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LIPID BASED PARENTERAL DRUG DELIVERY SYSTEM

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ABSTRACT

Lipid-based drug delivery systems in the form of triglyceride emulsions, micellar systems and liposomes have been used for parenteral administration for the last few decades. Large number of new chemical entities (NCE) presents formulation and bioavailability problems because of the dose and poor solubility in solvent and co-solvent systems. In addition, high drug concentrations can lead to irritation and pain at the site of injection. There is an increasing interest to expand the range of targetable lipid based systems to solubilize a wide variety of drugs, to improve stability, ease of processing and manufacture in a sterile form. New class of parenteral lipid based drug delivery system includes Tocol emulsions, solid lipid nanoparticles and nanosuspensions, sterically stabilized phospholipid micelles, lipid micro-bubbles and lipoprotein drug carriers. This review article covers the challenges faced by the formulation scientist at each stage of product development of lipid based drug delivery system.

INTRODUCTION [1-14]**:** In the past, surfactant systems as well as phospholipids emulsified triglyceride emulsions have been used as drug carriers for parenteral nutrition. Since many drugs are hydrophobic, they are sufficiently soluble in vegetable oils to enable the formulations like drug-loaded emulsions e.g. the intravenous anaesthetic Propofol. Lipid based drug delivery system are described under following titles like tocol emulsions, solid lipid nanoparticles and nanosuspensions, sterically stabilized phospholipid micelles, lipid microbubbles and lipoprotein drug carriers respectively.

Tocols: Tocols represent a family of tocopherols, tocotrienols, and their derivatives. They are fundamentally derived from the simplest tocopherol, 6-hydroxy-2-methyl-2-phytylchroman, which is also referred as ‘‘tocol’’. The most common tocol is D-α-tocopherol, also known as vitamin E.

Tocols can be an excellent solvents for water insoluble drugs and are compatible with other cosolvents, oils and surfactants, ‘‘solubility in vitamin E’’ parameter (SVE) to predict solubility of a drug in vitamin E.

SVE can be defined as the solubility in chloroform divided by the solubility in methanol, expressed in mg/ml. An SVE of greater than 10, preferably greater than 100, would indicate solubility in vitamin E. Many tocol emulsions have been developed like Paclitaxel emulsion, an antineoplastic drug [1].

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Certain practical considerations and guidelines for the solubility studies of tocol emulsions have been proposed by Illum *et al* and given in **Table 1** [2, 3].

In conventional injectable formulations, non-aqueous solvents, such as ethanol, and solubilizers, such as Cremophor, Tween 80 are often added to enable adequate solubilization of highly hydrophobic drugs.

TABLE 1: SOLUBILITY OF DRUGS IN ORGANIC SOLVENTS AND VITAMIN E

Drug	Solubility (mg/ml)				Parameter	
	Water	Methanol	Chloroform	Vitamin E	SVE	Solubility
Itraconazole	Insoluble	Insoluble	500	60	>1000	10.6
Paclitaxel	Insoluble	0.03	6	11	200	11.9
Cyclosporine	Slightly soluble	0.71	313	100	520	10.7
Ergosterol	Insoluble	1.5	32	50	25	9.6
Cholesterol	0.22	5	200	150	40	9.6
Prednisolone	Insoluble	33	5	Insoluble	0.02	13.6

Manufacturing and packaging conditions are necessary due to the ability of these components to leach undesirable substances like plasticizers from intra-venous infusion tubing and bottles. Recent advances in the use of α-tocopherol or other tocopherols, tocotrienols or derivatives as a solvent to dissolve water insoluble drugs have been described in current literature [4-5].

The drugs that have shown increased solubility in tocol emulsions include cyclosporine, paclitaxel, few steroids and antibiotics. These recent advancement have expanded the application of tocopherols and tocotrienols as a solvent for delivery of hydrophobic drugs, particularly when combined with d-alpha tocopheryl polyethylene-glycol succinate (TPGS), phospholipids, and certain co-solvents and emulsifiers. In addition, vitamin E, tocopherol esters including TPGS, were recently found to be useful in pharmaceutical formulations as solubilizers and cosolvents for the administration of medicaments [6-7].

The potential disadvantages of tocol based emulsions may include: drug solubility limitations; requirement of biocompatible surfactants for formulation and stability; limited methods for sterilization; and intolerance of tocopherol in chronic administration.

Marketed Formulations: Taxol® is the first marketed formulation containing paclitaxel approved by the FDA in 1992. It is formulated in a mixture of polyoxy-ethylated castor oil and ethyl alcohol. Cremophor EL has been associated with a wide range of toxicities, including bronchospasm, hypotension, and other hypersensitivity-type reactions [8, 9].

TOCOSOL™ paclitaxel tocol emulsion is currently in advanced clinical development. It offers several advantages over the existing Cremophor: ethanol formulation, including a ready-to use product that incorporates high drug loading of paclitaxel (10 mg/ml), smaller dose, and shorter infusion periods.

The commercially available product, Cordarone® IV is currently formulated in a vehicle containing a 10% (w/v) polysorbate 80 and 2% (w/v) benzyl alcohol. The first parenteral fat emulsion i.e., Intralipid was developed for parenteral nutrition in 1960's. A major disadvantage is the critical physical stability of the emulsions due to a reduction of the zeta potential (ZP) which can lead to agglomeration, drug loss and breaking of the emulsion [10].

