPHINGOSOMES

Sphingosomes may be defined as concentric, bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic sphingolipid (Ravi et al., 2011). This was developed in order to circumvent the instability often seen in liposomes. Hydrolysis is avoided by use of lipids which contain ether or amide linkage instead of ester linkage (such are found in sphingolipid) or phospholipid derivatives with the 2- ester linkage replaced by carbomoyloxy function. Hence, sphingosomes are stable liposomes formulated with sphingolipid in order to avoid aggregation or leakage of content in liposomes due to chemical degradation such as oxidation and hydrolysis of their phospholipid content (Ravi et al., 2011).

Sphingosomes could be administered by oral, pulmonary, dermal and parenteral route of administration such as intravenous, intramuscular, subcutaneous, and intra-arterial. Marketed sphingosomes include Margibo®, Oncovin®, which are vincristine marketed by Eli Lilly Company and Vinorelbine (Navelbine®) by GlaskosmithKline (Saurabh et al., 2012; Ravi et al., 2011). Advantages of sphingosomes include increased stability, reduction in toxicity of the encapsulated drug, improve pharmacokinetic effect (increase circulation time), flexibility to couple with site specific ligand to achieve active targeting, provide selective passive targeting to tumor tissue and increased efficacy and therapeutic index (Saurabh et al., 2012). The limitations are higher cost of preparation and low entrapment efficacy (Biju et al., 2006).

NIOSOMES

Niosomes are vesicles composed mainly of non-ionic bilayer forming surfactants (Figure 5) (Attama et al., 2012; Uchegbu and Vyas, 1998). They are structurally analogous to liposomes, but the synthetic surfactants used have advantages over phospholipids in that they are significantly less costly and have higher chemical stability than their naturally occurring phospholipid counterparts (Attama et al., 2012; Conacher et al., 2000). Niosomes are obtained on hydration of synthetic non-ionic surfactants, with or without incorporation of cholesterol or other lipids. Niosomes are similar to liposomes in functionality and also increase the bioavailability of the drug and reduce its clearance like liposomes. Niosomes can also be used to target drugs to some specific sites of the body, similar to liposomes. As with liposomes, the properties of the niosomes depend both on the composition of the bilayer and the method of production. Antigen and small molecules have also been delivered using niosomes (Lakshmi et al., 2007). However, niosomes are preferred over liposomes because it exhi-bits high chemical stability and economy than liposomes. One of the reasons for preparing niosomes is the assumed higher chemical stability of the surfactants than that of phospholipids, which are used in the preparation of liposomes. The anti glaucoma dermal formulation dorzolamide

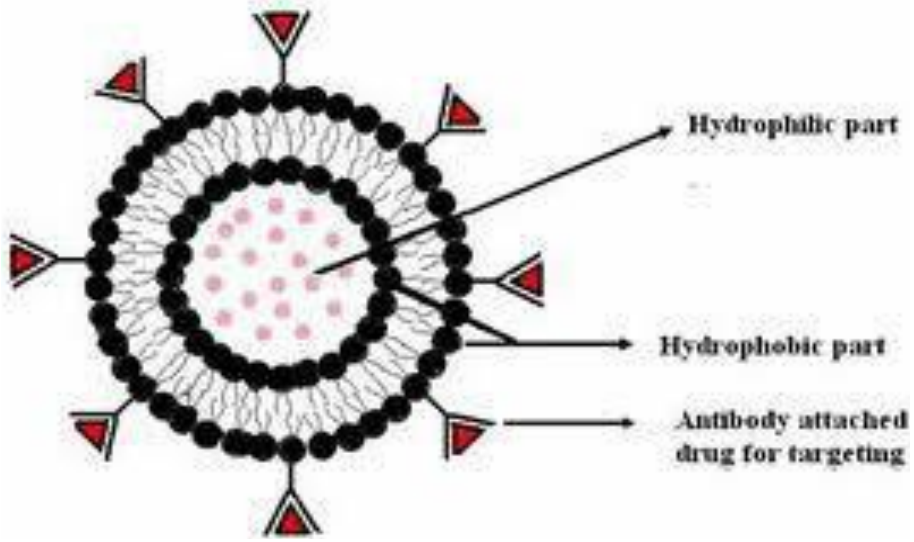

Figure 5. Diagrammatic representation of Niosomes.
Source: Chiranjeevi et al. (2013).

and acetazolamide (Dorzox®) dermal formulations of niosomes are marketed by Cipla. However, the limitations of niosomes as a delivery system include: physical instability during storage due to vesicles aggregations, fusion and leaking which may lead to hydrolysis of encapsulated drugs which affects the shelf life of the dispersion (Saurabh et al., 2012).

PHARMACOSOMES

Pharmacosomes are the colloidal dispersions of drugs covalently bonded to lipids. As the system is formed by linking a drug (pharmakon) to a carrier (soma), they are termed as “pharmacosomes” (Chiranjeevi et al., 2013). Depending upon the chemical structure of the drug–lipid complex they may exist as ultrafine vesicular, micellar, or hexagonal aggregates. They are an effective tool to achieve desired therapeutic goals such as drug targeting and controlled release. The criterion for the development of the vesicular pharmacosome is dependent on surface and bulk interactions of lipids with drug. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH_2, etc.) could be esterified to the lipid, with or without spacer chain that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer in the organism (Jitendra and Praful, 2012). The prodrug conjoins hydrophilic and lipophilic properties, thus acquires amphiphilc characters, and therefore found to reduce interfacial tension, and at higher concentrations exhibits mesomorphic behavior (Pandita and Sharma, 2013; Kumar and Arnab, 2012; Jitendra and Praful, 2012; Kavitha et al., 2010; Semalty et al., 2010; Kaur and Kanwar, 2002).

Advantages of pharmacosomes include: they are suitable for both hydrophilic and lipophilic drugs, high and predetermined entrapment efficiency as drug and carrier are covalently linked together, no need of removing the free un-entrapped drug from the formulation which is required in case of liposomes, drug is covalently bonded, membrane fluidity has no effect on release rate of drugs, depends upon the phase-transition temperature of the drug-lipid complex, there is no drug leakage as the drug is covalently linked to the carrier and the possibility of drug targeting (Jitendra and Praful, 2012). Limitations however include: covalent bonding is needed to protect the leakage of drugs. pharmacosomes, on storage, undergo fusion and aggregation, as well chemical hydrolysis (Jitendra and Praful, 2012). Synthesis of a compound depends upon its amphiphilic nature and require surface and bulk interaction of lipids with drugs (Jitendra and Praful, 2012).

TRANSFERSOMES

Transfersome technology was developed with the intention of providing a vehicle to allow delivery of bioactive molecule through the dermal barrier (Attama et al., 2012). Transfersomes (Figure 6) are essentially ultra-deformable liposomes, composed of phospholipids and additional edge active amphiphiles such as bile salts that enable extreme distortion of the vesicle shape. The vesicle diameter is in the order of 100 nm when dispersed in buffer (Cevc et al., 1998). These flexible vesicles are thought to permeate intact through the intact dermis under the

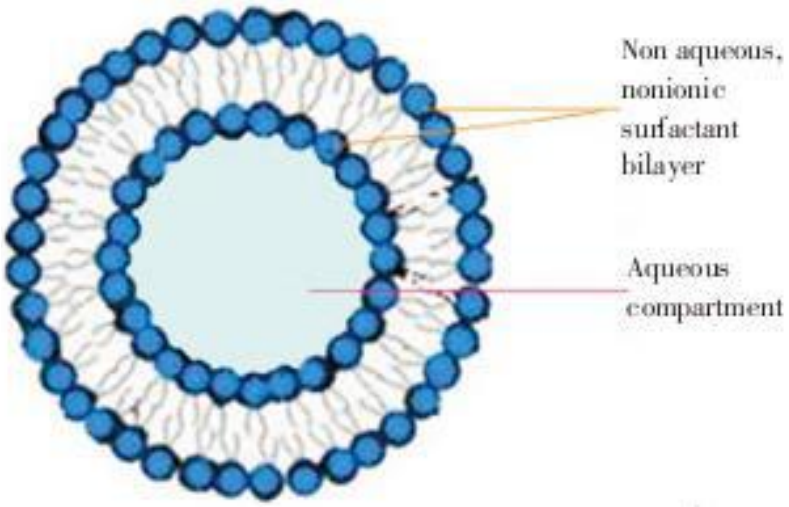

Figure 6. Structure of transfersomes.
Source: Chiranjeevi et al. (2013).

forces of the hydrostatic gradient that exists in the skin (Cevc et al., 2002). Drug or antigen may be incorporated into these vesicles in a manner similar to liposomes (Attama et al., 2012). Transfersomes were developed in order to take the advantage of phospholipids vesicles as transdermal drug carrier. These self-optimized aggregates, with the ultra flexible membrane, are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency (Walve et al., 2011). These vesicular transfersomes are several orders of magnitudes more elastic than the standard liposomes and thus well suited for the skin penetration. The flexibility of transfersomes membrane minimizes the risk of complete vesicle rupture in the skin and allows transfersomes to follow the natural water gradient across the epidermis, when applied under non-occlusive condition (Walve et al., 2011).

Transfersomes possess structures consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. They can act as a carrier for low as well as high molecular weight drugs for example, analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin (Jain et al., 1998). They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes. They have high entrapment efficiency, in case of lipophilic drug up to 90%. They protect the encapsulated drug from metabolic degradation. They act as depot, releasing their contents slowly and gradually. They can be used for both systemic as well as topical delivery of drugs and easy to scale up (Jain et al., 1998). However, it has the disadvantages of being chemically unstable because of their predisposition to oxidative degradation. It is expensive to formulate and purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles (Walve et al., 2011; Jain et al., 1998).

Phytosomes/herbosomes

Phytosomes, also referred to as herbosomes are cell like structures which result from the stoichiometric reaction of the phospholipids (phosphatidylcholine, phosphatidylserine etc.) with the standardized extract or polyphenolic constituents in a non-polar solvent, which are better absorbed than conventional herbal extracts (More et al., 2012). Most of the phospholipids possess nutritional properties, like phosphatidylserine which acts as a brain cell nutrient, phosphatidylcholine is also important in liver cell regeneration. Soya phospholipids have lipid reducing effect with hydrogenated phospholipids serving as basis for preparation of stable liposomes. Because of their amphiphilic properties, herbosomal formulations enhance the bioavailability of active phytochemical constituents as they are readily permeable and cross the lipid rich biomembranes easily (More et al., 2012). The active components of the herbal extracts are well protected from destruction by digestive secretions and gut bacteria. Herbosomes have gained importance in various fields like pharmaceuticals, cosmeceuticals and nutraceuticals in preparing different formulations such as solutions, emulsions, creams, lotions, gels, etc. Several companies involved in production and marketing of herbosomal products are Indena, Jamieson natural resources, Thorne Research, Natural factors, and Natures herb (Singha et

al., 2011). The phytosome process has been applied to many popular herbal extracts including *Ginkgo biloba*, grape seed, hawthorn, olive fruits and leaves, green tea, ginseng, kushenin, marsupsin and curcumin. Increased bioavailability of the phytosomes over the simpler, non-complexed plant extract has been demonstrated by pharmacokinetics and activity studied in animals and humans (More et al., 2012; Shalini and Ram, 2011).

