REVIEW ARTICLE

Pharmaceutical Particulate Carriers: Lipid - Based Carriers

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ABSTRACT

Drug delivery research areas is continuously broaden and modified as a results of the realization of many factors (such as poor drug solubility and/or absorption, rapid metabolism, high fluctuation in the drug plasma level and variability) adversely affect in-vivo results, in conventional drug delivery system. Lipids are one of the basic building blocks of biological membranes. Nanoscale-based delivery strategies are beginning to make a significant impact on global pharmaceutical planning and marketing. Among the approaches for exploiting nanotechnology developments in medicine, various nanoparticulates offer some unique advantages as pharmaceutical carriers in delivery systems and image enhancement agents. The review illustrates the various classes of particulate lipid-based carriers among them; lipoproteins, lipid nanoparticles either; solid lipid nanoparticles, nanostructured lipid carriers, or lipid drug conjugates, lipid nanocapsules, and liposomes. Lipid-based particulate carriers' applications in various areas were also addressed.

KEY WORDS: Lipoproteins; Solid Lipid Nanoparticles; Nanostructured Lipid Carriers; Lipid Drug Conjugates; Lipid Nanocapsules; Liposomes

Drug delivery is continuously looking into newer avenues due to realization of the factors like poor drug solubility and/or absorption, rapid metabolism, high fluctuation in the drug plasma level and variability which are playing major role in disappointing *in-vivo* results leading to failure of the conventional delivery system. Lipids are one of the basic building blocks of biological membranes.[1] Since the last decade, drug delivery has taken a new dimension with the increasing application of lipid as a carrier for the delivery of poorly water soluble, lipophilic drugs.[2, 3] The unique properties of lipids *viz.*, their physiochemical diversity, biocompatibility and proven ability to enhance bioavailability of poorly water soluble, lipophilic drugs have made them very attractive candidates as carriers (Table 1). With the above promises, the emerging field of lipid-based drug delivery systems have attracted considerable academic attention.[4]

Table 1: Classification of lipid-based pharmaceutical carriers

Lipid-based pharmaceutical carriers			
Lipoproteins	**Lipid nanoparticles**	**Lipid nanocapsules**	**Liposomes**
Chylomicron	Solid lipid nanoparticles		Conventional liposomes
Very low-density lipoprotein (VLDL)	Nanostructured lipid carriers		Modified lipisomes
Intermediate-density lipoprotein (IDL)	Lipid drug conjugates		
Low-density lipoprotein (LDL)			
High-density lipoprotein (HDL)			

Table 2: Physicochemical properties of lipoproteins[7]

Lipoprotein	Transport Route	Size(nm)	Protein (%)	Total lipids (%)
Chylomicron	Intestines to liver	75-1200	1.5-2.5	97-99
VLDL	Liver to tissues	30-80	5-10	90-95
IDL	Liver to tissues	25-35	15-20	80-85
LDL	Liver to tissues	18-25	20-25	75-80
HDL	Tissues to liver	5-12	40-55	45-60

1. Lipoproteins

Large protein structures may be utilized as pharmaceutical carriers of drugs and DNA for targeted and other specialized delivery in biological systems. Lipoproteins are such structures which function as natural biological carriers and transport various types of lipids in blood circulation. There are many studies suggesting that lipoproteins can serve as efficient carriers for anticancer drugs, gene or other type of compounds.[5] Lipoproteins as drug carriers offer several advantages.[6] Firstly, they are endogenous components and do not trigger immunological response. They have a relatively long half-life in the circulation. Secondly, they have small particle size in the nanometer range, allowing the diffusion from vascular to extravascular compartments. Thirdly, lipoproteins can potentially serve as the carriers for targeted drug delivery through specific cellular receptors. Fourthly, the lipid core of lipoprotein provides a suitable compartment for carrying hydrophobic drugs.[6]

Lipoproteins can be classified into five major classes, based on their densities from gradient ultracentrifugation experiments. The lipoprotein classification includes chylomicron, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). These classes of lipoproteins have different sizes, different protein to lipid ratios and different types of apolipoproteins.[7] The general physicochemical properties of lipoproteins are presented in Table 2.

