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Review Article

CURRENT TRENDS IN LIPID BASED DELIVERY SYSTEMS AND ITS APPLICATIONS IN DRUG DELIVERY

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ABSTRACT

Lipid-based delivery systems are an accepted, proven, commercially viable strategy to formulate pharmaceuticals, for topical, oral, pulmonary or parenteral delivery. Lipid based formulations can be tailored to meet a wide range of product requirements dictated by disease indication, route of administration, cost consideration, product stability, toxicity, and efficacy. The proven safety and efficacy of lipid-based carriers make them attractive candidates for the formulation of pharmaceuticals, as well as vaccines, diagnostics and nutraceuticals. These systems allows oral delivery of poorly soluble API when solubilization through modification of molecular scaffold is not an option The efficacy of these biocompatible systems may be improved if their delivery rate, biodegradation, and site-specific targeting can be predicted, monitored, and controlled. However, the number of applications for lipid-based formulations has expanded as the nature & type of active drugs under investigation has become more varied. This article mainly focus on lipid formulations namely microemulsions, self emulsifying delivery systems, nanoemulsions, pickering emulsions, liposomes, phytosomes, transfersomes, ethosomes, archaesomes, vesosomes, lipid microparticles and lipid nanoparticles and their prominent applications in pharmaceutical drug delivery.

Keywords: Lipid based delivery system, Emulsions, Archaeosomes, Vesosomes

INTRODUCTION

New chemical entities (NCEs) are designed using increasingly available receptor structural information. Such chemical entities formed are polycyclic and very hydrophobic. About 50% of NCEs are poorly soluble and hence have poor bioavailability. As an oral drug delivery system, lipids are studied as components of various oily liquids and dispersions that are designed to increase solubility and bioavailability of drugs belonging to the class II and IV of the biopharmaceutical drug classification system[1]. Lipid carriers are equally important for transdermal systems as they form a protective barrier, make the skin water resistant, reduce the trans-epidermal water loss and thus protect the skin against dehydration. By filling up microscopic indentations in the skin they lead to a noticeable smoothening of the skin which simultaneously also reduces minor wrinkles[2]. It is also being proved that the unique properties of lipids viz their physiochemical diversity, biocompatibility which reduces local irritancy, make them ideal carriers for topical usage[3].

Increasing interest in lipid-based delivery systems are due to following reasons like:

- Versatility of lipidic excipients
- Formulation versatility and the choice of different drug delivery systems
- Low risk profile
- Enhanced oral bioavailability and reduced plasma profile variability
- Enhanced permeation of these systems when used topically
- Formation of vesicular system which is passive, non-invasive and is available for immediate commercialization.
- Better characterization of lipidic excipients
- High market attractiveness for products with proprietary technology.
- Improved ability to address the key issues of technology transfer and manufacture scale-up.

Novel Lipid drug delivery systems can be broadly classified as emulsions, vesicular systems and lipid particulate systems

Emulsion

Microemulsions, self emulsifying drug delivery system, nanoemulsions and pickering emulsions are novel emulsion systems with many advanced applications.

Microemulsions

Microemulsions are transparent, less viscous, thermodynamically stable, optically isotropic system of oil and water stabilized by an interfacial film of amphiphilic compounds such as surfactant and co-surfactant[4,5]. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and require low shear rate as at higher shear conditions there is an abrupt breakdown of the bicontinuous structure, resulting in flow-induced phase separation[6]. The main difference between emulsions and microemulsions lies in the size and shape of dispersed particles as microemulsions have size of smaller magnitude (10 – 200 nm) than those of conventional emulsions (1 – 20 µm). Also emulsions consist of roughly spherical droplets whereas microemulsions constantly evolve between various structures ranging from droplet-like swollen micelles to bicontinuous structures.[7]

Microemulsions help to improve solubilization capacity and bioavailability of drugs when given orally, improve permeation of drugs when given topically. It was found that absolute bioavailability of cyclosporine loaded in the microemulsion system was increased about 3.3 and 1.25 fold due to the reduced droplet size.[8] The studies on topical Fluconazole microemulsions clearly revealed about 70% to 99 % increase in permeation rate with varying concentration of both oil, surfactant and cosurfactant.[9]. Newer microemulsion formulation of propofol helps to overcome many problems with macroemulsion Diprivan® which include severe discomfort and pain at the site of intravenous injection, a propensity for rapid bacterial growth because of the presence of the soy bean oil carrier, the inability to use propofol with patients who are allergic to egg products or choose not to consume egg products for various reasons, and problems with continued use in patients requiring sedation. [10]From the animal study it was reported that HPMC gel base containing Piroxicam microemulsions showed maximum percentage oedema inhibition after 1 hr resulting in best analgesic and anti inflammatory effects.[11]

Self emulsifying delivery systems

Development of Self-emulsifying drug delivery systems mainly intents to improve solubility/dissolution, absorption and bioavailability of poorly water-soluble compounds. They are of self emulsifying drug delivery systems (SEDDS) and self micro emulsifying drug delivery systems (SMEDDS).