Comparatively, phytosomes are formed when phosphatidylcholine and the individual plant compound form a 1:1 or 2:1 complex depending on the substance (Figure 7), while in liposomes, hundreds and thousands of phosphatidylcholine molecules surround the water soluble molecule. Also, phytosomes have active chemical constituents anchored through chemical bonds to the polar head of the phospholipids, while in liposomes the active principle is dissolved in the medium of the cavity or in the layers of the membrane without chemical bonds formation (More et al., 2012; Shalini and Ram, 2011).

ETHOSOMES

Ethosomes are soft vesicles made of phospholipids, ethanol (in higher quantity) and water. The size range of ethosomes may vary from tens of nanometers to microns (µ) (Akiladevi and Sachinandan, 2010). Ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux in comparison to conventional liposomes (Akiladevi and Sachinandan, 2010; Touitou, 1996). Although, the exact mechanism for better permeation into deeper skin layers from ethosomes is still not clear. The synergistic effects of combination of phospholipids and high concentration of ethanol in vesicular formulations have been suggested to be responsible for deeper distribution and penetration in the skin lipid bilayers. They are composed mainly of phospholipids, (phosphatidylcholine, phosphatidylserine, phosphatitidic acid), high concentration of ethanol and water. The high concentration of ethanol makes the ethosomes unique. The ethanol in ethosomes causes disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicle's ability to penetrate the stratum corneum. Also, because of their high ethanol concentration, the lipid membrane is packed less tightly than conventional vesicles but has equivalent stability, allowing a more malleable structure and improves drug distribution ability in stratum corneum lipids (Akiladevi and Sachinandan, 2010).

Ethosomes are mainly used for the delivery of drugs through transdermal route. The main factor which limits the application of transdermal route for drug delivery is the permeation of drugs through the skin. Human skin has selective permeability for drugs. Unlike liposomes, that are known mainly to deliver drugs to the outer layers of skin, ethosomes can enhance permeation through the stratum corneum barrier (RRC, 1990; Touitou et al., 1998; Asbill et al., 1990). Ethosomes can entrap drug molecule with various physicochemical characteristics that is, of hydrophilic, lipophilic, or amphiphilic. Ethosomal drug delivery is non-invasive and delivers the drug to the deep skin layers or the systemic circulation (Akiladevi and Sachinandan, 2010).

Advantages of ethosomal drug delivery (Akiladevi and Sachinandan, 2010; Patel, 2007)

In comparison to other transdermal and dermal delivery systems:

1. The ethosomal system is passive, non-invasive and is available for immediate commercialization.
2. Ethosomal drug delivery system can be applied widely in pharmaceutical, veterinary and cosmetic fields.
3. Simple method for drug delivery in comparison to iontophoresis, phonophoresis and other complicated methods.
4. Enhanced permeation of drug through the skin for transdermal drug delivery.
5. Delivery of large molecules (peptides, protein molecules) is possible.
6. It contains non-toxic raw material in formulation.
7. High patient compliance.

STEALTH LIPOSOMES

Stealth liposomes, also known as immune-liposomes or cryptosomes are liposomes that evade detection in an immune system. Stealth liposomes or cryptosomes are designed to circulate for longer periods of time *in vivo*, but they are different from "long-circulating liposomes" (Kanika, 2012; Mayank et al., 2012). Stealth liposomes use polyethylene glycol (PEG) as a steric stabilizer. The properties of the stealth liposome depend on the way PEG is linked to the lipids (Figure 8). It is important to note that stealth liposomes are not fully inert vesicles; they can eventually become detected by the immune system. It could be used for slow release of drug or for imaging purposes (Kanika, 2012; Mayank et al., 2012). Incorporation of polymers, such as polyethylene glycol-lipid derivatives, or glycolipids into liposomes results in sterically stabilized liposomes which have several advantages over liposome formulations traditionally used in the past, including reduced recognition and uptake by macrophages, extended circulation half-lives, targeted drug delivery (Li et al., 2009), dose-independent pharmacokinetics, and increased uptake *in vivo* by solid tumors (Chen et al., 2011), breast cancer (Mayank et al., 2012; Li et al., 2011).

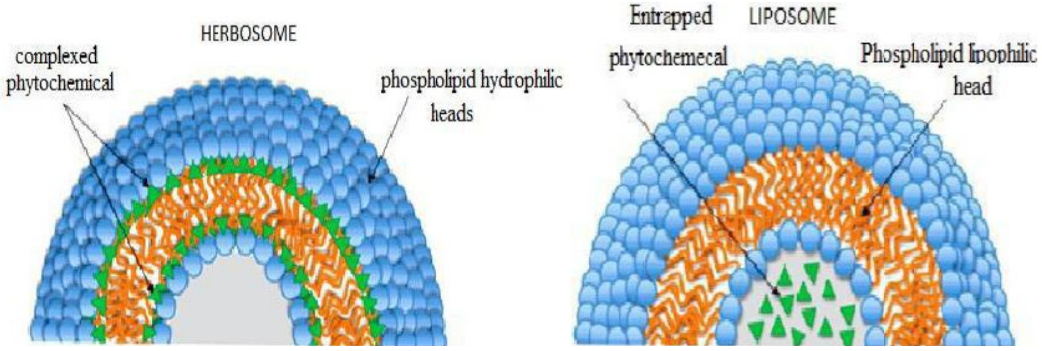

Figure 7. Comparison between herbosomes and liposomes.
Source: Singha et al. (2011) and Shalini and Ram (2011).

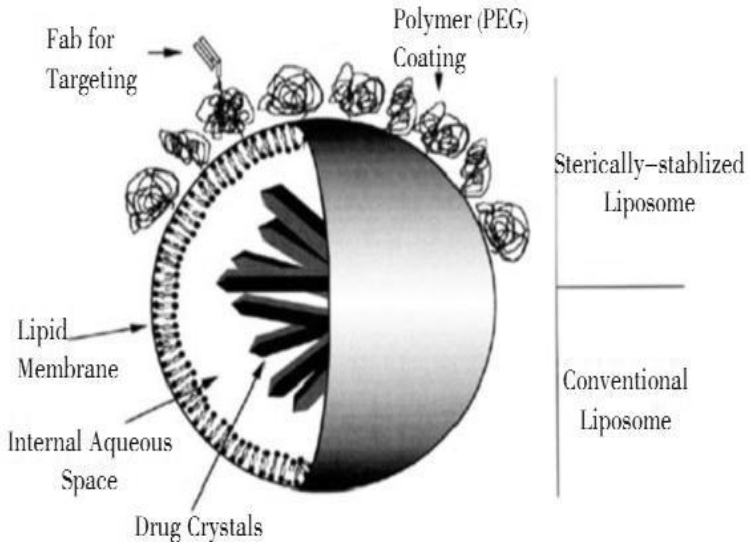

Figure 8. Stealth liposomes.
Source: Kanika (2012).

COLLOIDOSOMES

Colloidosomes are microcapsules whose shell consists of densely packed colloidal particles. Their physical properties such as permeability, mechanical strength, and biocompatibility can be precisely controlled through the proper choice of colloids and preparation conditions for their assembly (Daeyeon and David, 2008). The high degree of control over their physical properties makes colloidosomes attractive structures for encapsulation and controlled release of materials ranging from fragrances and active ingredients to molecules produced by living cells (Daeyeon and David, 2008). Colloidosomes are hollow, elastic shells whose permeability and elasticity can be controlled. It is a novel class of microcapsules whose shell consists of coagulated or fused colloidal particles at interface of emulsion droplet (Parthibarajan et al., 2011). Colloidosomes can be classified based on: (i) method of formulation technique into emulsion based colloidosomes which include: Water-in-oil emulsion based colloidosomes, oil-in-water emulsion based colloidsomes and water-oil-water emulsion based colloidosomes. (ii) Based on nature of colloids they can be classified into: Aqueous or oily gel core colloidosomes, hairy colloidosomes, nano particle colloidosomes, layer by layer colloidosomes and non-spherical colloidosomes (Parthibarajan et al., 2011).

Colloidosomes can be fabricated as rigid porous super structures to enhance the viability of the cells. They may also be used for the following range of therapeutic and pharmaceutical applications: Drug/protein delivery carrier, controlled and sustained drug release, for enhanced drug solubilization, in tumor therapy, antimicrobial, antifungal, antiviral, could be used in cosmetics and dermatology,

ocular drug delivery, brain delivery, DNA delivery and in enzyme immobilization (Parthibarajan et al., 2011). However, a major problem in the colloidosome manufacture is the poor yield of particles. If the shell locking is inefficient, the colloidosomes simply coalesce and fall apart on transfer into water; a large proportion of the colloidosomes are normally lost during the transfer from organic to water medium (Parthibarajan et al., 2011).

ULTRASOMES

Ultrasomes are specialized liposomes encapsulating an endonuclease enzyme extracted from *Micrococcus luteus*. Endonuclease recognizes ultra violet (UV) damage and is reported to accelerate its repair four-folds (Pang et al., 2007). Ultrasomes also protect the immune system by repairing UV-DNA damage and reducing the expression of tumor necrosis factor (TNF-α), interleukins (IL-1, IL-6 and IL-8) (Pang et al., 2007). They stimulate the production of melanin by melanocytes in the tanning response following UV exposure and are used in cosmeceuticals and anti-aging formulations (Bhumika and Arvind, 2012).

PHOTOSOMES

These are artificial spherical submicroscopic vesicles with diameter between 25 and 5000 nm. Photosomes are composed of amphiphilic molecules with core that consists of an aqueous cavity, which is encapsulated by one or more bimolecular phospholipid sheets separated from each other by aqueous layers (Chiranjeevi et al., 2013). Photosomes contain the enzyme photolysase encapsulated in a liposome structure and are incorporated in sun-care product to protect the sun-exposed skin by releasing a photo-reactivating enzyme extracted from a marine plant, *Anacystis nidulans* (Bhumika and Arvind, 2012). This enzyme can be activated by light and can work during the day to support the skin deoxyribonucleic acid (DNA) repair process.

Combined with ultrasomes, they constitute the "intelligent" DNA repair system (Bhumika and Arvind, 2012) and are the most widely used in cosmetic delivery systems (Chiranjeevi et al., 2013) and photodynamic therapy (Ravi et al., 2011; Kanika, 2012).

LAYEROSOMES

The layerosomes are conventional liposomes coated with one or multiple layers of biocompatible polyelectrolytes in order to stabilize their structure. The formulation strategy is based on an alternative coating procedure of positive poly-lysine (pLL) and negative poly-glutamic acid (pGA) polypeptides on initially charged small unilamellar liposomes. This surface modification stabilizes the structure of the liposomes, yielding a stable drug delivery system. Oral administration and incorporation in biomaterials are the potential fields of application (Saurabh et al., 2012).

