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NOVEL APPROACHES IN LIPID BASED DRUG DELIVERY SYSTEMS

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ABSTRACT

The use of lipids in drug delivery is by no means a new trend. "Old" lipid dosage forms such as suppositories, creams or emulsions have been on the market for a long time, and some of them in use since a long time. However, over the last decade, approaches in new designs of lipid carriers have considerably evolved for the delivery of poorly soluble drugs. Lipid based drug delivery systems (DDS) can play a direct role in improving efficacy and drug safety, whereby new and improved therapies are possible. The spectrum of applications for lipid based formulations has widened as the nature and type of active drugs under investigation vary. Lipid based formulations may also protect active compounds from biological degradation or transformation, which in turn can lead to an enhancement of drug potency. In addition, lipid based particulate DDS have been shown to reduce the toxicity of various drugs by changing the biodistribution of the drug away from sensitive organs. This article mainly focuses on novel lipid formulations namely emulsions, vesicular systems and lipid particulate systems and their subcategories as well as on their prominent applications in pharmaceutical drug delivery.

Keywords: drug delivery system, emulsions, vesicular systems, lipid particulate systems.

INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action.

Lipid based drug delivery systems (DDS) represent a diverse group of formulations, each having different structural and functional characteristics which can be modified by adjusting the contents of different lipid excipients and other additives. The spectrum of varying properties seems unlimited, but is, in practice, restricted by cost, convenience, safety and regulatory demands. The introduction of new excipient combinations and DDS will most likely stimulate the use of lipid based DDS and lead to new and improved therapies in the future. Many drugs on the market, and in different development stages, have non-optimal properties that potentially could be improved by a suitable delivery system.

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 interests 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.

DESIGN OF LIPID BASED DDS

Several lipids based DDS have been developed over the years. Novel lipid drug delivery systems can be broadly classified as emulsions, vesicular systems and lipid particulate systems.

EMULSIONS

The word "emulsion" comes from the Latin word for "to milk", as milk is an emulsion of milk fat and water, among other components. Emulsion can be defined as heterogenous systems of one liquid dispersed throughout another in the form of droplets usually exceeding 0.1 micrometer in diameter. Oral formulation of emulsion can be used in enhancing bioavailability, giving controlled rate of drug release, affording protection to oxidation or hydrolysis. Topical formulation of emulsion can be easily applied and formulated to eliminate oiliness and staining, carrying water which is an excellent softener to skin. Emulsion includes microemulsion, self-emulsifying delivery system, nanoemulsion, pickering emulsion.

Microemulsions

Hoar and Schulman introduced the concept of microemulsion in 1940. They titrated a milky type emulsion with hexanol to generate a single-phase clear solution[4]. Schulman and coworkers (1959) consequently coined the term of microemulsion, and it has since been defined and indeed redefined on many occasions[5]. Considering the objectives of this review, however, the definition provided by Danielsson and Lindman in 1981 will be used as the point of reference[6]. Microemulsions are thus defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution. Microemulsions are readily distinguished from normal emulsions by their transparency, low viscosity and more fundamentally their thermodynamic stability. 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 have generated considerable interest over the years as potential drug delivery systems[8]. Advantages associated with microemulsions include their thermodynamic stability, optical clarity and ease of preparation. The existence of microdomains of different polarity within the same single-phase solution enables both water-soluble and oil soluble materials to be solubilised, and at the same time if this is so desired. Furthermore it is also possible to incorporate amphiphilic drugs into the microemulsion, sometimes even leading to an increase in the extent of existence of the microemulsion region[9].

Self emulsifying delivery systems

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation[10-11]. Recently, SEDDS have been formulated using medium chain tri-glyceride oils and nonionic surfactants, the latter being less toxic. Upon peroral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility[12-13]. Potential advantages of these systems include enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, and protection of drug(s) from the hostile environment in gut[14-15].