Potential advantages of these systems include enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, high drug loading cabability, selective targeting of drug(s) toward specific absorption window in GIT, marked control over delivery profiles and protection of drug(s) from the hostile environment in gut.[12,13]

Ketoprofen when presented in SEDDS formulation showed enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of Ketoprofen.[14]

Acetyl salicylic acid, a drug that degrades in the GI tract, when formulated in a Galacticles™ Oral Lipid Matrix System (SEDDS formulation) showed an improved oral bioavailability of undegraded acetylsalicylic acid by 73% when compared to the reference formulation which suggests that the SEDDS formulation has a capacity to protect drugs from degradation in the GI tract[15].

Table 1: Marketed formulations of self emulsifying delivery system

Trade name	Active Ingredient	Formulation	Manufacturer	Indication
Neoral	Cyclosporin A/I	Soft gelatine capsule	Novartis	Immune suppressant
Norvir	Ritonavir	Soft gelatine capsule	Abbott laboratories	HIV antiviral
Fortovase	Saquinavir	Soft gelatine capsule	Hoffmann-La Roche Inc	HIV antiviral
Agenerase	Amprenavir	Soft gelatine capsule	Galaxosmithkline	HIV antiviral
Lipirex	fenofibrate	Hard gelatine capsule	Sanofi-aventis	Anti hyperlipidemic
Convulex	Valproic acid	Soft gelatine capsule	Phamacia	Anti epileptic
Gengraf	Cyclosporin A/III	Hard gelatine capsules	Abbott Laboratories	Immuno suppressant
Rocaltrol	Calcitriol	Soft gelatine capsule	Roche	Calcium regulator
Sandimmune	Cyclosporine A/II	Soft gelatine capsule	Novartis	Immuno suppressant
Targretin	Bexarotene	Soft gelatine capsule	Novartis	Antineoplastic

Nanoemulsions

Nanoemulsions are composed of oil and water and are stabilized by surfactants and alcohol within a size range of 200-600nm. In contrast to microemulsions, nanoemulsions are metastable and can be diluted with water without changing the droplet size distribution[16].Nanoemulsion stability is influenced by environmental parameters such as temperature and pH which changes upon Nanoemulsion delivery to patients.

Advanced form is self-nanoemulsifying drug delivery systems (SNEDDS) which are anhydrous homogenous liquid mixtures consisting of oil, surfactant, drug and co-emulsifier or solubiliser, which spontaneously form oil-in-water nanoemulsion of approximately 200 nm or less in size upon dilution with water under gentle stirring. SNEDDS can improve oral bioavailability of hydrophobic drugs. Solid SNEDDS can offer better patient compliance and minimize problems associated with capsules filled with liquid SNEDDS[17]

Nanoemulsion formulations have distinct applications over macroemulsion systems when delivered parenterally because of the fine particle size nanoemulsion are cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Upon oral administration these have increased absorption, improved clinical potency, and decreased drug toxicity[18]. Because of its properties like transparency, low viscosity, they are ideal for cosmetic preparations. The nanoemulsion of CoQ10 and vitamin E acetate was proven to be a promising cosmetic ingredient to prevent premature skin aging by protecting the mitochondrial DNA against UV-induced mutations.[19]

Pickering Emulsions

A 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.[20] Solid particles added, will bind to the surface of the interface and prevent the droplets from coalescing thus making emulsion more stable. Properties such as hydrophobicity, shape, and size of the particle can have an effect on the stability of the emulsion.[21]Additionally, it has been demonstrated that the stability of the Pickering emulsions can be improved by the utilization of amphiphilic particles so-called Janus particles due to the higher adsorption energy of the particles at the liquid-liquid interface.[22] The skin absorption of caffeine from silica stabilized pickering emulsion was three fold higher than emulsifier stabilized emulsion attributed to the higher adhesion potential of pickering emulsions.[23]