EMULSOMES

Emulsomes are a new generation of colloidal carrier systems in which internal core is made of fats and triglycerides which is stabilized by high concentration of lecithin in the form of o/w emulsion. Emulsomes have the characteristics of both liposomes and emulsions (Dinesh et al., 2012). The solidified or semi-solidified internal oil core provides a better opportunity to load lipophilic drugs in high concentrations. Simultaneously, a prolonged controlled release can also be expected and the ability to encapsulate water-soluble medicaments in the aqueous compartments of surrounding phospholipid layers (Gupta et al., 2007). The solvent free and surfactant free emulsomes technology have demonstrated high drug encapsulation capacity for water insoluble antifungal (Pal et al., 2012) and anticancer drugs showing enhanced drug delivery and improved preclinical efficacy for parenteral routes. An example of the successful application of emulsomes technology is the development of an injectable ready-to-use emulsome-based formulation for the antifungal agent amphotericin B (Gupta and Vyas, 2007). Emulsomes have enhanced bioavailability, reduced toxicity and improved pharmacological activity (Dinesh et al., 2012).

GENOSOMES

Genosomes are complex of genetic material like DNA and suitable lipid. They are also known as lipoplexes that are used to deliver genes (Dinesh et al., 2012). They are artificial macromolecular complexes for functional gene transfer. Cationic lipids are most suitable for this delivery system because they possess high biodegradability and stability in the blood stream (Ravi et al., 2011; Kanika, 2012). Mostly DNA-cationic liposome complexes were used to translocate DNA across cellular membranes *in vivo*, because interaction between DNA-lipid membranes has proved crucial to the understanding of the colloidal state of the genosomes. These DNA lipid complexes could be later aggregated into higher order assemblies, creating stacked lipid-DNA multilayers, for generating more protection (Dinesh et al., 2012).

VIROSOMES

Virosomes are reconstituted viral envelopes, including membrane lipids and viral spike glycoproteins, but devoid of viral genetic material. Influenza virus is most commonly used for virosome production (Sanjib and

Bhaskar, 2011). Virosomal technology has been successfully applied for many years in vaccines delivery (Pevion, 2013). They are spherical, unilamellar vesicles with a mean diameter of 150 nm (Figure 9). Essentially, they represent reconstituted empty influenza virus envelopes, devoid of the nucleocapsid including the genetic material of the source virus. Virosomes are not able to replicate but are pure fusion-active vesicles. In contrast to liposomes, virosomes contain functional viral envelope glycoproteins: influenza virus hemagglutinin (HA) and neuraminidase (NA) intercalated in the phospholipid bilayer membrane. Further characteristics of virosomes depend on the choice of bilayer components (Pevion, 2013).

The virosome can be optimized for a maximum incorporation of the drug or the best physiological effect by modifying the content or type of lipids in the mem-brane. Depending on whether positively or negatively loaded phospholipids are implemented, it is even possi-ble to generate carriers for antisense-oligonucleotides or other genetic molecules. On the surface of the virosomes, various ligands like cytokines, peptides and monoclonal antibodies can be adopted. Even tumor-specific monoclonal antibody fragments (Fab) can be linked to virosomes for targeting the carrier to selected tumor cells. For the targeted delivery of the encapsulated drugs, virosomes selectively bind through binding mole-cules (for example, Fab fragments and ligands) to the target cell. The patient's non-diseased tissues are not affected. Virosomal HA triggers receptor-mediated uptake of the virosome into an endosome in the target cell. The endolysosomal pathway protects the drug from degradation since the drugs are transported directly into the cytosol of the cell. This characteristic trait of viro-somes is especially desirable for cancer therapies, which often have severe side effects because of the toxicity of the agents. The incorporated pharmaceutically active substances are protected from active substances and low pH, which might degrade or hamper them into the endosome before they reach the cytosol. This is a major advantage of the virosomal carrier system and is clearly distinct from other liposomal and proteoliposomal carrier systems (Pevion, 2013).

Virosomes represent an innovative, broadly applicable carrier system with various prospective applications for the treatment and prevention of cancer, neurodegenerative disorders and infectious diseases. Various pharmaceutically active substances like antibiotics, cytostatics, nucleic acids, fungicides and antigens can be encapsulated into the virosomal carrier. Even the surface of virosomes can be readily modified (Pevion, 2013).

Advantages of virosomal drug delivery (Sanjib and Bhaskar, 2011)

1. Virosomal technology is approved by the Food and Drug Administration (FDA) for use in humans, and has a high safety profile.
2. Virosomes are biodegradable, biocompatible, and non-toxic.
3. They have no disease-transmission risk and no auto immunogenity or anaphylaxis
4. Broadly applicable with almost all important drugs (anticancer drugs, proteins, peptides, nucleic acids, antibiotics, fungicides).
5. Promotes fusion activity in the endolysosomal pathway.
6. Protects drugs against degradation.
7. Enables drug delivery into the cytoplasm of target cell.

VESOSOMES

Vesosomes are multicompartment structures which has distinct inner compartments separated from the external membrane (Figure 10) (Soumya et al., 2012). Each compartment of vesosome can encapsulate different materials and have different bilayer composition. Vesosome could entrap both colloidal particles and biological macromolecules relatively efficiently (Soumya et al., 2012; Kisak et al., 2004). While small molecules are released from unilamellar liposomes in minutes, they are retained in vesosomes from hours to days, even though the liposomes and vesosomes have the same bilayer composition and size (Müller and Lucks, 1996; Kisak et al., 2004). Vesosomes are formed by adding ethanol to a variety of saturated phospholipids. At temperatures below the gel-liquid crystalline transition, Tm, the interdigitated lipid-ethanol sheets are rigid and flat; when the temperature is raised above Tm, the sheets become flexible and close on themselves and the surrounding solution to form closed compartments.

During this closure, the sheets can entrap other vesicles, biological macromolecules, or colloidal particles. The result is efficient and spontaneous encapsulation without disruption of even fragile materials to form biomimetic nano-environments for possible use in drug delivery, colloidal stabilization, or as microreactors. The vesosome structure can take full advantage of the 40 years of progress in liposome development including steric stabilization, pH loading of drugs, and intrinsic biocompatibility. However, the multiple compartments of the vesosome give better protection to the interior contents in serum, leading to extended release of model compounds in comparison to unilamellar liposomes (Kisak et al., 2004). The properties of vesosomes enable localized drug delivery to specific parts of the body and also extend the duration of drug effect.

ARCHAEOSOMES

Archaeosomes constitute a novel family of liposomes

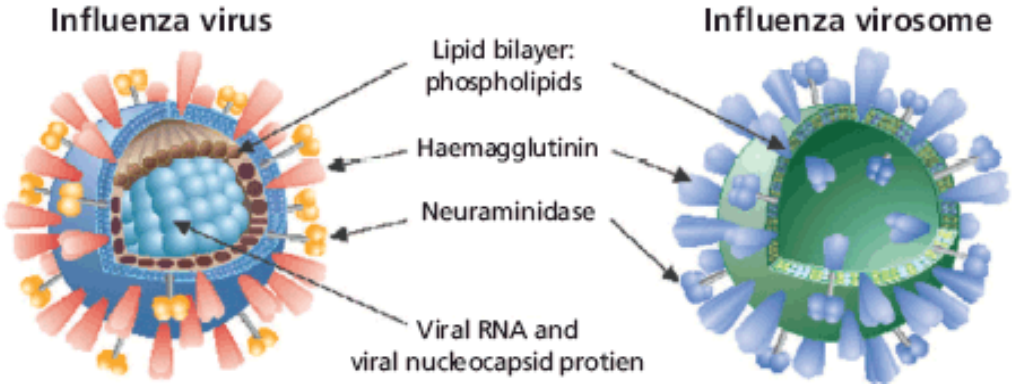

Figure 9. Virosomes encapsulating drug.
Source: Sanjib and Bhaskar (2011).

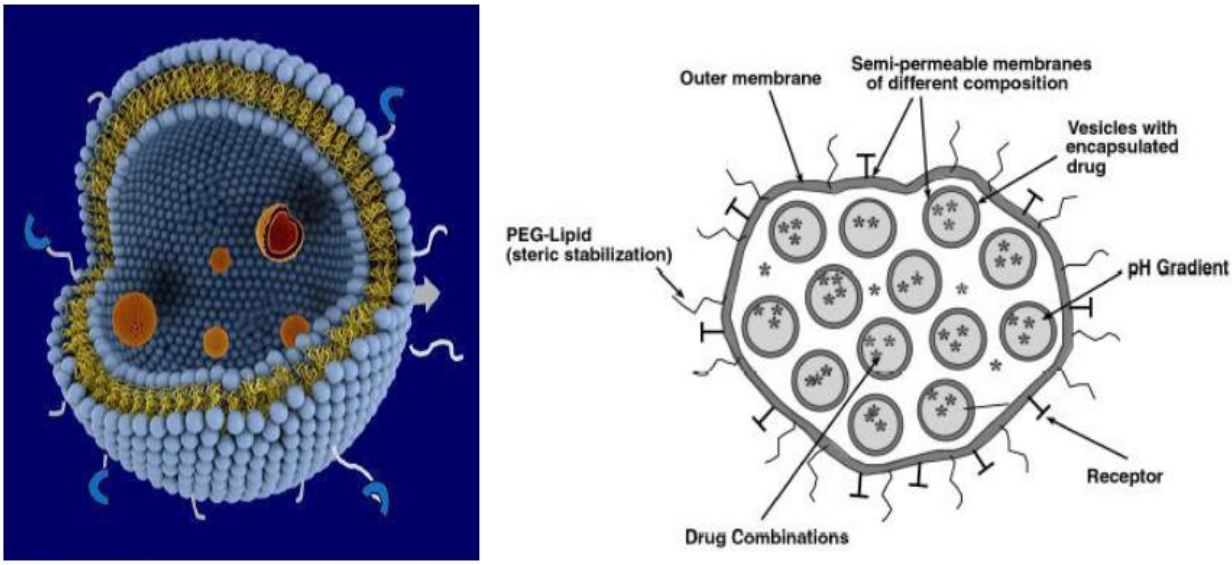

Figure 10. Structure of vesosomes.
Source: Soumya et al. (2012) and Asadujjaman and Mishuk (2013).

made with one or more of the fully saturated bipolar tetra ether lipids, which exerts a higher stability in comparison with conventional lipids to several conditions such as high temperature, alkaline or acidic pH, and presence of phospholipases, bile salts and serum media (Asadujjaman and Mishuk et al., 2013; Benvegnu et al., 2005). They are nano-sized vesicles prepared from total polar lipids either extracted from the selected genera and species of the Archaea domain or synthetic archaeal lipids (Soumya et al., 2012). Archaeal-type lipids consist of archaeol (diether) and/or caldarchaeol (tetraether) core structures wherein regularly branched and usually fully saturated phytanyl chains (20 to 40 carbons in lengths) are attached via ether bonds to the 2,3 carbons of the glycerol backbone (Soumya et al., 2012). They have remarkable structural differences from liposomes which include: the archaeosomes surface is highly entropic, possessing half the surface tension than that of liposomes and its permeability to protons and sodium ion is nearly one third of that determined for liposomes; the inclusion of macrocyclic archaeols and caldarchaeols further impairs archaeosomes permeability to water and small solutes (Soumya et al., 2012; Mathai et al., 2001). Incorporation of polyethylene glycol and coenzyme Q10 into archaeosomes has been found to alter the tissue distribution profiles of intravenously administered vesicles. Also, intravenous and oral delivery of nanometric-sized archaeosomes to an animal model was well tolerated with no apparent toxicity (Omri et al., 2000, 2003; Soumya et al., 2012).