SEDDS are promising approach for oral delivery of poorly water-soluble compounds. It can be achieved by pre-dissolving the compound in a suitable solvent and fill the formulation into capsules. The oral drug delivery of hydrophobic drugs can be made possible by SEDDS. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favour the drug remaining in the lipid droplets[16].

Nanoemulsions

Nanoemulsions are oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm. Usually, the average droplet size is between 100 and 500 nm. The particles can exist as oil-in-water and water- in-oil forms, where the core of the particle is either oil or water, respectively. Nanoemulsions are made from surfactants approved for human consumption and common food substances that are “Generally Recognized as Safe” (GRAS) by the FDA. These emulsions are easily produced in large quantities by mixing a water-immiscible oil phase with an aqueous phase under high shear stress, or mechanical extrusion process that is available worldwide[17].

The olfactory region of the nasal mucosa provides a direct connection between the nose and brain, and by the use of nanoemulsions loaded with drugs, conditions such as Alzheimer’s disease, migraine, depression, schizophrenia, Parkinson’s diseases, meningitis, etc. can be treated[18-19].

Use of nanoemulsions in transdermal drug delivery represents an important area of research in drug delivery, which enhances the therapeutic efficacy and also the bioavailability of the drugs without any adverse effects. Many studies have shown that nanoemulsion formulations possess improved transdermal and dermal delivery properties in vitro, as well as in vivo[20-23]. Nanoemulsions have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsions and gels[24-25].

Nanoemulsion can reduce the frequency and dosage of injections throughout the drug therapy period as this emulsion guarantee the release of drugs in a sustained and controlled mode over long periods of time. Additionally, the lack of flocculation, sedimenta- tion and creaming, combined with a large surface area and free energy, offer obvious advantages over emulsions of larger particle size, for this route of administration[26].

Another interesting application, which is experiencing an active development, is the use of nanoemulsion formulations, for controlled drug delivery and targeting[27]. Because of their submicron size, they can

easily be targeted to the tumor area. The development of magnetic nanoemulsions is an innovative approach for cancer therapy.

A vaccine carrier system using nanoemulsions is currently being researched. This medication delivery system uses nanotechnology to vaccinate against human immunode- ficiency virus (HIV). There is recent evidence that HIV can infect the mucosal immune system. Therefore, developing mucosal immunity through the use of nanoe- mulsions may become very important in the future fight against HIV[28]. The oil-based emulsion is administered in the nose, as opposed to traditional vaccine routes. Research is demonstrating that genital mucosa immunity may be attained with vaccines that are administered into the nasal mucosa[29].

Until now, the submicron emulsion system has not yet been fully exploited for pulmonary drug delivery. Nebulization of submicron emulsions will be a new and upcoming research area. However, extensive studies are required for the successful formulation of inhalable submicron emulsions due to possible adverse effects of surfactants and oils on lung alveoli function (adverse interactions with lung surfactant).

Pickering Emulsions

Lipid based emulsions stabilized by solid particles such as calcium carbonate, latex, silica, clays, titanium dioxide are known as pickering emulsions. Recently, there is an increasing interest in pickering emulsions because they open new avenues of emulsion stabilization. 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[30]. 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[31].

VESICULAR DRUG DELIVERY SYSTEMS

Newer vesicular systems are evolved every day. Drug deliveries as well as other biomedical applications of lipid vesicles and other surfactant microstructures are presently enjoying huge popularity among a diversity of researchers in several disciplines. Lipid vesicular system includes liposome, proliposome, phytosome, transfersome, ethosome, archaeosome, vesosome, niosome.