Various types of bioactive molecules have been incorporated into reconstituted chylomicron

structure for delivery purposes. In gene delivery, Hara *et al.*[8] developed reconstituted chylomicron which incorporated a hydrophobic DNA complex and used it as an *in-vivo* gene transfer vector and found that the DNA-incorporated chylomicrons induced a high gene expression in mouse liver after the reconstituted chylomicron was administered through portal vain injection. As a targeted therapeutic approach to hepatitis B, anti-viral iododeocyuridine was incorporated into recombinant chylomicrons, resulting in the drug molecules being selectively targeted to the liver parenchymal cells.[9]

As a drug carrier, VLDL is an interesting candidate because it contains a relatively small amount of proteins (about 5-10 % protein) and a large amount of triglycerides (about 50-65% within the emulsion core) which can be used to solubilize hydrophobic substances sufficiently. By mimicking the compositions and structure of VLDL, Shawer *et al.*[10] developed a VLDL-resembling phospholipid nanoemulsion system that carried a new anti-tumor boron compound for targeted delivery to cancer cells. Cytotoxic drugs such as 5-fluorouracil, 5-iododeoxyuridine, doxorubicin, and vindesine can be effectively incorporated into VLDL, and the resultant complexes showed effective cytotoxicity to human carcinoma cells.[11]

Among various lipoproteins, LDL has been widely studied as a drug carrier for targeted and other specialized deliveries, because many types of cancer cells show elevated expression of LDL receptors than the corresponding normal cells.[12] Comparing with chylomicron, VLDL, and IDL, LDL also has a longer serum half-life of 2-4 days[13], making it a desirable drug carrier. Low density lipoprotein was found to be suitable as carriers for cytotoxic drugs to target cancer cells. LDL drug complexes can be formed through various processes without changing the lipoprotein integrity.[5] LDL may serve as a carrier for site-specific delivery of drugs to atherosclerotic lesions.[14]

HDL has mainly been utilized for the delivery of water insoluble anticancer drugs through the targeting function.[15] When the anticancer drug, Taxol, was incorporated into HDL, stable complexes were formed and they were examined for cancer-cell targeting.[15] Reconstituted HDL was explored as a drug carrier system for a lipophilic prodrug, IDU-OI_2.[16] These studies indicated that the lipophilic prodrug could be efficiently incorporated into reconstituted HDL particles. The utilization of HDL for drug targeting may lead to a more effective therapy for infectious diseases, such as hepatitis B, since the HDL-drug complexes were demonstrated to be selectively taken by parenchymal liver cells.[16] Interestingly, it was observed that HDL-drug complex specifically increased the cytotoxicity to carcinoma cells. Earlier study showed that HDL could increase the sensitivity of HeLa cells to the cytotoxic effects of doxorubicin.[17] Similar to LDL-drug complex, the lipoprotein receptor pathway appears to be involved in the interactions between HDL-drug complex and cancer cells.

2. Lipid nanoparticles

At the beginning of the 1990s there were only the research groups of Müller (Berlin, Germany), Gasco (Turin, Italy) and Westesen (Braunschweig, Germany) working on lipid nanoparticles. Currently more than 20 research groups are working on lipid nanoparticles worldwide, estimated by the published articles. This proves the increasing interest in the field of lipid nanoparticles, which have been investigated for various pharmaceutical applications, e.g. parenteral[18], peroral[19], dermal[20], ocular[21] and pulmonary[22]. Moreover, since the last decade, they have been studied intensively for dermal application, both in pharmaceutical and cosmetic uses.

2.1. Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) were developed at the beginning of the 1990s as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles. SLN are produced by

replacing the liquid lipid (oil) of an o/w emulsion by a solid lipid or a blend of solid lipids, i.e. the lipid particle matrix being solid at both room and body temperature. SLN are composed of 0.1% (w/w) to 30% (w/w) solid lipid dispersed in an aqueous medium and if necessary stabilized with preferably 0.5% (w/w) to 5% (w/w) surfactant. The incorporation of cosmetic and pharmaceutical actives is feasible. The mean particle size of SLN is in the submicron rage, ranging from about 40 to 1000 nm.[23]

Solid lipid nanoparticles (SLN) are a comparatively stable colloidal carrier system in which melted lipid is dispersed in an aqueous surfactant by high-pressure homogenization or microemulsification.[24] 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.[25, 26] 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 liver. They have comparatively higher drug entrapment efficiency, render the drug more stable in their lipid matrix, and provide a controlled release lasting up to several weeks. 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 steric stabilization, whereas the use of complex lipids (mono-, di-, triglycerides of different chain lengths) results in an increased loading efficiency.[27]