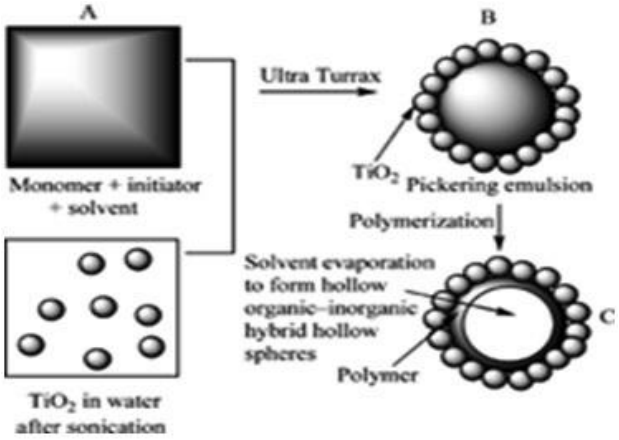

Figure 1: Pickering emulsion stabilized by TiO_2

Vesicular Drug Delivery Systems

Newer vesicular systems are evolved every day. Lipid vesicular system include:

Liposomes

Liposomes are nanosized artificial vesicles with lipid bilayer composed of phospholipids and cholesterol. Liposomes have many drawbacks like tendancy to be taken up by the RES system, modification of system for delivery to special sites, cost etc lead to development of newer drug delivery systems like transfersomes, ethosomes etc[24]. Also cholesterol commercially available is derived from egg or wool grease. These animal sources are potentially not suitable for human pharmaceuticals due to the potential viral contamination. Also, cholesterol is readily oxidized creating a stability problem for lipid based drug products. Some of these oxidation by-products like 25-hydroxy cholesterol, 7-keto-cholesterol, 7a- and 7ß-hydroxycholesterol, cholestane-3ß,5a,6ß-

triol and the 5- and 7-hydroperoxides, were found toxic causing aortic smooth muscle cells to die.

Liposomes act as vesicles to target anticancer drugs resulting in reduced side effects but prolonging their circulation time through pegylation and thus improving effectiveness in the body. Liposome helps in the biopreservation of RBCs. Liposome-encapsulated hemoglobin (LEH) has evolved to carry oxygen, capable of surviving in the circulation and can be produced in large-scale production. Topically liposomes has several advantages including biodegradability, non-toxicity, moisturizing and restoring action, sustained dermal release and similarity to biological membranes enabling penetration into epidermal barrier compared to other delivery systems.[25]

Table 2: Different modifications in liposomes for improver drug delivery

Modified liposomes	Application
Immunoliposome	Adsorb DNA nonspecifically on their surface and transfer it directly to cytoplasm, without being presented to lysosomes for degradation
Genosome	Complex formulations of DNA with various cationic liposomes which is used as a form of non-viral gene therapy as the complex does not require any components of a virus in order to transport genetic material
Marinosome	Based on a natural marine lipid extract containing a high polyunsaturated fatty acid (PUFA) which are not present in normal skin epidermis like ecosapentanenoic acid etc which are metabolized by skin epidermal enzymes into anti-inflammatory and anti-proliferative metabolites that are beneficial in treating inflammatory skin disorders
Ultrasome	Specialized liposomes encapsulating an endonuclease enzyme extracted from micrococcus luteus; the enzyme recognizes the sun damage to the skin and initiates removal of damaged DNA
Asymmetric oxygen carrier system (AOCS)	Designed to carry oxygen into the skin, are composed of perfluorocarbon core surrounded by a monolayer of phospholipids, followed by a bilayer system

Phytosomes

Phytosomes are lipid vesicles formed from the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids, tannins,) in an aprotic solvent.[26] Phytosomes provide a new basis for delivery of phytoconstituents by improving its bioavailability which is attained by reducing the polarity of active substance, enhancing their rate and the extent of solubilisation into aqueous intestinal fluids and their capacity to cross biomembranes. They have been used to deliver liver-protecting flavonoids because they can be made easily bioavailable by phytosomes.[27].