Liposomes[32]

Liposomes were discovered in the early 1960's by Bangham and colleagues and subsequently became the most extensively explored drug delivery system. Structurally liposomes are concentric bilayered vesicles in which as aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or sysnthetic phospholipids. Lipomes are formed when phospholipids are hydrated. The most common natural phospholipids are phosphatidylcholine (PC). These are amphiphillic molecules in which a glycerol bridge links to a pair of hydrophobic acyl hydrocarbon chains with a hydrophilic polar head group phosphocholine. Amphiphillic nature of phospholipids and their analogues render them the ability to form closed concentric bilayers in the presence of water. Liopsomes are formed when thin films of amphiphilic nature are hydrated and stacks of liquid crystalline bilayers become fluid and swell. The hydrated lipid sheets detach during agitation and self close to form large multilamellar vesicles (MLVs). Sonification is done to get small unilamellar vesicles (SUVs). Extrusion is also done to get large unilamellar vesicles (LUVs). Several methods exist for improved loading of drugs using pH gradients and potential difference across liposomal membranes. The pH gradient is created by preparing liposomes with a low pH inside the vesicles followed by the addition of the base to the extra liposomal medium. Accumulation occurs at the low pH side. So the unprotonated form of basic drug can diffuse through the bilayer. At the low pH side, the molecules are predominately protonated which lowers the concentration of drug in the unprotonated form and thus promotes the diffusion of more molecules at the low pH side of the bilayer. Stealth liposomal technology is designed for the intravenous drug delivery.

Proliposomes[33]

In order to increase the surface area of dried lipid film and to faciliatate hydration, the lipid is dried over a finely divided particulate support. These dried lipid coated particulates are called pro-liposomes. Pro-liposomes form dispersion of MLVs on adding water into them. This method overcomes the stability problems of liposomes encountered during their storage as dispersion, dry or frozen form. It is ideally suited for preparations where the drug to be entrapped incorporated into lipid membrane.

Phytosomes

Phytosome is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipids and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipids-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. When treated with water, phytosomes assumes a micellar shape forming liposomal-like structures[34].

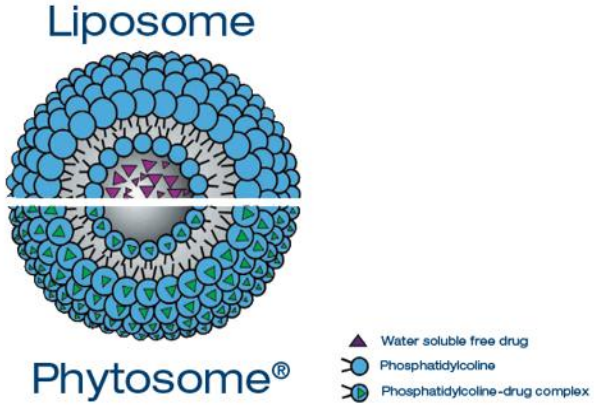

Figure 2: Major difference between liposome and phytosome: the molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment).

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[35].

Transfersomes

Transfersome is a term which means "carrying body", which is originated from 'transferre' a Latin word, implying 'to take across', and 'soma', a Greek word means for a 'body'. A lipid particulate delivery system for transfersome is an artificial vesicle designed to be like a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and, potentially targeted, drug delivery. Transfersomes are a special type of liposomes, consisting of phosphatidylcholine and a surfactant which act as an edge activator[36].

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[37]. These vesicular transfersomes are several orders of magnitudes more elastic than the standard liposomes and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. There is provision for this, because of the high vesicle deformability, which permits the entry due to the mechanical stress of surrounding, in a self-adapting manner. Flexibility of transfersomes membrane is achieved by mixing suitable surface-active components in the proper ratios[38]. The resulting flexibility of transfersome 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 nonocclusive condition. Transfersomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayers properties[39]. The following figure shows possible micro routes for drug penetration across human skin intracellular and transcellular[40].

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 or interferon[41-42]. 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. 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[43].

Ethosomes

Ethosomes are the trivial modification of liposome, a well well-known drug delivery service. Being soft, malleable lipid vesicles they are used for enhanced delivery of active agents. Ethosomal systems are vesicular systems composed mainly of phospholipid, ethanol, propylene glycol and water[44]. Unlike classic liposomes, that are known mainly to deliver drugs to the outer layers of skin, ethosomes were shown to enhance permeation through the stratum corneum barrier[45-50]. Ethosomes are shown to entrap drug molecule with various physiochemical characteristics i.e. of hydrophilic, lipophilic or amphipilic[51].