Several anticancer agents have been encapsulated in lipid nanoparticles, and their *in-vitro* and *in-vivo* efficacy has been evaluated by suitable studies. SLN have been shown to improve the efficacy and residence time of the cytotoxic drugs with concomitant reduction in the side-effects associated with them.[28] Various drugs ranging from antipsychotics, anti-Parkinson, antlieschemic to antibiotics have been encapsulated in lipid nanoparticles with the aim to either modify the biodistribution or for brain targeting.[24, 29] Moreover, unmodified SLN showed significantly higher accumulation in liver as compared to that of PEG-modified SLN. Oxymatrine, a hepatoprotective agent, was incorporated in SLN and its liver-targeting efficacy was determined in rats.[30]

2.2. Nanostructured lipid carriers

The second generation of the lipid nanoparticle technology, the particles are produced using blends of solid lipids and liquid lipids (oils). To obtain the blends for the particles matrix, solid lipids are mixed with liquid lipids (oils), preferably in a ratio of 70:30 up to a ratio of 99.9:0.1. Due to the oil in these mixtures a melting point depression compared to the pure solid lipid is observed, but the blends obtained are also solid at body temperature. This second generation of nanoparticles is called nanostructured lipid carriers (NLC). The overall solid content of NLC could be increased up to 95%. This second generation of submicron particles can be loaded with cosmetic and pharmaceutical active substances as well. NLC were developed to overcome some potential limitations associated with SLN. Compared to SLN, NLC shows a higher loading capacity for a number of active compounds, a lower water content of the particle suspension and avoid/minimize potential expulsion of active compounds during storage.[2] By now NLC are mainly investigated for dermal application[31] with seldom investigations focused on the parenteral route[32].

Nanostructured lipid carriers (NLCs) have been proposed as a new SLN generation with improved characteristics. The general idea behind the system is to improve the poor drug loading capacity of SLN by "mixing solid lipids with spatially incompatible lipids leading to special structures of the lipid matrix", while still preserving controlled release features of the particles. Three different types of NLCs have

been proposed (NLC I: The imperfect structured type, NLC II: The structureless type and NLC III: The multiple type). Unfortunately, these structural proposals have not been supported by experimental data. They assume a spherical shape and they are not compatible with lipid platelet structures. The experimental data concludes that NLCs are not spherical solid lipid particles with embedded liquid droplets, but rather, they are solid platelets with oil present between the solid platelet and the surfactant layer.[27, 33]

2.3. Lipid drug conjugates

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 (e.g., with a fatty acid) or by covalent linking (e.g., to the esters or ethers). Lipid drug conjugates bulk is then homogenized in the presence of a stabilizer in water using high pressure homogenization.[27, 34]

3. Lipid nanocapsules

Lipid nanocapsules (LNCs) are patented nanocarriers designed to encapsulate lipophilic drugs without organic solvents. Their synthesis is based on an original phase-inversion process, allowing the production of nanocarriers in a sodium hydroxide aqueous solution with a size ranging from 25 to 100 nm.[35] The size distribution of the carrier is unimodal with a low polydispersity index. The LNC structure is composed of a lipid core in which the solubilized lipophilic drug is limited by a membrane of lecithin and pegylated poly-ethyleneglycol hydroxystearate chains conferring some degree of stealthiness.[36] All the excipients of the LNC are FDA approved. At a temperature of 37 °C, the core is liquid, whereas the membrane is rigid. Previous studies have demonstrated the ability to entrap amiodarone[37], ibuprofen[38], tripentone[39], etoposide[40], and paclitaxel[41] into LNCs. In preclinical studies, etoposide and paclitaxel-loaded LNC showed a higher cytotoxicity effect than free drugs after systemic administration. This can be explained by sustained drug release and P-glycoprotein (P-gp) inhibition.[40] Interestingly, radioactive components such as 99mTc and 188Re can be used to label LNC allowing the imaging of the distribution for diagnostic and therapeutic uses[42] (Table 3).