The phytosome process has been applied successfully to many popular herbal extracts including *Ginkgo biloba*, grape seed, hawthorn, milk thistle (*Silybum marianum*), green tea (*Thea sinensis*) and ginseng (*Panax ginseng*).[28,29]

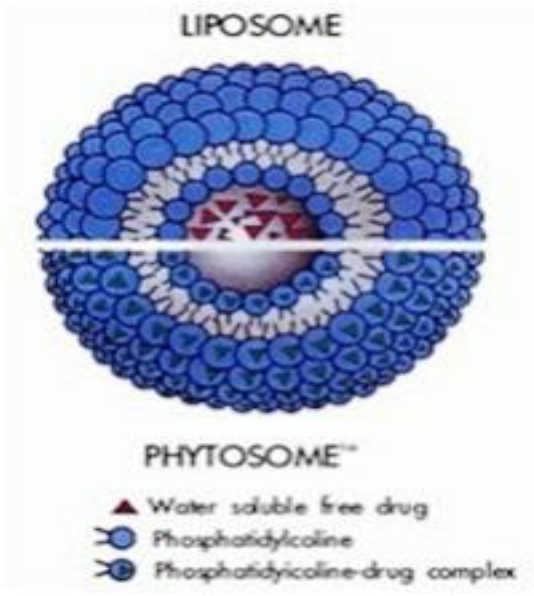

Figure 2: Difference between Phytosome and a liposome

Transfersome

Transfersomes are ultradeformable, self optimized aggregates for transdermal application containing a mixture of lipids and biocompatible membrane softeners. Though basic organization is broadly similar to a liposome, the *Transfersome* differs by its softer, more deformable, and better adjustable artificial membrane they posses. Transfersome penetrate the stratum corneum by either intracellular route or the transcellular route by the generation of "osmotic gradient" due to evaporation of water. [30]Thus a transfersome vesicle, when applied on an open biological surface, such as nonoccluded skin, tends to penetrate its barrier and migrate into the water-rich deeper strata to secure adequate hydration. As the vesicles are elastic, they can squeeze through the pores in stratum corneum (though these pores are less than one-tenth of the diameter of vesicles).[31]

Transfersome vesicles can transport molecules that are too big to diffuse through skin Eg: systemic delivery of therapeutically meaningful amounts of macromolecules, such as insulin[32]or interferon. [33]Other applications include the transport of small molecule drugs which have certain physicochemical properties which would otherwise prevent them from diffusing across the barrier. Now a day, Transfersome can be used to target peripheral subcutaneous tissue. The Non-steroidal anti-inflammatory drug (NSAID) ketoprofen in a Transfersome formulation in the trade mark Diractin gained marketing approval by the Swiss regulatory agency (SwissMedic) in 2007. Topical immunization using cationic transfersomes based DNA vaccine offers all the advantages of DNA vaccines, and in addition overcome the disadvantages of classical invasive methods of vaccination.[34]

Table 3: Therapeutic applications of Transfersomes

Drug	Effects observed
Indinavir	Reduce side effects,Improved skin permeability
Propranolol	Improved transdermal flux
Insulin	High encapsulation efficiency. Transfer across the skin with an efficiency of >50%. Provide noninvasive means of therapeutic use
Interferone	Controlled release. Overcome stability problem.
Tamoxifen	Improved transdermal flux
Meletonin	Improved systemic absorption
Meloxicam	Improved biological activity
Valsartan	Improved skin permeability
Tetracaine	Noninvasive treatment by topical drug application
Lidocaine	Noninvasive treatment by topical drug application
Norgesterol	Improved transdermal flux Tamoxifen
Oestradiol	Improved transdermal flux Tamoxifen

Ethosomes

Ethosomes are soft, malleable vesicles comprised of hydro alcoholic or hydro/alcoholic/glycolic phospholipids in which the concentration of alcohol is high (20-50%).[35] Ethosomes are mainly

proposed for transdermal drug delivery as they permeate through the skin layers more rapidly and possess significantly higher transdermal flux in comparison with other lipid vesicles.[36,37]

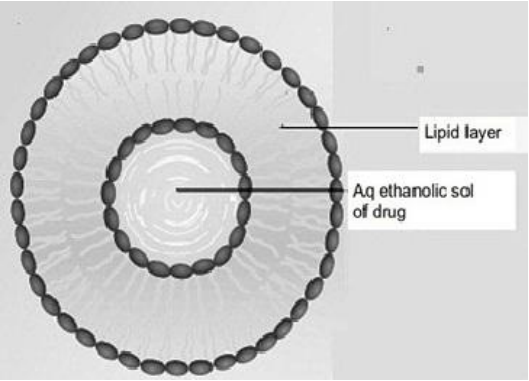

Figure 3: Ethosome vesicle

The main advantage of ethosome over liposome is their increased permeation of drug which may be due to either ethanol effect or ethosome effect. Ethanol acts as a penetration enhancer by penetrating into intercellular lipids thereby increasing the fluidity of cell membrane lipids and decreasing the density of lipid multilayer of cell membrane. This is followed by the 'ethosome effect', which includes inter lipid penetration and permeation by the opening of new pathways due to the malleability and fusion of ethosomes with skin lipids, resulting in the release of the drug in deep layers of the skin.[38] .