Archaeosomes

Archeosomes are archebacteria lipids consisting vesicles. They are less sensitive to oxidative stress, high temperature, and alkaline pH[52-53]. Archaeosomes are nothing but liposomes in 200nm size range, which are prepared from ether lipids extracted from various Archaeobacteria Archaeosomes (liposomes comprised of glycerolipids of Arcaea) are lipid vesicles and their membranes are constituted of ether linked isoprenoid phytanyl core lipid or purified lipid sub fractions[54-57]. Archaeosomes constitute a novel family of liposomes 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[58].

It has been shown that incorporation of polyethylene glycol and Coenzyme Q10 into archaeosomes can alter the tissue distribution profiles of intravenously administered vesicles[59]. It 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[60-61].

Vesosome

Vesosome consists of one or more bilayers enclosing an aqueous core that contains unilamellar vesicles that function as internal compartments which contain the drug and which can vary in composition from each other. The external bilayer defines the lumen, limits emission of the vesicle contents, and protects the vesicle contents from degradation due to lipolytic enzymes. Its unique properties enable localizeddrug delivery in specific parts of the body and extend the duration of drug effect.

Niosomes[62-64]

Non ionic surfactant vesicles (NSVs or Niosomes) are now widely studied as an alternative to liposomes. Non-ionic surfactant vesicle results from self assembly of hydrated surfactant monomers. Niosomes are essentially non ionic surfactant based multi or unilamellar vesicles in which an aqueous solution is entirely enclosed by a membrane resulted from the organization of surfactant macromolecules as bilayers. Ether injection, hand shaking method, sonification, reverse phase evaporation, aqueous dispersion and extrusion are various methods of preparation of niosomes.

LIPID PARTICULATE SYSTEMS

In recent decades, lipids of biocompatible microparticles and nanoparticles have evolved as potential

polymers carriers. Their unique size dependant properties and the ability to fit in drug into nanocarriers, evolve them as potential drug delivery systems. Some advantageous features of lipid particulate systems include:

- Physiologically compatible and physicochemically stable carrier systems
- Controlled drug release
- Higher levels of drug targeting
- 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.
- Uncomplicated scale-up.

Lipid microparticles

Polymeric microspheres have been tested successfully as sustained release drug delivery system however their safety still remains uncertain which leads to the development of solid lipid microparticles (SLMs)[65]. 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[66].

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 carriers 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[67]. 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[68-69].

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[70]. NLC system minimizes or avoids the following disadvantages of SLNs like low drug loading capacity, drug expulsion during storage and high water content[71].

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[72]. 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[73].

Many applications like drugs with irritant effects like tretinoin turns out to be less irritating if applied when encapsulated within SLN[74]. Lipid nanoparticles can be used to improve the bioavailability of drugs, e.g. cyclosporine A60, clozapine, to improve the stability of chemically labile hydrophobic antioxidants like retinol, CoQ10, alpha-lipoic acid, beta-carotene and alpha-tocopherol and to obtain sustained release of lipophilic drugs like camptothecin[75-76]. Idarubicin-loaded SLN acted as a prolonged release system after duodenal administration to rats[77].

CONCLUSION

Lipid based drug delivery systems, a physiologically well-tolerated class of formulations, provide a vast array of possibilities to formulate and potentially increase the bioavailability of an ever-growing number of poorly soluble drugs. In recent years, progressive elucidation of the various mechanisms through which lipids can increase bioavailability – a unique combination of solubilisation, dispersion or encapsulation, and stimulation of the digestive process, potential inhibition of receptor-mediated efflux or pre-systemic metabolism, or (even if poorly understood), passage through the lymphatic system – have all contributed, and will continue to contribute to a greater number of products in preclinical and clinical development, and in the market. On the way of conclusion, the prospect of these delivery systems looks promising.

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