LNC formulation is based on at least three principal components: an oily phase, an aqueous phase and a nonionic surfactant. The oily phase is essentially constituted of triglycerides of capric and caprylic acids known under the commercial name of Labrafac®. The hydrophilic surfactant, Solutol® HS 15, is derived from polyethylene

Table 3: Various strategies for drug delivery to the sites of action using lipid nanocapsules

Strategies	Example	Encapsulating drug and rate	Study design	Results
P-gp inhibition	LNC coated with PEG-type non-ionic surfactants	Etoposide 89.9 ± 2.3 %	*in-vitro* on glioma cell lines	increase cytotoxicity[40]
Passive targeting	post-insertion of longer PEG chains	drug-free	biodistribution after an IV injection into healthy rats	half-life time over 5 hr *vs* under 21 min for conventional LNC[36]
Active targeting	attachment of Mab of Fab fragments	drug-free	*in-vitro* cell binding on cells	effective binding of immune-nanocapsules[45]
local administration	CED technique for delivery of LNC into the brain	^{299} Re-SSS:Fc-diOH > 98%	9 L brain tumor intracranial xenograft model	significant improvement in median survival time[46]
Oral administration	LNC formulation to inhibit P-gp on the GIT	paclitaxel 99.9 ± 1%	oral administration by gastric intubation into healthy rats	augmentation of mean plasmatic concentration of paclitaxel[41]

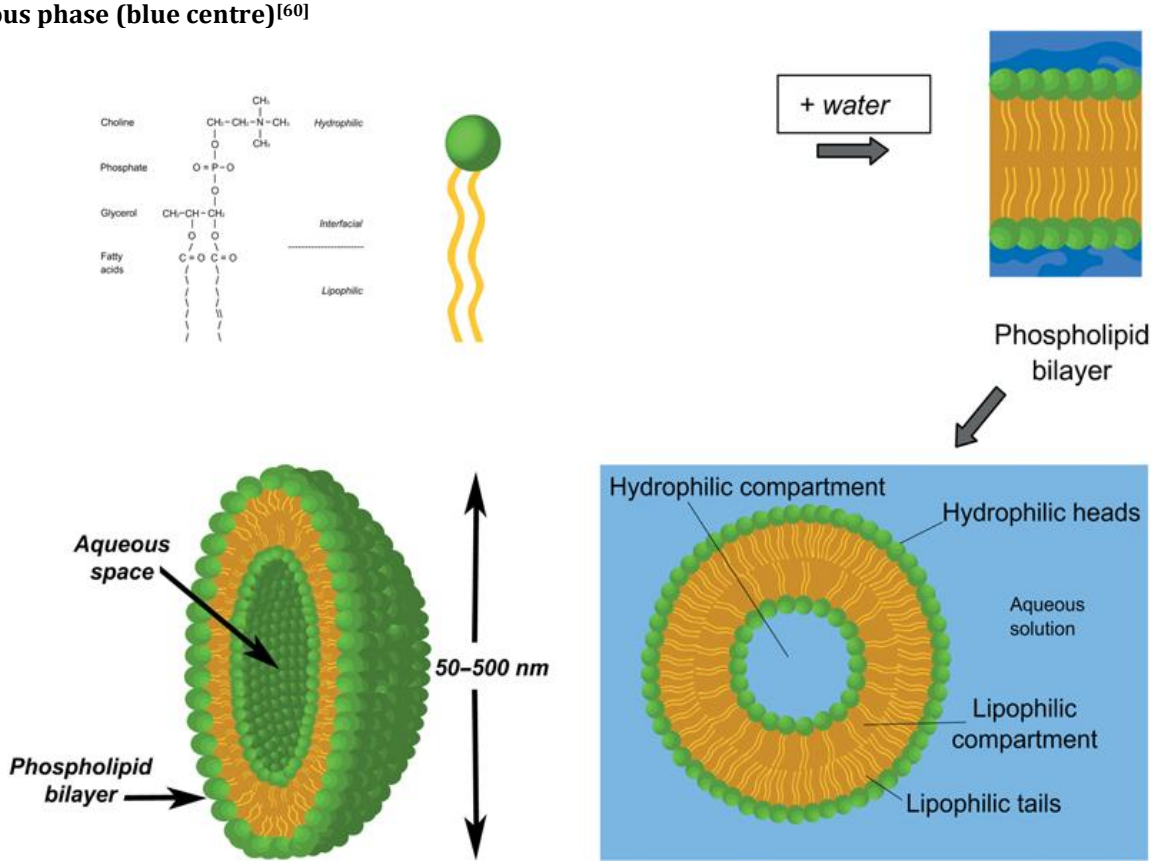
glycol and is a mixture of free PEG 660 and PEG 660 hydroxystearate. The aqueous phase consists of MiliQ® water plus sodium chloride salt, NaCl. Furthermore, another surfactant, Lipoid®, composed of 69% phosphatidylcholine soya bean lecithin, is used in small proportions to significantly increase LNC stability[43], which is especially necessary in the case of 50–100 nm LNC formulations. All components are approved by the FDA for oral, topical and parenteral administration. [35]