UFASOMES

Unsaturated fatty acid vesicles (ufasomes) are suspensions of closed lipid bilayers that are composed of fatty acids, and their ionized species (soap) which are restricted to narrow pH range from 7 to 9. In ufasomes, fatty acid molecules are oriented in such a way that their hydrocarbon tails are directed toward the membrane interior and the carboxyl groups are in contact with water (Patel et al., 2011). The formation of ufasomes is believed to occur due to associative interaction in mixtures of fully ionized and unionized fatty acids at pH > 7.0 (Dinesh et al., 2012). In ufasomes, fatty acid molecules are oriented in such a way that their hydrocarbon tails are directed toward the membrane interior and the carboxyl groups are in contact with water. Stability of ufasomes depends on proper selection of fatty acid, amount of cholesterol, buffer, pH range, amount of lipoxygenase, and the presence of divalent cations (Dinesh et al., 2012). Recent innovations can provide opportunity to formulate ufasomes with tailorable features such as extension of pH range, insensitivity toward divalent cations, and enhanced stability (Patel et al., 2011). Ufasomes have potential as carriers for the oral administration of poorly absorbable drugs as well as for the horizontal transfer of genes from plants (Murakami et al., 1986; Fukui et al., 1986; Naik and Dixit, 2008) and have more stabilized membrane than liposomes (Dinesh et al., 2012; Saurabh et al., 2012).

DISCOMES

Discomes are non-ionic surface active agents based discoidal vesicles; they are niosomes solubilized with non ionic surfactant solutions (polyoxyethylene cetyl ether class) and are used for ligand mediated drug targeting (Saurabh et al., 2012; Kanika, 2012).

ENZYMOSOMES

Enzymosomes are liposomal systems designed to provide a mini bio-environment in which enzymes are covalently immobilized and/or coupled to the surface of liposomes. They are used to target drugs to tumor cell (Saurabh et al., 2012; Kanika, 2012). Enzymes on complex with lipids generate enzymosomes. Preservation of enzyme activity and preservation of vesicles structural integrity are two desirable features from enzymosomes (Dinesh et al., 2012).

CARBOHYDROSOMES

Chemically, carbohydrosome is methyl-2, 3-di-o-lauroyl-*β*-D-ribose-5 phosphocholine (DLRPC). They are novel vesicular 3-dimensional structures formed from zwitterionic, cationic, or anionic carbohydrate-based lipids (Dinesh et al., 2012). These molecules self assemble into liposome-like structures in an aqueous solution. These supramolecular structures are called carbohydrosome because these are carbohydrate analogues of glycerol based liposomes. In carbohydrosome, glycerol back bone is replaced by ribose. Alteration of conventional glycerol backbone by complete substitution provides new opportunity for assessing supramolecular structure formation and attaching macromolecules or ligands for biological targeting. The phase transition temperature (Tm) is 16°C higher than conventional liposome (DLPC). This increase in Tm indicates more efficient packing of bilayer below the Tm. Carbohydrosomes is superior to glycerol-based liposomes because they possess: a larger backbone that increase in the spacing between head and tail, an increase in hydrophobicity, and a decrease in backbone flexibility (Dinesh et al., 2012). Current modifications for conventional liposomes are limited to the hydrophobic tails and hydrophilic head groups but the carbohydrosomes can be modified at the ribose backbone (Dinesh et al., 2012).

MARINOSOMES

Marinosomes are liposomes based on a natural marine lipid extract containing high ratio of polyunsaturated fatty acids (PUFA) like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Dinesh et al., 2012), which are not present in normal skin epidermis. They are metabolized by skin epidermal enzymes into anti-inflammatory and anti-proliferative metabolites that are beneficial in treating inflammatory skin disorders (Soumya et al., 2012). However, the preventing effect of marinosomes was highly dependent on the lipid concentration used and the liposome mean diameter (Dinesh et al., 2012). Active and passive loading of drug, as well as complex structural rearrangements directly depends on transmembrane pH gradient (Cansell et al., 2001). All these results allowed considering marinosomes as potential candidates for cosmeceutical and oral PUFA supplements in view of the prevention and treatment of deficiencies (Dinesh et al., 2012; Cansell et al., 2003; Nacka et al., 2001; Patravale and Mandawgade, 2008).

ESCHERIOSOMES

These are lipoidal vesicles, prepared from polar lipids extracted from *Escherichia coli* (Dinesh et al., 2012). Majorly phosphatidyl ethanolamine, cardiolipin, and phosphatidyl glycerol are classes of phospholipid, present in *E. coli* (Dinesh et al., 2012; De Siervo, 1965).

E. coli contains an altered fatty acid and phospholipid composition when grown in the presence of sub-lethal concentrations of a variety of organic solvents and food additives (Ingram, 1977). But during progression from exponential growth phase to the stationary growth phase, the phospholipid composition of the cell is altered. Unsaturated fatty acids are converted to cyclopropane fatty acids, and phosphatidyl glycerol appears to be converted to cardiolipin (Cronan, 1968; Dinesh et al., 2012). Also, ethanol has been found to decrease the level of lipids in *E. coli* (Buttke and Ingram, 1977). These novel fusogenic liposomes have strong tendency to fuse with the plasma membrane of target cells and thereby deliver the entrapped contents into their cytosol (Ahmad et al., 2006).

Escheriosomes are helpful in controlling intracellular pathogens by expression of particular enzymes (Singha et al., 2008). Escheriosomes-encapsulated antigen elicit strong humoral immune response in immunized animals, in general, escheriosomes are considered as potential candidate vaccine carrier system capable of eliciting both cell-mediated as well as humoral immune responses (Syed et al., 2003). Escheriosome-based delivery helps for generating protective immunity against *C. albicans* infection (Chauhan et al., 2011), induce protective immune responses against experimental murine brucellosis (Mallick et al., 2007), developing vaccine against leishmaniasis as well as other intracellular infections (Sharma et al., 2006; Dinesh et al., 2012).

SUBTILOSOMES

Subtilosomes are prepared from phospholipids isolated from *Bacillus subtilis* (Dinesh et al., 2012; Deeba et al., 2005). They are novel potential carrier system used in drug delivery. Cardiolipin and phosphatidyl glycerol are abundant in *B. subtilis*. Research into this novel area as drug delivery carrier has been going on (Dinesh et al., 2012; Deeba et al., 2005).

Cubosomes

Cubosomes are nanoparticles whose size ranges from 10 to 500 nm in diameter (Figure 11). They appear like dots square shaped, slightly spherical (Faisal et al., 2009; Madhurilatha et al., 2011). Cubosomes are discrete, submicron, nanostructured particles of bicontinuous cubic liquid crystalline phase (Deepak and Dharmesh, 2011). These nanostructured particles of a liquid crystalline phase with cubic crystallographic symmetry are liquid instead of solid (Deepak and Dharmesh, 2011). Cubosomes are typically produced by high-energy dispersion of bulk cubic phase, followed by colloidal stabilization using polymeric surfactants. After formation of the cubosomes, the dispersion is formulated into a product and then applied to a substrate of interest, usually body tissue (Norlen and Amoudi, 2004). Two main approaches are used to produce cubosome particles. The top-down approach applies high energy to fragment bulk cubic phase (Deepak and Dharmesh, 2011). The bottom-up approach forms cubosomes from molecular solution by, for example, dilution of an ethanol-monoolein solution (Spicer et al., 2001). Top-down or high-energy techniques require formation of cubosomes prior to their use in a product. Bottom-up techniques avoid high-energy drawbacks and allow formation of cubosomes in use by a consumer or during product formulation. Both techniques require a colloidal stabilizer, like the tri-block copolymer Poloxamer 407, to prevent cubosome aggregation (Landh, 1994).

Powdered cubosome precursors are powders composed of dehydrated surfactant coated with polymer; hydration of the precursor powders forms cubosomes with a mean particle size of 600 nm. Precursor forms of cubosomes are among the modification possible to overcome its difficulty in loading of drugs (Deepak and Dharmesh, 2011). Monoglyceride based cubosome dispersion can be proposed for topical use, such as for perctuneous or mucosal applications. Because of the microbicidal properties of monoglycerieds, this could be used to design intravaginal drug for the treatment of sexually transmitted diseases (Deepak and Dharmesh, 2011).

MISCELLANEOUS TYPES

Cochleates

Cochleates and nanocochleates are cigar like spiral rolls (Figure 12) formed of negatively charged phospholipid bilayers, which are rolled up through the interaction with multivalent counter ions (Ca^{2+} or Zn^{2+}) as bridging agents between the bilayers (Thiruganesh et al., 2009; Zarif et al., 2000). As a particulate system, cochleates possess unique properties like superior mechanical stability and better protection for encapsulated drugs compared with liposomes due to their solid matrix (Thiruganesh et al., 2009). Cochleates also maintain their phospholipid bilayer structures. These solid particles are so flexible that they can readily convert to liposomes by extracting the bridging counter ions out of the inter bilayer spaces. Such unique properties have made cochleates an ideal system for delivering insoluble ingredients which can be loaded in the matrix of a phospholipid bilayer while avoiding the instability problem of liposomes (Thiruganesh et al., 2009; Zarif et al., 2000). Cochleate delivery vehicles are stable phospholipid-cation precipitates composed of simple, naturally occurring materials (that is, phosphatidylserine and calcium). They have a unique multilayered

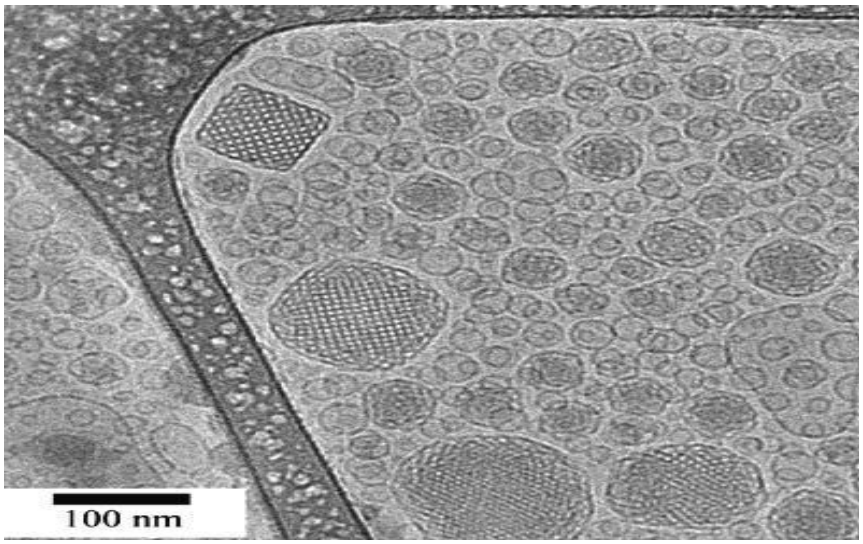

Figure 11. Structure of cubosomes.
Source: Deepak and Dharmesh (2011).