The *in vitro* release rate of azelaic acid was more rapid from ethosomal systems (plain and viscous formulations) than from liposomal systems.[39] In clinical study of Fluconazole, it was reported that mean percentage reduction in dimension of skin lesions in candidiasis patient was 50-75% with ethosomal gel as compared to 35-60% with liposomal gel, 25- 30% with fluconazole marketed cream, 15-20% with hydroethanolic solution of drug.[40]

Results of cellular uptake of lamivudin ethosomes showed significantly higher intracellular uptake of ethosomes (85.7%±4.5%) as compared with drug solution (24.9%±1.9%).[39]

Table 4: Therapeautic application of ethosomes in drug delivery

Drug	Applications	Comments
Acyclovir	Treatment of Herpetic infection	Improved drug delivery
Azelaic acid	Anti keratinizing agent used in treatment of acne	Improved transdermal delivery
Zidovudine	Treatment of AIDS	Improved transdermal flux
Lamivudin	Treatment of AIDS	Improve transdermal drug delivery
Trihexypenidyl HCl	Treatment of Parkinsonian syndrome	Increased drug entrapment efficiency, reduced side effect & constant systemic levels
Erythromycin	Efficient healing of *S. aureus* -induced deep dermal infections	Improved drug penetration and systemic effect.
Insulin	Treatment of Diabetes	Improved therapeutic efficacy of drug
Diclofenac	Anti inflammatory, analgesic	Improve biological activity,Reduce sideeffects
Testosterone	Treatment of male hypogonodism	Enhance skin permeation
Fluconazole	Treatment of candidiasis	Enhanced skin permeation
Cannabidol	Prevents inflammation and edema	Significant accumulation of the drug in the skin
Cyclosporin	Treatment of inflammatory skin disease	Improve oral absorption and bioavailability, protect from GIT degradatiomn
Minodixil	Hair growth promotion effect	Higher skin retention
Methotrexate	Treatment of psoriasis	Treatment of psoriasis
Salbutamol	Anti-asthmatic	Enhanced skin permeation
Bacitracin	Treatment of dermal infections	Reduced drug toxicity

Archaeosomes

Archaeosomes are nano-sized vesicles prepared from total polar lipids (TPL) either extracted from the selected genera and species of the Archaea domain or synthetic archaeal lipids. Archaeal-type lipids consist of archaeol (diether) and/or caldarchaeol (tetraether) core structures wherein regularly branched and usually fully saturated phytanyl chains (20-40carbons in lengths), are attached via ether bonds to the sn-2,3 carbons of the glycerol backbone[41].There are remarkable structural differences from liposomes: the archaeosomes surface is highly entropic, possessing half the surface tension than that of liposomes and its permeability to protons and sodium cation 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.[42,43]

It has been shown that incorporation of polyethylene glycol and Coenzyme Q10 into archaeosomes can alter the tissue distribution profiles of intravenously administered vesicles (Omri et al 2000). Omri et al (2003) had also reported that intravenous and oral delivery of nanometric-sized archaeosomes to an animal model was well tolerated with no apparent toxicity. The results of these studies are very promising for the utilisation of archaeosomes in the encapsulation and delivery of different bioactive compounds.[44, 45]

Vesosomes

Vesosomes are multicompartment structures which has distinct inner compartments separated from the external membrane. In simple terms it can be said as a larger vesicle that deliberately encapsulates many smaller vesicles in it. Each compartment of vesosome can encapsulate different materials and have different bilayer composition. In addition, while it has proven difficult to encapsulate anything larger than molecular solutions within lipid bilayer by conventional vesicle self-assembly, the vesosome construction process lends itself to trapping colloidal particles and biological macromolecules relatively efficiently.[46,47]The disadvantage of conventional liposomes is that many important drugs are released faster than optimal *in vivo*. This problem is significantly addressed by the vesosome: 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.[48]