Immunonanocapsules have been designed, by the conjugation of LNCs to whole OX26 MAb, for the purpose of actively transporting drugs to the brain parenchyma.[44] Furthermore, Fab fragments conjugated to LNCs have also been evaluated because of the interest of their reduced MPS uptake via the Fc receptor-mediated mechanism, which allows prolonged systemic circulation.[45] This coupling has been facilitated by the incorporation of lipid PEG 2000, functionalized with reactive maleimide groups (DSPE–PEG 2000–maleimide), into LNC shells by a post-insertion procedure allowing the covalent attachment of the ligands to LNCs. Further research has included *in-vitro* studies on cells over-expressing TfR, such as the Y3.AG.1.2.3. hybridoma cell line and rat brain cerebral endothelial cells, as well as immunonanocapsule distribution in healthy rats after intravenous injection.[46]

4. Liposomes

Liposomes are currently in common use as universal drug carriers in the cosmetic and pharmaceutical industries. In healthcare, there are antitumor anthracyclines such doxorubicin and antifungal amphotericin B liposomal formulations available.[47] Liposomes are spherical vesicles consisting of one or more phospholipid bilayers surrounding a water space. The diameter of the liposome varies from 0.02 to 10 μm. Vesicle formulations are usually based on natural and synthetic phospholipids and cholesterol.[48]

Figure 1: Top left structural formula of the phosphatidylcholine molecule. In the presence of water phospholipid bilayers are formed, which create vesicles, enclosing an aqueous core. Lipid soluble substances can be stored in the outer lipid phase (yellow ring) and water soluble substances in the inner aqueous phase (blue centre)[60]



Regarding the variety of liposomal formulations, the vesicles are universal carriers for both hydrophilic and hydrophobic compounds (Figure 1).

Nanoliposomes, or nanometric versions of liposomes, are colloidal structures formed by the input of energy to a right combination of constituent molecules (mainly phospholipids) in an aqueous solution. These lipid vesicles are under intensive research and development by the pharmaceutical, cosmetic, and food industries as nanocarrier systems for the protection and delivery of bioactive agents. The phospholipid molecules used in the structure of lipid vesicles are the main component of naturally occurring bilayers. The key common characteristic of bilayer-forming molecules is their amphiphilicity. It should be noted that not all nanostructures composed of phospholipids are liposomes. Certain mixtures of lipid and/or phospholipid molecules can also result in non-liposomal structures, such as lamellar, hexagonal, micellar, or cubic phases.[49] Nevertheless, liposomes are closed, continuous, vesicular structures composed mainly of phospholipid bilayer(s) in an aqueous environment.[50] These vesicular structures have been the subject of extensive research, and several related technologies have been developed for specialized applications, which include ultradeformable vesicles for transdermal drug delivery[51] or arsenoliposomes for anticancer therapy[52]. Liposomes and nanoliposomes can be manufactured by using safe ingredients obtained from natural sources, such as egg, soy, or milk.[53]

When amphiphilic molecules such as phospholipids are placed in an aqueous environment, they form aggregated complexes in an attempt to shield their hydrophobic sections from the water molecules while still maintaining contact with the aqueous phase via the hydrophilic head groups. If a sufficient amount of energy is provided to the aggregated phospholipids, they can arrange themselves in the form of organized, closed bilayer vesicles (i.e., liposomes or nanoliposomes) (Figure 1). During this process, liposomes can entrap hydrophilic solutes that are present in the hydration media. Lipophilic molecules, or lipid-soluble compounds such as certain vitamins, nutrients, and drugs, can also be incorporated into liposomal bilayers by dissolving these molecules together with the lipids. Alternatively, lipid-soluble substances may be complexed with cyclodextrins and then encapsulated within the aqueous compartment of liposomes and nanoliposomes.[54] It should be noted that the formation of liposomes and nanoliposomes is not a spontaneous process. Lipid vesicles are formed when phospholipids, such as lecithin, are placed in water and, consequently, form one bilayer or a series of bilayers, each separated by water molecules, once adequate energy is supplied. Input of energy (e.g., in the form of sonication, homogenization, heating, etc.) results in the arrangement of the lipid molecules, in the form of bilayer vesicles, to achieve a thermodynamic equilibrium in the aqueous phase. Lasic *et al.*[55] proposed that symmetric membranes prefer to be flat (spontaneous curvature $\equiv C_o=0$) and energy is required to curve them. The type of lipids used and the presence or absence of sterols is among the parameters that determine membrane curvature.