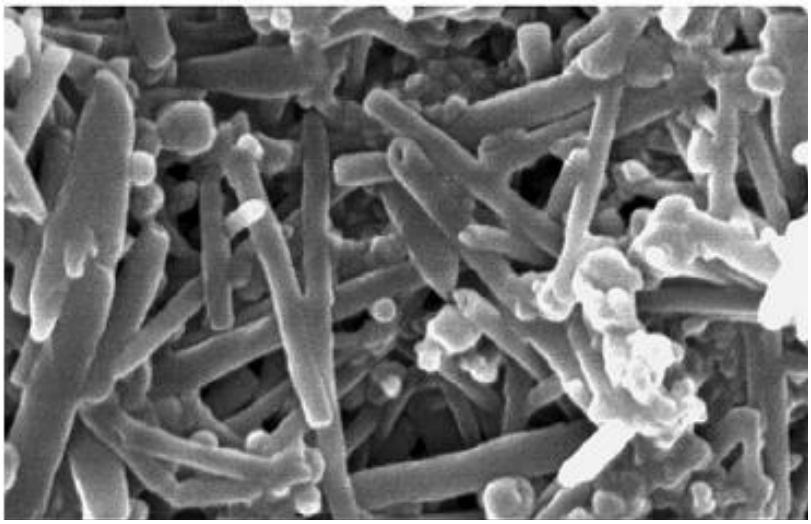

Figure 12. SEM images of cochleates.
Source: Thiruganesh et al. (2009).

structure consisting of alternating layers of calcium and phospholipid in large, continuous, solid, lipid bilayer sheets rolled up in a spiral or stacked, with little or no internal aqueous space. This structure provides protection from degradation for associated “encochleated” molecules (Thiruganesh et al., 2009).

Divalent cation concentrations *in vivo* in serum and mucosal secretions are such that the cochleate structure is maintained. Hence, the majority of cochleate-associated molecules are present in the inner layers of a solid, non-aqueous, stable, impermeable structure (Morishita and Peppas, 2006). Cochleates were discovered in 1975 by Dr. D. Papahadjoupoulos and coworkers, and have been used in the 80s and 90s to transport antigens and peptides for vaccine delivery. Nanocochleates were introduced in 1999 to develop smaller but more consistent particles. It was demonstrated that by using a binary phase system, such as two non miscible hydrogels, cochleates can be formed in such a way to display a small mean particle of less than 500 nm. These nanocochleates are highly suitable for the encapsulation of hydrophobic drugs (Mannino et al., 1998).

Cochleates were initially prepared in micrometer sizes either by direct addition of multivalent ion solution to liposome’s solution or by the dialysis method. However, the particle size could not be reduced to nanometer

range (Thiruganesh et al., 2009; Jin et al., 2000). In recent past, a new method named “hydrogel isolated cochleation” has been used to prepare nanometer-sized cochleates (Thiruganesh et al., 2009). Nanochocleates are stable, lipid based delivery formulations whose structure and properties are very different from liposomes. These unique structures provide protection from degradation for encochleated/encapsulated molecules. Because the entire cochleate structure is a series of solid layers, components within the interior of the cochleate structure remain intact (Thiruganesh et al., 2009).

ADVANTAGES OF NANOCOCHLEATE OVER OTHER DRUG CARRIER SYSTEMS (THIRUGANESH ET AL., 2009)

The advantages of cochleates are numerous. They are more stable because of the less oxidation of lipids. They can be stored by freeze drying, which provides the potential to be stored for long periods of time at room temperatures, which would be advantageous for worldwide shipping and storage prior to administration. They can maintain their structure even after lyophilization, whereas liposome structures are destroyed by lyophilization. They can exhibit efficient incorporation of hydrophobic drugs into the lipid bilayer of the cochleate structure. They can exhibit efficient incorporation of antigens with hydrophobic moieties into the lipid bilayer of the cochleate structure. They have the potential for slow release of a drug, antigen or biologically relevant molecules *in vivo* as cochleates dissociate. They have a lipid bilayer, which serves as a carrier and is composed of simple non toxic lipids which are found in animal and plant cell membranes. Cochleates are also easy to produce (Thiruganesh et al., 2009).

LIPID MICROTUBES

Microtubules are hollow and open ended tubules with a lumen diameter of approximately 0.5 µm and walls formed by one or more lipid bilayers (Price and Patchan, 1991; Nancy et al., 2011). They form spontaneously while passing through a phase transition temperature during a controlled cooling process. The chiral interactions between lipid molecules cause the bilayer to twist and form a tubular structure (Nancy et al., 2011). Since the chiral packing of the molecules is very structured, the walls are highly ordered, and release of agent from within lumen occurs via the two ends of each microtubule (Price and Patchan, 1991). Lipid microtubules have been shown to provide the sustained release of proteins such as transforming growth factor-β, tetracycline and 2-methoxynaphthalene (Price and Patchan, 1991; Spargo et al., 1995; Nancy et al., 2011). Other types of lipid drug delivery include the liquisol compacts (Sandip et al., 2012), lipobeads (Ashish et al., 2011), iscomes (Attama et al., 2012), leptosomes (Dinesh et al., 2012; Faisal et al., 2009) and solid dispersions (Mogal et al., 2012)

CONCLUSION

The application of lipids as vehicle for the delivery of drugs has revolutionarized drug delivery with some old drugs with very serious side effects being safe for use. Some anti-inflammatory drugs for example, indomethacin, (SLM, SEFs) have shown that indomethacin lipid formulations could be used with minimal gastro-intestinal irritation. Lipid drug delivery systems have advantages over polymer based systems which include enhanced drug absorption, reduce side effects, controlled drug release and site specific targeting. Most lipid formulations have high stability, high carrier capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration, including oral, topical, parenteral and pulmonary routes.

REFERENCES

Ahmad N, Deeba F, Faisal SM, Khan A, Agrewala JN, Dwivedi V, Owais M (2006). Role of fusogenic non-pc liposomes in elicitation of protective immune response against experimental murine salmonellosis. Biochimie 88(10):1391–1400.

Akiladevi D, Sachinandan B (2010). Ethosomes a noninvasive approach for transdermal drug delivery. Int. J. Curr. Pharm. Res. 2(4):1-4.

Allison AC, Gregonadis G (1974). Liposomes as immunological adjuvants. Nature p. 252.

Almeida AJ, Souto EB (2007). Solid lipid nanoparticles as a drug delivery system for peptides and proteins. Adv. Drug Deliv. Rev. 59:478-490.

Alving CR, Richards RL (1990). Liposomes containing lipid A: A potent non-toxic adjuvant for a human malaria sporozoite. Vaccine Immunol. Lett. 25: 275-279.

Amselem S, Alving CR, Domb AJ (1992). Polymeric biodegradable lipospheres as vaccine delivery system. Polym. Adv. Tech. 3:351-357.

Anuhya B (2012). Liposomes as potential carriers in drug delivery, gene delivery and preparation, formulation and evaluation of liposomes. J. Pharm. Res. 5(2):1210-1216.

Arica B, Ozer AY, Ercam MT, Hincal AA (1995). Characterization, *in vitro* and *in vivo* studies on primaquine diphosphate liposomes. J. Microencapsul. 12(5): 469-485.

Asadujjaman MD, Mishuk AU (2013). Novel approaches in lipid based drug delivery systems. J. Drug Del. Ther. 3(4):124-130.

Asbill CS, El-Kattan AF, Michniak B (2000). Enhancement of transdermal drug delivery-chemical and physical approaches. Crit. Rev. Therapeut. Drug Carrier Sys. 17:621.

Ashish KJ, Abhinav A, Govind PA (2011). Nanolipobeads based drug delivery system for effective management of peptic ulcer. Int. J. Curr. Pharm. Res. 3(2):141-149.

Attama AA, Momoh MA, Builders PF (2012). Lipid nanoparticulate drug delivery systems: a revolution in dosage form design and development, recent advances in novel drug carrier systems, A.D. Sezer (Ed.), InTech. DOI: 10.5772/50486, http://www.intechopen.com/books/recent-advances-in-novel-drug-carrier-systems/lipid-nanoparticulate-drug-delivery-systems-a-revolution-in-dosage-form-design-and-development.