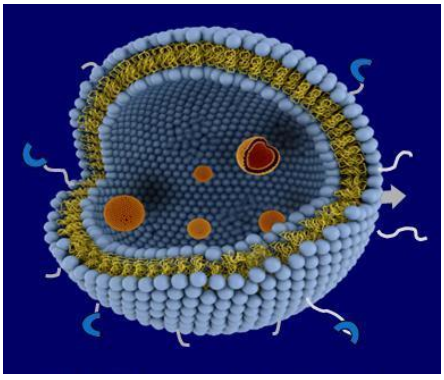

Figure 4: A vesosome – Vesicle within vesicle

Lipid Particulate Delivery Systems

Biocompatible lipid micro- and nanoparticles have evolved as potential carriers to polymers in recent decades. Due to their unique size dependant properties as well as ability to incorporate drug into nanocarriers, these evolve as potential drug delivery systems that could be used for secondary and tertiary level of drug targeting. Advantages of lipid particulate systems include:

- Controlled drug release
- Higher levels of drug targeting
- Physiologically compatible and physicochemically stable carrier systems
- Allows large-scale production at a relatively low production cost
- Protection of incorporated active compounds against degradation
- Solid matrix is composed of well tolerated lipids.
- Easy to scale-up.

Lipid microparticles

Polymeric microspheres have also been successfully tested as sustained release drug delivery system but their safety still remains uncertain which leads to the development of Solid Lipid Microparticles (SLMs)[49].Lipid microspheres known as lipospheres are composed of a solid hydrophobic fat core (triglycerides) stabilized by a layer of phospholipid molecules embedded on their surface. These fat based encapsulation system contain the bioactive compound in the internal core, dissolved or dispersed in the solid fat matrix. [50]The in vitro drug release studies revealed that indomethacin release is prolonged when Sucroester® WE15 used as surfactant in combination with Compritol® 888 ATO as lipid matrix material.[51]

Lipid nanoparticles

Polymeric nanoparticles have many disadvantages like cytotoxicity of the polymers after internalization in to the cell as well as its difficulty in large scale production which leads to the use of physiological lipids or lipids as drug carriers. Solid lipid nanoparticles (SLNs), nanostructure lipid carriers (NLC) and Lipid drug conjugates (LDC) are innovative carrier systems which overcome the above associated problems as well.

The SLNs are sub-micron colloidal carrier which are composed of physiological lipid, dispersed in water or in an aqueous surfactant solution. Advantages of SLN are the use of physiological lipids, the avoidance of organic solvents, a potential wide application spectrum (dermal, per oral, intravenous) and the high pressure homogenization as an established production method. [52]Potential disadvantages such as poor drug loading capacity, their particle growing, unpredictable gelation tendency, drug expulsion after polymeric transition during storage and relatively high water content of the dispersions (70-99.9%) have been observed[53,54]

Nano structured lipid carriers (NLC) are mixtures of solid and fluid lipids, the fluid lipid phase is reported to be embedded into the solid lipid matrix or to be localized at the surface of solid platelets and the surfactant layer[55]. NLC system minimizes or avoids the following disadvantages of SLNs[56]

- Low drug loading capacity
- Drug expulsion during storage
- High water content

Another major problem of SLN is the low capacity to load hydrophilic drugs due to partitioning effects during the production process. Thus only highly potent low dose hydrophilic drugs may be suitably incorporated in the solid lipid matrix[57]. In order to overcome this limitation, the so called Lipid Drug conjugate (LDC) nanoparticles with drug loading capacities of up to 33% have been developed.[58]

Many applications like drugs with irritant effects like tretinoin turns out to be less irritating if applied when encapsulated within SLN.[59] Lipid nanoparticles can be used to improve the bioavailability of drugs, e.g. cyclosporine A[60], clozapine, to improve the stability of chemically labile hydrophobic antioxidants like retinol, CoQ10, alpha-lipoic acid, beta-carotene and alpha-tocopherol[61] and to obtain sustained release of lipophilic drugs like camptothecin[62]. Idarubicin-loaded SLN acted as a prolonged release system after duodenal administration to rats[63]. NanoRepair Q10 ®cream and N a n o R e p a i r Q 1 0 ® S e r u m (Germany) which were introduced to the cosmetic market in October 2005 epitomizes the success of lipid nanoparticles in tackling photo-aging related crisis.[64]

CONCLUSION

Lipid drug delivery systems offer many advantages; however, the development of these systems requires proper understanding of the physicochemical nature of the compound as well as the lipid excipients and gastrointestinal digestion. One of the major challenges of lipid excipients and delivery systems is the varying range of compounds they contain. To overcome this, proper characterization and evaluation of these delivery systems, their stability, classification and regulatory issues, which consequently have affected the number of these formulations that eventually reach the market, have to be constantly assessed. The prospect of these delivery systems looks promising.

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