Applications of liposomes in pharmacology and medicine can be divided into therapeutic and diagnostic applications of liposomes containing drugs or various markers and their use as a model, tool, or reagent in the basic studies of cell interactions, recognition processes and the mode of action of certain substances.[56] New drug delivery systems such as liposomes are developed when an existing formulation is not satisfactory and reformulations of superior therapeutic efficacy and safety over existing formulation. Indeed, liposome formulations of some drugs have shown a significant increase in therapeutic efficacy and/or therapeutic indices in preclinical models and in humans, compared to their non-liposomal formulations.

Currently, liposomes are being used as excipient for preparing better tolerated preclinical and clinical formulations of several lipophilic, poorly water-soluble drugs such as amphotericin B[57], porphyrins, minoxidil, some peptides and

anthracyclines, furthermore, in some cases hydrophilic drugs, such as anticancer agent doxorubicin[58] or acyclovir can be encapsulated in the liposome interior at concentrations several fold above their aqueous solubility. This is possible due to precipitation of the drug or gel formation inside the liposome with appropriate substances encapsulated.[59]

Liposome was modified with cetylated polyethylenimine (PEI) to be a non-viral gene transfer system. This polycation liposome (PCL) showed remarkable transfection efficiency to COS-1 cells *in-vitro*, in comparison with conventional cationic liposomes preparations. Cytotoxicity against COS-1 cells and hemolytic activity of PCL or PCL-DNA complex were quite low in comparison with conventional cationic liposomes. Most conventional cationic liposomes require phosphatidylethanolamine or cholesterol as a component, though PCL dose not. Furthermore, the transfection efficacy of PCL was enhanced, instead of being diminished, in the presence of serum. Effective gene transfer was observed in all eight malignant and two normal line cells tested as well as in COS-1 cells. The effect of the molecular weight of PEI on PCL-mediated gene transfer was examined[61] and a conclusion was reached; PEIs with a molecular weight of 600 and 1800 Da were quite effective but PEI of 25,000 was far less effective. Effectiveness of gene transfer by using PCL was also observed *in-vivo*. Taken together; PCL represented a new system useful for transfection and gene therapy.[61] Uhl *et al*.[62] proved that hyperpolarization of cationic liposomes improved their stability in the presence of human serum albumin.

The usefulness of double liposomes for oral immunization was studied; liposomes containing liposomes inside, as an oral vaccine carrier was examined. Ovalbumin (OVA) encapsulating liposomes sized to 230 nm were prepared by the glass-beads (GB) method and sequential sonication and extrusion. For the purpose of stabilizing the model antigen, double liposomes, DL, containing small liposomes were prepared by the glass-beads method and the reverse-phase evaporation method. They were named GB-DL and REV-DL, respectively. DL showed suppressed release of OVA and stabilized OVA in pepsin solution as compared with single liposomes (SL). BALB/c mice were immunized with OVA solution, SL and DL suspension by oral administration. Significantly higher levels of immunoglobulin-A (IgA) in feces were observed in mice immunized with SL and REV-DL as compared with OVA solution and REV-DL tended to show the higher level of IgA than SL. REV-DL elicited significantly higher anti-OVA IgG responses as compared with OVA solution. Furthermore, GB-DL tended to raise the IgG level as compared with SL. The results suggest that DL have the potential to be an effective carrier for oral immunization.[63]

Liposomes have been used as targeting bullets by conjugating them with antibodies or specific receptor binding ligands. This technology has been employed quite successfully for delivering anticancer drugs using monoclonal antibodies where they could not only reduce the toxicity of anticancer agents but also enhanced the pharmacokinetic properties of slow absorbing drugs. Many anti-cancer agents such as doxorubicin, daunorubicin, annamycin, vincristine, paclitaxel and cisplatin, camptothecin and 5-fluorouracil derivatives have been successfully encapsulated in liposomes.[64] Liposomization and other micro, nano-encapsulation techniques are associated with the problem of clumping and flocculation, which limits their shelf life. The short half-life *in-vivo* caused by the endoplasmic clearance of liposome from the body is another hurdle in achieving the best therapeutic results. To tackle some of these problems a new generation of stealth liposomes has evolved[65] which involves attachment of PEG molecules. PEGylation has helped in improving the stability of such formulations both *in-vitro* and *in-vivo* and till date it remains the key technology for stabilization and sustained release of macromolecules within the circulation. Some heat sensitive and pH sensitive liposome have also been designed and developed where the constituents are chosen in a manner so that they release their contents under the influence of either heat[66] or pH changes[67].