Attama AA, Nkemnele MO (2005). *In vitro* evaluation of drug release from self micro-emulsifying drug delivery systems using a biodegradable homolipid from *Capra hircus*. Int. J. Pharm. 304–310.
Attama AA, Okafor CE, Builders PF, Okorie O (2009). Formulation and in vitro evaluation of a PEGylated microscopic lipospheres delivery system for ceftriaxone sodium. Drug Deliv. 16:448–616.
Aungst BJ, Saitoh H, Burcham DL, Huang SM, Mousa SA, Hussain MA (1996). Enhancement of the intestinal absorption of peptides and non-peptides. J. Control. Rel. 41:19–31.
Balakumar K, Raghavan CV, Selvan NT, Prasad RH, Abdu S (2013).Self nanoemulsifying drug delivery system (SNEDDS) of Rosuvastatin calcium: Design, formulation, bioavailability and pharmacokinetic evaluation.Colloids Surf. Biointer. 112:337-43.
Bangham AD, Horne RW (1964). Negative staining of phospholipids and their structural modification by surface active agents as observed in the electron microscope. J. Mol. Biol. 8:660-668.
Bayomi MA, Al-Angary AA, Al-Mashal AA, Al-Dardiri MM (1998). *In vivo* evaluation of arteether liposomes. Int. J. Pharm. 175:1-7.
Benvegnu T, Re´thore´ G, Brard M, Richter W, Plusquellec D (2005). Archaeosomes based on novel synthetic tetraether-type lipids for the development of oral delivery systems. Chem. Commun. 536-5538.
Bhumika S, Arvind S (2012). Future prospect of nanotechnology in development of anti-ageing formulation. Int. J. Pharm. Pharm. Sci. 4(3):57-66.
Biju SS, Talegaonkar S, Mishra PR (2006). Vesicular Systems: An overview. Indian J. Pharm. Sci. 68:141-153.
Blasi P, Giovagnoli S, Schoubben A, Ricci M, Rossi C (2007). Solid lipid nanoparticles for targeted brain drug delivery. Adv. Drug Del. Rev. 59:454-477.
Bogman K, Erne-Brand F, Alsenz J, Drewe J (2003). The role of surfactants in the reversal of active transport mediated by multidrug resistance proteins. J. Pharm. Sci. 92(6):1250–1261.
Bon SAF, Cauvin S, Colver PJ (2007). Colloidosomes as micron-sized polymerisation vessels to create supracolloidal interpenetrating polymer network reinforced capsules. Soft Matt. 3(2):194-199.
Boonme P, Maneenuan D, Wongpoowarak W (2011). Using algebraic geometry to describe boundaries of microemulsion regions in nonionic systems. J. App. Pharm. Sci. 1(3):57-61.
Buttke TM, Ingram LON (1978). Mechanism of ethanol-induced changes in lipid composition of *Escherichia coli*- inhibition of saturated fatty acid synthesis *in vivo*. Biochem. 17(4):637–644.
Cansell M, Moussaoui N, Lefrancois C (2001). Stability of marine lipid based-liposomes under acid conditions. Influence of xanthan gum. J. Liposome Res. 11(2-3):229–242.
Cansell M, Nacka F, Combe N (2003). Marine lipid-based liposomes increase *in vivo* FA bioavailability. Lipids. 38(5):551–559.
Cavalli R, Gasco MR, Chetoni P, Burgalassi S, Saettone MF (2002). Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. Int. J. Pharm. 238(1-2):241-245.
Cevc G, Gebauer D, Stieber J, Schatzlein A, Blume G (1998). Ultraflexible vesicles transfersomes, have an extremely low pore penetration resistance and transport therapeutic amounts of insulin across the intact mammalian skin. Biochim. Biophys. Acta 1368:201–215.
Cevc G, Schaltzlein A, Richardsen H (2002). Ultradeformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented, evidence from double label CLSM experiments and direct size measurements, Biochim. Biophys. Acta 1564:21–30.
Chauhan A, Swaleha Z, Ahmad N, Farazuddin M, Vasco A, Abida M, Mohammad O (2011). Escheriosome mediated cytosolic delivery of *Candida albicans* cytosolic proteins induces enhanced cytotoxic T lymphocyte response and protective immunity. Vaccine 29(33):5424–5433.
Chen M, Chen J, Hou T, Fang Y, Sun W, Hu R, Cai B (2011). Effect of phospholipid composition on pharmaceutical properties and anti-tumor activity of stealth liposomes containing brucine. Zhongguo Zhong Yao Za Zhi. 36(7):864-867.
Chiesa M, Garg J, Kang YT, Chen G (2008). Thermal conductivity and viscosity of water-in-oil nanoemulsions, Colloids Surf. A Physicochem. Eng. Asp. Doi:10.1016/j.colsurfa.2008.05.028.
Chimanuka B, Gabriels M, Detaeveriner MR, Plaizier-Vercammen JA (2002). Preparation of β-artemether liposomes, their HPLC-UV evaluation and relevance for clearing recrudescent parasitaemia in Plasmodium chabaudi malaria-infected mice. J. Pharm. Biomed. Anal. 28:13-22.
Chime SA, Attama AA, Builders PF, Onunkwo GC (2013a). Sustained release diclofenac potassium-loaded solid lipid microparticle, based on solidified reverse micellar solution (SRMS): *In vitro* and *in vivo* evaluation. J. Microencapsul. 30(4):335-45.
Chime SA, Attama AA, Kenechukwu FC, Umeyor EC, Onunkwo GC (2013c). Formulation, *in vitro* and *in vivo* Characterisation of Diclofenac Potassium Sustained Release Tablets Based on Solidified Reverse Micellar Solution (SRMS). Bri. J. Pharm. Res. 3(1):90-107.
Chime SA, Onyishi VI, Brown SA, Attama AA, Idogwu EC, Onunkwo GC (2013b). Diclofenac potassium–loaded dika fat solid lipid microparticles: *In vitro* and *in vivo* characterisation. Biol. Med. Rx. 1(3):227-234.
Chiranjeevi G, Muthukumaran M, Krishnamoorthy B (2013). A review on potency of vesicular systems in targeting drug delivery. Res. J. Pharm. Biol. Chem. Sci. 4(2):156-170.
Chono S, Fukuchi R, Seki T, Morimoto K (2009). Aerosolized liposomes with dipalmitoyl phosphatidylcholine enhance pulmonary insulin delivery. J. Con. Rel. 137(2):104-109.
Chudasama A, Patel V, Nivsarkar M, Vasu K, Shishoo C (2011). A novel lipid-based oral drug delivery system of nevirapine. Int. J. Pharm. Tech. Res. 3(2):1159-1168.
Cole ET, Cade D, Benameur H (2008). Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. Adv. Drug Deliv. Rev. 60:747-756.
Conacher M, Alexander J, Brewer JM (2000). Niosomes as immunological adjuvants, In: I. Uchegbu (ed.), Synthetic Surfactant Vesicles. Singapore International Publishers Distributors, pp. 185–205.
Cortesi R, Campioni M, Ravani L, Drechsler M, Pinotti M, Esposito E (2013). Cationic lipid nanosystems as carriers for nucleic acids. N Biotechnol. In press.
Corveleyn S, Remon JP (1998a). Formulation of a lyophilized dry emulsion tablet for the delivery of poorly soluble drugs. Int. J. Pharm.166:65–74.
Corveleyn S, Remon JP (1998b). Bioavailability of hydrochlorothiazide: conventional versus freeze-dried tablets. Int. J. Pharm. 173:149–155.
Cronan JE (1968). Phospholipid alterations during growth of *Escherichia coli*. J. Bact. 95(6):2054–2061.
Cullis PR, Hope MJ, Bally MB, Madden TD, Mayer LD, Fenske DB (1997). Influence of pH gradients on the transbilayer transport of drugs, lipids, peptides and metal ions into large unilamellar vesicles. BBA-Rev. Biomem. 1331:187-211.
Daeyeon L, David AW (2008). Double emulsion-templated nanoparticle colloidosomes with selective permeability. Adv. Mater. 20:3498–3503.
De Siervo AJ (1969). Alterations in the phospholipid composition of Escherichia coli B during growth at different temperatures. J. Bacteriol.100(3):1342–1349.
Deeba F, Tahseen HN, Sharad KS, Ahmad N, Akhtar S, Saleemuddi, M, Mohammad O (2005). Phospholipid diversity- correlation with membrane-membrane fusion events. Bioch. Biophys. Acta. 1669(2):170–181.
Deepak P and Dharmesh S (2011). Cubosomes: A Sustained Drug Delivery Carrier. Asian J. Res. Pharm. Sci. 1(3):59-62.
Dilip KP, Surendra T, Suresh KN, Roohi K (2003). Nanostructured lipid carrier (nlc) a modern approach for topical delivery: a review. World J. Pharm. Pharm. Sci. 2(3):921-938.
Dinesh K, Deepak S, Gurmeet S, Mankaran S, Mahendra SR (2012). Lipoidal soft hybrid biocarriers of supramolecular construction for drug delivery. Int. Sch. Res. Net. ISRN Pharm. DOI:10.5402/2012/474830.
Domb AJ, Maniar M (1996). Liposphere for controlled delivery of substances. Eurpean Patent EP0502119.
Domb AJ, Manier M (1990). Lipospheres for controlled delivery of pharmaceuticals, pesticides, fertilizer. Nova pharmaceutical

corporation 90-US6519 (9107171), 79:8-11.
Domb AJ, Bergelson L, Amselem S (1996). Lipospheres for controlled delivery of substances. In Benita S. (ed), microencapsulation: method and industrial applications. Marcel Dekker Inc. NY. 337- 410.
Domb AJ, Marlinsky A, Maniar M, Teomim L (1995). Insect repellant formulations of N.N diethyl- m- toluamide (DEET) in a liposphere system: Efficiency and skin uptake. J. Am. Mosqu. control Assoc. 11:29- 34.
EL- Kamel HA, AL-Fagih MI, Alsarra AI (2007). Testosterone solid lipid micro particles for transdermal drug delivery formulation and physicochemical characterization. J. Micro. 24(5):457-475.
Eradel MS, Gugor S, Ozsoy Y, Araman A (2009). Preparation and *in vitro* evaluation of indomethacin loaded solid lipid microparticles. Acta Pharm. Sci. 51:203- 210.
Elgart A, Cherniakov I, Aldouby Y, Domb AJ, Hoffman A (2012). Lipospheres and pro-nanolipospheres for delivery of poorly water soluble compounds. Chem. Phys. Lipids. 165(4):438-53.
Faisal SM, Yan W, McDonough SP, Chang CF, Pan MJ, Chang YF (2009). Leptosome-entrapped leptospiral antigens conferred significant higher levels of protection than those entrapped with PC-liposomes in a hamster model. Vaccine 27(47):6537–6545.
Fouad EA, El-badry M, Mahrous GM, Alsarra V, Alashbban Z, Alanazi FK (2011). *In vitro* investigation for embedding dextromethorphan in lipids using spray drying. Digest J. Nano. Biol. 6(3):1129-1139.
Frelichowska J, Bolzinger MA, Valour JP, Mouaziz H, Pelletier J, Chevalier Y (2009). Pickering w/o emulsions: drug release and topical delivery. Int. J. Pharm. 368:7-15.
Fukui H, Murakami M, Takada K, Muranishi S (1986). Combinative promotion effect of azone and fusogenic fatty acid on the large intestinal absorption in rat. Int. J. Pharm. 31(3):239–246.
Gabriels M, Plaizier-Vercammen JA (2003). Physical and Chemical evaluation of liposomes containing artesunate. J. Pharm. Biomed. Anal. 31:655-667.
Gelperina S, Kisich K, Iseman MD, Heifets L (2005). The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis. Amer. J. Resp. Cri. Care Med. 172:1487- 1490.
Gupta S, Dube A, Vyas SP (2007). Antileishmanial efficacy of amphotericin B bearing emulsomes against experimental visceral leishmaniasis. J. Drug Targ. 15(6):437–444.
Gupta S, Vyas SP (2007). Development and characterization of amphotericin B bearing emulsomes for passive and active macrophage targeting. J. Drug Targ. 15(3):206–217.
Haritha M, Priyanka M, Abeda A, Neeharika R, Kumar PB (2013). Dry emulsion: a promising dosage form to deliver lipophilic drug molecules with improved stability and effectiveness. Ind. J. Res. Pharm. Biotech. (1)1:119-121.
Ingram LO (1977). Changes in lipid composition of Escherichia coli resulting from growth with organic solvents and with food additives. App. Environ. Microbiol. 33(5):1233–1236.
Isacchi B, Bergonzi MC, Grazioso M, Righeschi C, Pietretti A, Severini C, Bilia AR (2012). Artemisinin and artemisinin plus curcumin liposomal formulations: Enhanced anti-malarial efficacy against *Plasmodium berghei*-infected mice. Eur. J. Pharm. Biopharm. 80:528-534.
Jain S, Sapee R, Jain NK (1998). Pro ultra flexible lipid vesicles for effective transdermal delivery of norgesterol. Proceedings of 25th conference of C.R.S., U.S.A. 32-35.
Janga KY, Jukanti R, Velpula A, Sunkavalli S, Bandari S, Kandadi P, Veerareddy PR (2012). Bioavailability enhancement of zaleplon via proliposomes: Role of surface charge. Eur. J. Pharm. Biopharm. 80(2):347-357.
Jessy SVB (2013). Proliposomes: A brief overview of novel delivery system. Int. J. Pharm. Biol. Sci. 4(1):150–160.
Jin T, Zarif L, Mannino RJ (2000). Nano-cochleate formulations, process of preparation and method of delivery of pharmaceutical agents. USA patent 6153217.
Jingling T, Jin S, Fude C, Zhonggui H (2006). Preparation of self-emulsifying drug delivery systems of Ginkgo biloba extracts and in vitro dissolution studies. Asian J. Trad. Med. 1:3-4.
Jitendra LP, Praful DB (2012). A review on: Pharmacosomes as a novel vesicular drug delivery system, World J. Pharm. Res. 1(3):456-469.
Joshi NH, Shah N (2008). Review of lipids in pharmaceutical drug delivery system, part I. Amer. Pharm. Rev. Russel Public.
Junyaprasert VB, Boonme P, Songkro S, Krauel K, Rades T (2007a). Transdermal delivery of hydrophobic and hydrophilic local anesthetics from o/w and w/o Brij 97-based microemulsions. J. Pharm. Pharm. Sci. 10(3):288-298.
Junyaprasert VB, Boonme P, Wurster DE, Rades T (2008). Aerosol OT microemulsions as carriers for transdermal delivery of hydrophobic and hydrophilic local anesthetics. Drug Del. 15(5):323-330.
Junyaprasert VB, Boonsaner P, Leatwimonlak S, Boonme P (2007b). Enhancement of the skin permeation of clindamycin phosphate by Aerosol OT/1-butanol microemulsions. Drug Dev. Ind. Pharm. 33(8):874-880.
Jyoti W, Anroop N, Rachna K (2012). Emulsion forming drug delivery system for lipophilic drugs, Acta Pol. Pharm. Drug Res. 69(2):179-191.
Kanika (2012). Recent technical advances in emerging vescicular systems. Int. J. Pharm. Prof. Res. 3(1):568-584.
Kaur M, Kanwar M (2002). Ocular preparations: The formulation approach. Drug Dev. Ind. Pharm. 28(5):473–493.
Kaur IP, Bhandari R, Bhandari S, Kakkar V (2000). Potential of solid lipid nanoparticles in brain targeting. J. Cont. Rel. 127:97-109.
Kavitha D, Naga-Sowjanya J, Panaganti S (2010). Pharmacosomes: An Emerging Vesicular System. Int. J. Pharm. Sci. Rev. Res. 5(3):168-171.
Khan F, Islam MS, Roni MA, Jalil RU (2012). Systematic development of self-emulsifying drug delivery systems of atorvastatin with improved bioavailability potential. Sci Pharm. 80(4):1027-43.
Khopade AJ, Jain NK (1997). Long circulating lipospheres targeted to inflamed tissue. Pharmizie, 52, 165-166.
Kim S (1993). Liposomes as carriers of cancer chemotherapy. Drugs 46:618-638.
Kisak ET, Coldren B, Evans, CA, Boyer C, Zasadzinski JA (2004). The Vesosome – A Multicompartment Drug Delivery Vehicle. Curr. Med. Chem. 11:1241-1253.
Kuentz M (2012). Lipid-based formulations for oral delivery of lipophilic drugs. Drug Discov. Today Technol. 2012, DOI: 10.1016/ j.ddtec.2012.03.002.
Kumar DP, Arnab D (2012). Pharmacosomes: A potential vesicular drug delivery system. Int. Res. J. Pharm. 3(3):102-105.
Lai F, Pireddu R, Corrias F, Fadda AM, Valenti D, Pini E, Sinico C (2013a). Nanosuspension improves tretinoinphotostability and delivery to the skin. Int. J. Pharm. 458(1):104-109.
Lai F, Fadda AM, Sinico C (2013b). Liposomes for brain delivery. Expert Opin. Drug Deliv. 10(7):1003-22.
Lakshmi PK, Devi GS, Bhaskaran S, Sacchidanand S (2007). Niosomal methotrexate gel in the treatment of localized psoriasis: phase I and phase II studies. Ind. J. Dermatol. Venereal. Leprol. 73(3):157-161.
Landh T (1994). Phase Behavior in the System pine needle oil monoglycerides-poloxamer 407-water at 20 degree. J. Phy. Chem. 98:8453-8467.
Lasic DD, Papahadjopoulos D (eds) (1998). Medical application of liposomes. Elsevier Science B. V., Amsterdam, Netherlands. p. 45.
Lee D, Weitz DA (2008). Double emulsion-templated nanoparticle colloidosomes with selective permeability. Adv. Mater. 20(18):3498-3503.
Li RJ, Ying X, Zhang Y, Ju RJ, Wang XX, Yao HJ, Men Y, Tian W, Yu Y, Zhang L, Huang RJ, Lu WL (2011). All-trans retinoic acid stealth liposomes prevent the relapse of breast cancer arising from the cancer stem cells. J. Cont. Rel. 2011, 49(3):281-291.
Li XM, Ding LY, Xu Y, Wang Y, Ping Q (2009). Targeted delivery of doxorubicin using stealth liposomes modified with transferring. Int. J. Pharm. 373(1-2):116-123.
My Vision Test News Archive. Liposomes prolong avastin retention within the eye (2009). Accessed online at http://www.myvisiontest.com/newsarchive.php?id=816 on 30th April, 2012.
Long C, Zhang L, Qian Y (2006). Preparation and crystal modification of ibuprofen loaded solid lipid microparticles. Chin. J. Chem. Eng.

14(4):518- 525.
Madden TD, Harrington PR, Tai LCL, Bally MB, Mayer LD, Redelmeier TE, Loughrey HC, Tilcock CPS, Reinish TW, Cullis PR (1990). The accumulation of drugs within large unilamellar vesicles exhibiting a proton gradient- A survey. Chem. Phys. Lipids 53:37-46.
Mader C, Kupau S, Sleytr UB, Sara M (2000). S-layer coated liposomes as a versatile system for entrapping and binding target molecules. Biochem. Biophys. Acta Biol.1463(1):142-150.
Madhurilatha T, Paruchuri SK, Suria PK (2011). Overview of cubosomes: a nano particle. Int. J. Res, Pharm. Chem. 1(3):535-541.
Makino K, Shibata A (2006). Surface properties of Liposomes depending on their composition. Adv. Planar Lipid Bil. Liposomes 4:49-77.
Malam Y, Loizidou M, Seifalian AM (2009). Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. Trends Pharmacol. Sci. 30(11):592-599.
Mallick AI, Singha H, Khan S, Anwar T, Ansari MA, Khalid R, Chaudhuri P, Owais M (2007). Escheriosome mediated delivery of recombinant ribosomal L7/L12 protein confers protection against murine brucellosis. Vaccine 25(46):7873–7884.
Mannino RJ, Canki M, Feketeova E, Scolpino AJ, Wang Z, Zhang F, Kheiri MT, Gould-Fogerite S (1998). Targeting Immune response induction with cochleate and liposome-based vaccines Adv. Drug Deliv. Rev. 32(3):273-287.
Masters DB, Domb AJ (1998). Lipospheres local anesthetic timed release for perineural site application. Pharm. Res. 15:1038-1045.
Mathai JC, Sprott GD, Zeidel ML (2001). Molecular mechanisms of water and solute transport across archaebacterial lipid membranes. J. Biol. Chem. 276:27266-27271.
Mayank G, Ragini S, Goel RK, Gopal N (2012). Recent advances in various emerging vescicular systems- An overview. Asian Pac. J. Trop. Biomed. S1176-S1188.
Mehnert W, Mäder K (2001). Solid lipid nanoparticles: production, characterization and applications. Adv. Drug Deliv. Rev. 47(2-3):165–196.
Mengmeng N, Lu Y, Lars H, Wei W (2011). Liposomes containing glycocholate as potential oral insulin delivery systems: preparation, *in vitro* characterization, and improved protection against enzymatic degradation. Int. J. Nanomed. 6:1155–1166.
Milak S, Medicott N, Tucker IG (2006). Solid lipid micro particles containing loratidine prepared using a micro mixer. J. Micro. 23:823–831.
Mogal SA, Gurjar PN, Yamgar DS, Kamod AC (2012). Solid dispersion technique for improving solubility of some poorly soluble drugs. Der. Pharm. Let. 4(5):1574-1586.
Mohammed M, Adel M, Magda S (2012). Pharmaceutical particulate carriers: lipid - based carriers. Nat. J. Physio. Pharm. Pharmacol. 2(1):10 – 22.
More MS, Shende MA, Kolhe DB, Jaiswal NM (2012). Herbosomes: Herbo phospholipid complex an approach for absorption enhancement. Int. J. of Bio. Pharm. Res. 3(8):946-955.
Morishita M, Peppas NA (2006). Is the oral route possible for peptide and protein drug delivery. Drug Discov. Today. 11:905–908.
Müller RH, Keck CM (2004). Drug delivery to the brain-realization by novel drug carriers. J. Nanosci. Nanotechnol. 4:471–448.
Müller RH, Lucks JS (1996). Arzneistoffträger aus festen Lipidteilchen– Feste Lipid Nanosphären (SLN). EP 0605497.
Müller RH, Maeder K, Gohla S (2000). Solid lipid nanoparticles (SLN) for controlled drug delivery- a review of the state of the art. Eur. J. Pharm. Biopharm. 50:161-77.
Murakami M, Yoshikawa H, Takada K, Muranishi S (1986). Effect of oleic acid vesicles on intestinal absorption of carboxyfluorescein in rats. Pharm. Res. 35–40.
Nacka F, Cansell M, Entressangles B (2001). *In vitro* behavior of marine lipid-based liposomes. Influence of pH, temperature, bile salts, and phospholipase A2. Lipids 36(1):35–42.
Naik PV, Dixit SG (2008). Ufasomes as plausible carriers for horizontal gene transfer. J. Disp. Sci. Tech. 29(6):804–808.
Nancy JM, Xiaojun Y, Nicholas PZ, Ravi VB (2001). Lipid-based microtubular drug delivery vehicles. J. Cont. Rel. 71:141–152.
Nastruzzi C, Cortesi R, Esposito E, Gambari R, Borgatti M, Bianchi N, Feriotto G, Mischiati C (2000). Liposomes as carriers for DNA PNA hybrids. J. Cont. Rel. 68(2):237-249.
New RCC, Torchilin VP, Weissig V (eds) (2003). Liposomes (practical approach). Oxford University Press, London. pp. 20.
Norlen, Amoudi A (2004). The Cubic Rod- Packing and Membrane Templating Model. J. Inves. Dermatol. 123:715-718.
Ochekpe NA, Olorunfemi PO, Ngwuluka NC (2009). Nanotechnology and drug delivery part 2: nanostructures for drug delivery. Trop. J. Pharm. Res. 8(3):275-287.
Omri A, Agnew BJ, Patel GB (2003). Short-term repeated-dose toxicity profile of archaeosomes administered to mice via intravenous and oral routes. Int. J. Toxicol. 22:9–23.
Omri A, Makabi-Panzu B, Agnew BJ, Sprott GD, Patel GB (2000). Influence of coenzyme Q10 on tissue distribution of archaeosomes and pegylated archaeosomes administered to mice by oral and intravenous routes. J. Drug targ. 7:383–392.
Pal A, Gupta S, Jaiswal A, Dube A, Vyas SP (2012). Development and evaluation of tripalmitin emulsomes for the treatment of experimental visceral leishmaniasis. J. Liposome Res. 22(1):62–71.
Pandita A, Sharma P (2013). Pharmacosomes: An emerging novel vesicular drug delivery system for poorly soluble synthetic and herbal drugs. ISRN Pharm. 348186.
Pang KS, Lichuan L, Huadong S (2007). Interaction of drug transporters with excipients. In role of lipid excipients in modifying oral and parenteral drug delivery. Wasan, K.M. (ed.), Wiley, John Wiley and Sons. pp. 1–31.
Pardeike J, Hommoss A, Müller RH (2009). Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int. J. Pharm. 366(1-2):170-184.
Parthibarajan R, Rubina RC, Gowrishankar NL, Pranitha D (2011). Colloidosomes drug delivery- A review. Int. J. Pharm. Bio. Sci. 1(3):183-197.
Patel BR, Patel PR, Patel M (2008). Self- emulsifying drug delivery systems. Pharm. Sci. Tech. 7:1-3.
Patel DM, Jani RH, Patel CN (2011). Ufasomes- A vesicular drug delivery. Syst. Rev. Pharm. 2:72-78.
Patel S (2007). Ethosomes- A promising tool for transdermal delivery of drug. Pharm. Info. Net. 5:3.
Patidar A, Thakur DS, Kumar P, Verma J (2010). A review on novel lipid based nanocarries. Int. J. Pharm. Pharm. Sci. 2(4):30-35.
Patravale VB, Mandawgade SD (2008). Novel cosmetic delivery systems: an application update. Int. J. Cos. Sci. 30(1):19–33.
Payne NI, Timmis P, Ambrose CV, Warel MD, Ridgway F (1986). Proliposomes: a novel solution to an old problem. J. Pharm. Sci. 75(4):325–329.
Pevion Biotech Limited. Virosomal Drug Delivery.http://www.pevion.com/images/content/Delivery-Sheet-01-06-01-006.pdf, assessed 3/9/2013.
Pickering SU (1907). Emulsions. J. Chem. Soc. 91:2001-2021.
Pignatello R, Leonardi A, Pellitteri R, Carbone C, Caggia S, Graziano ACE, Cardile V (2013). Evaluation of new amphiphilic PEG derivatives for preparing stealth lipid nanoparticles. Coll. Surf. A. 434:136-144.
Porter CJH, Trevaskis NL, Charman WN (2007). Lipids and lipid based formulations: optimizing the oral delivery of lipophilic drugs. Nature Rev. 6:231-248.
Pouton CW (2000). Lipid formulations for oral administration of drugs: non emulsifying, self – emulsifying and self micro emulsifying drug delivery systems. Eur. J. Pharm. Sci. 11:93-98.
Price R, Patchan M (1991). Controlled release from cylindrical microstructures. J. Microencapsul. 18:301–306.
RRC (1990). New (ed), Preparation of liposomes and size determination, Liposomes-A practical approach. Oxford University Press, New York. p. 36.
Rajan BM, Nirav SS (2011). A review: Self emulsifying drug delivery system. Int. J. Pharm. Pharm. Sci. 3(2):23-28.
Ravani L, Esposito E, Bories C, Moal VL, Loiseau PM, Djabourov M, Cortesi R, Bouchemal K (2013).Clotrimazole-loaded nanostructured lipid carrier hydrogels: thermal analysis and *in vitro* studies. Int. J.