The versatility of liposome preparations is exemplified by the numerous routes of administration that can be utilized to administer drugs. In this respect, the potential uses of liposomes for delivery applications surpass those achieved by many other drug release devices or formulations. Many routes have been demonstrated to be of potential use for sustained delivery of drugs from liposome preparations, among them, intramuscular[68] ,subcutaneous[69], intravenous[70], intra-articular[71], nasal[72], pulmonary[73], vaginal[74-76], oral [63, 77, 78], ocular[79, 80, 81], and topical[82] routes.

4.1. Modified Liposomes

Liposomes have been extensively studied for the transdermal delivery of drugs. After finite dose applications to hairless mouse skin, Ganesan *et al.*[83] reported that, for lipophilic drugs, greater amounts were delivered from vesicles compared to aqueous solution. Fresta and Puglisi[84] found that vesicles of unsaturated phospholipid produced high percutaneous absorption and tissue distribution rather than skin accumulation. Cevc and Blume[85] claimed that certain types of lipid vesicles (ultradeformable vesicles) can penetrate intact to the deep layers of the skin and may progress far enough to reach the systemic circulation, but they must be applied under non-occlusive conditions. The superiority of ultradeformable vesicles over "standard" liposomes for transdermal drug delivery was shown, and the importance of open (i.e. non-occluded) application was emphasised; Further, ultradeformable vesicles provided arachidonic acid induced edema suppression equivalent to a lotion containing five times the drug concentration of that in ultradeformable vesicles, after 0.5 h. When standard liposomes were evaluated, no edema suppression was found after 0.5 h. After 2 h, however, liposomes produced a measurable suppression which was about one-third that of ultradeformable vesicles and about half that of the lotion. The authors stated that the late effect of the vesicle formulation arose from free drug permeation following its release from liposomes.[86] Successful systemic delivery of insulin by ultradeformable vesicles has been reported from *in-vivo* mice and human studies. The efficiency of the formulation was comparable to that obtained after subcutaneous injection of the same preparation.[87]

The presence of a surfactant increases the elasticity of the lipid bilayers. Accordingly, it was concluded that flexible liposomes are more efficient in transdermal drug delivery.[88] It was suggested that such surfactants (edge activators) can impart deformability to the liposomes, which allows for improved transdermal drug delivery. The incorporation of ethanol in lipid vesicles is an alternative approach to fluidize the lipid membrane and thus enhance drug provision.[89] Ethanol containing vesicles (termed "ethosomes" by the inventors) improved the transdermal delivery of melatonin, an anti-jet lag agent with a poor skin permeation and long lag time.[90] Successful topical delivery of low molecular weight heparin was reported after incorporation into surface charged flexible vesicles made of lipids with Tween 80. These vesicles were termed flexosomes and the cationic structures were the most efficient.[91] Moreover, hepatitis B loaded ultradeformable vesicles are able to provide a positive immune response.[92]

In fact, conventional liposomes size, generally above 100 nm, makes one doubt that penetration through the SC will be favored. Hence, it could be generalized that these type of particles may enter the outermost layers of disjunct SC but in general are unable to permeate SC or skin.[93] In contrast, large but ultradeformable lipid vesicles have been advertised with great emphasis for their ability to permeate skin through the transepidermal route under non-occluded conditions, as demonstrated by various indirect evidence[85]. Intact vesicles were found in SC, precisely in channel-like regions, and less at the boundary of SC and stratum granulosum.[93]

CONCLUSION

In summary, this review introduced a facile framework for the lipid-based pharmaceutical drug carriers. Lipids are able to form a range of different nanoparticulate structures. These

include lipoproteins, lipid nanoparticles, lipid nanocapsules, and liposomes. This review attempts to clarify some of the terminology used in the literature by providing an overview of the major features of each type of nanoparticles and the applications for each particular nanoparticulate formulations.

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