Pharm. 454(2):695-702.
Ravi K, Shivjee K, Shyam S, Amit KJ (2011). Vesicular system-carrier for drug delivery. Der. Pharm. Sinica 2(4):192-202.
Rawat M, Saraf S (2008). Liposphere: emerging carries in delivery of proteins and peptides. Int. J. Pharm. Sci. Nanotech. 1(3):207-214.
Sachan R, Khatri K, Kasture SB (2010). Self-emulsifying drug delivery system a novel approach for enhancement of bioavalibility. Int. J. Pharm. Tech. Res. 2(3):738-1745.
Salari JWO (2011). Pickering emulsions, colloidosomes & micro-encapsulation. Boxpress BV, Proefschriftmaken.nl.1-206.
Sandip V, Vishal S, Nilesh G, Bakde BV (2012). Liquisolid compact: A new technique for enhancement of drug dissolution. Int. J. Pharm. Chem. Sci. 1(3):664-669.
Sanjib B, Bhaskar M (2011). Virosomes- A Novel strategy for drug delivery and targeting. BioPharm. Int. Supp. 24:s9-s14.
Santos-Magalhães NS, Pontes A, Pereira VMW, Caetano MNP (2000). Colloidal carriers for benzathin penicillin G: nanoemulsions and nanocapsules. Int. J. Pharm. 208(1-2):71-80.
Saurabh B, Chandan PK, Geeta A, Harikumar SL (2012). A comparative review on vesicular drug delivery system and stability issues. Int. J. Res. Pharm. Chem. 2(3):704-713.
Semalty A, Semalty M, Rawat BS, Singh D, Rawat SM (2010). Development and evaluation of pharmacosomes of aceclofenac. Ind. J. Pharm. Sci. 5:576-581.
Semete B, Kalombo L, Katata L, Swai H (2010). Nano-drug delivery systems: Advances in TB, HIV and malaria treatment. Smart Biomol. Med. 15-52.
Shalini S, Ram KR (2011). Phytosomes: An emerging technology. Int. J. Pharm. Res. Dev. 2(5):1-7.
Sharma SK, Dube A, Nadeem A, Khan S, Saleem I, Garg R, Mohammad O (2006). Non PC liposome entrapped promastigote antigens elicit parasite specific $CD8^+$ and $CD4^+$ T-cell immune response and protect hamsters against visceral leishmaniasis. Vaccine, 2006, 24(11):1800–1810.
Sharma VK, Mishra DN, Sharma AK, Srivastava B (2010). Liposomes: Present prospective and future challenges. Int. J. Curr. Pharm. Rev. Res. 1(2):6-1.
Shenoy VS, Vijay IK, Murthy RSR (2005). Tumour targeting: biological factors and formulation advances in injectable lipid nanoparticles. J. Pharm. Pharmcol. 57:411–422.
Singha A, Saharanb V, Singha M, Bhandaria A (2011). Phytosome: drug delivery system for polyphenolic phytoconstituents. Ira. J. Pharm. Sci. Aut. 7(4):209-219.
Singha H, Mallick AI, Jana C, Isore DP, Goswami TK., Srivastava SK, Azevedo VA., Chaudhuri P, Owais M (2008). Escheriosomes entrapped DNA vaccine co-expressing Cu-Zn superoxide dismutase and IL-18 confers protection against Brucella abortus. Microbes and Infection.10(10-11):1089–1096.
Solans C, Izquierdo P, Nolla J, Azemar N, Garcia-Celma MJ (2005). Nano-emulsion. Current Opi. Colloid Interface sci. 10:102-110.
Soumya S, Doney AB, Sabitha M (2012). Current trends in lipid based delivery systems and its applications in drug delivery. Asian J. Pharm. Clin. Res. 5(3):4-9.
Souto EB, Doktoraovava S, Boonme P (2011). Lipid-based colloidal systems (nanoparticles, microemulsions) for drug delivery to the skin: materials and end-product formulations. J. Drug Del. Sci. Tech. 21(1):43-54.
Spargo BJ, Cliff RO, Rollwagen FM, Rudolph AS (1995). Controlled release of transforming growth factor-beta from lipid-based microcylinders. J. Microencapsul. 12(3):247–254.
Spicer PT, Hayden KL, Lynch ML, Ofori-Boateng A, Burns JL (2001). Novel process for producing cubic liquid crystalline nanoparticles (cubosomes). Langmuir. 17:5748-5756.
Stegemanna S, Leveillerb F (2007). When poor solubility becomes an issue: from early stage to proof of concept. Eur. J. Pharm. Sci. 31:249-261.
Stensrud G, Sande AS, Kristensen S, Smistad G (2000). Formulation and characterization of primaquine loaded liposomes prepared by a pH gradient using experimental design. Int. J. Pharm. 198:213-228.
Syed FM, Khan MA, Nasti TH, Ahmad N, Mohammad O (2003). Antigen entrapped in the escheriosomes leads to the generation of $CD4^+$ helper and $CD8^+$ cytotoxic T cell response. Vaccine 21(19-20): 2383–2393.
Thiruganesh R, Umadevi K, Ruttala H, Kiran K (2009). Nanocochleate-A new drug delivery system. FABAD J. Pharm. Sci. 34:91–101.
Touitou E (1996). Composition of applying active substance to or through the skin. U.S. Patent 5:540-934.
Touitou E, Dayan N, Levi-Schaffer F, Piliponsky A (1998). Novel lipid vesicular system for enhanced delivery. J. Lip. Res. 8:113.
Uchegbu IF, Vyas SP (1998). Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int. J. Pharm. 1998, 172, 33-70.
Umeyor EC, Kenechukwu FC, Ogbonna JD, Chime SA, Attama AA (2012a). Preparation of novel solid lipid microparticles loaded with gentamicin and its evaluation *in vitro* and *in vivo*. J. Microencapsul., 1-12. DOI: 10.3109/02652048.2011.651495.
Umeyor EC, Kenechukwu FC, Ogbonna JDN, Chime SA, Attama AA (2012). Investigation of solidified reverse micellar systems as novel carriers for oral delivery of gentamicin. J. Pharm. Res. 4914-4920.
Velev OD, Furusawa K, Nagayama K (1996a). Assembly of latex particles by using emulsion droplets as templates. 2. Ball-like and composite aggregates. Langmuir 12(10):2385-2391.
Velev OD, Furusawa K, Nagayama K (1996b). Assembly of latex particles by using emulsion droplets as templates. 1. Microstructured hollow spheres. Langmuir 12(10)2374-2384.
Velev OD, Nagayama K (1997). Assembly of latex particles by using emulsion Droplets. 3. Reverse (water in oil) systems. Langmuir 13(6):1856-1859.
Vighi E, Montanari M, Hanuskova M, Iannuccelli V, Coppi G, Leo E (2013). Design flexibility influencing the in vitro behavior of cationic SLN as a non viral gene vector. Int. J. Pharm. 440(2):161-169.
Walve JR, Bakliwal SR, Rane BR, Pawar SP (2011). Transfersomes: a surrogated carrier for transdermal drug. Int. J. App. Bio. Pharm. Tech. 2(1):204-213.
Welz C, Neuhuber W, Schreier H, Repp R, Rascher W, Fahr A (2000). Nuclear gene targeting using negatively charged liposomes. Int. J. Pharm. 196(2):251-252.
Wissing SA, Kayser O, Muller RH (2004). Solid lipid nanoparticles for parenteral drug delivery. Adv. Drug Deliv. Rev. 56:1257-1272.
Yadav AV, Murthy MS, Shete AS, Sakhare S (2011). Stability Aspects of Liposomes. Ind. J. Pharm. Educ. Res. 45(4):402-413.
Zarif L, Graybill J, Perlin DD, Mannino RJ (2000). Cochleates: new lipid based drug delivery system. J. Liposome Res. 10:523-538.