Solid Lipid Nanoparticles: SLN are particles made from solid lipids stabilized by surfactant. The lipids can be highly purified triglycerides, complex glyceride mixtures or even waxes. The main advantages of SLN are the better physical stability, protection from degradation, controlled and sustained drug release, good tolerability and site specific targeting. Potential disadvantages include insufficient loading capacity, drug loss after polymorphic transition during storage and high water content of the dispersions (80-99%).

Solid lipid nanoparticles (SLN) formulations by various routes of administration have been developed and characterized both *in vitro* and *in vivo* [11-15].

Nano lipid carrier (NLN) have been introduced in late 1990s in order to overcome the potential problems of SLN described above [16, 17].

The development of a nanoparticulate lipid carrier with nanostructure could increase the payload and prevent drug expulsion. This could be realized in three ways. In the first model, spatially different lipids composed of different fatty acids are mixed. This leads to larger distances between the fatty acid chains of the glycerides and imperfections in the crystal. Thus there is more room for the accommodation of guest molecules. In ‘‘imperfect type NLC’’ the highest drug load could be achieved by mixing solid lipids with small amounts of liquid lipids. In LDC nanoparticles, high drug loading capacities of up to 40% have been developed at the turn of the millennium [18, 19].

Here, an insoluble drug–lipid conjugate bulk is prepared either by salt formation or by covalent linking which could be firmly incorporated in the solid lipid matrix [20-21]. Hot pressure homogenization (HPH) is a suitable method for the preparation of SLN, NLC and LDC and can be performed at elevated or below room temperature [22-23].

The particle size is decreased by cavitation and turbulences. Different methods have been used for the production of SLN like precipitation, solvent emulsification-evaporation, and spray congealing method.

The physical stability of SLN dispersions has been investigated intensively by various particle size analyzing techniques like Photon Correlation Spectroscopy, Laser Diffraction, Thermal Analysis by Differential Scanning Calorimetry and surface charge by zeta potentiometer. The influence of lipid and carbohydrate types and its concentration, redispersion and spraying medium have been investigated by Freitas and coworkers [24].

SLN may be injected intravenously due to smaller particle size and can be used for targeted drug delivery to specific organs. These particles are cleared from the circulation by the reticuloendothelial system of liver and spleen. Reticuloendothelial system stealth facility was also used for tumor targeting using poly-oxyethylene functional groups. Few examples of drugs meant for parenteral application incorporated into SLN are given in **Table 2**.

TABLE 2: DRUGS INCORPORATED INTO SLN FOR PARENTERAL APPLICATION

Drugs	References
AZT-P& derivatives, Camptothecin	25, 26, 27
Camptothecin	28
Clobetasol propionate	29
Cyclosporine-A	30
Mifepristine	31
Paclitaxel	32, 33
Tobramycin	34
Thymopentin	35

Polymeric Micelle: The use of micelles prepared from amphiphilic copolymers combining hydrophilic and hydrophobic characteristics for solubilization of poorly soluble drugs has attracted much attention recently [36-38]. If the drug target is located inside the cell, it must have a certain degree of hydrophobicity in order to cross the cell membrane [39-40].

Polymeric micelles are particles with diameters typically smaller than 100 nm formed by amphiphilic polymers dispersed in aqueous media. Within the structure of an amphiphilic polymer, monomer units with different hydrophobicity can be combined randomly, represented by two conjugated blocks each consisting of monomers of the same, or be made from alternating blocks with different hydrophobicity.

Alternatively, the hydrophilic backbone chain of a polymer can be grafted with hydrophobic blocks. Polymeric micelles solubilize poorly water-soluble drugs by incorporating them into their hydrophobic core thus allowing for an increased bioavailability. The use of polymeric micelles often allows for high physical stability, extended circulation time, significant bio-distribution and lower toxicity of a drug. In some cases, targeting is achieved through the enhanced permeability and retention (EPR) effect [41].

The most convenient and simplified technique for the preparation of drug-loaded PEG–PE micelles involves simple dispersing a dry PEG–PE–drug mixture in an aqueous buffer. Solutions of PEG–PE and a drug of interest in miscible volatile organic solvents are mixed, and organic solvents are evaporated to form a PEG–PE–drug film. The film obtained is then hydrated in the presence of an aqueous buffer and the micelles are formed by intensive shaking.

The targeted drug-delivery system using polymeric micelles could be further enhanced by attaching ligands to the micelle surface, which include antibodies against specific receptors in tissues and organs [42-45]. The antibody was attached to the micellar surface using a procedure recently developed for the attachment of specific ligands to liposomes [46-47]. One of the polymers that have gained popularity as a hydrophilic polymer component of drug-delivery systems is highly biocompatible polyvinyl alcohol (PVP) [37].

PVP was used in formulations of such particulate drug carriers as liposomes [49], nanoparticles [50], microsphere [51] and diblock polymer micelles [52, 53]. These micelles can be loaded with a variety of hydrophobic drugs, and are very stable both in terms of the ability to retain their morphology and encapsulated material upon conditions modeling parenteral administration.

The attachment of anticancer antibody to the micelle surface (immunomicelles) could further enhance tumor targeting. Anticancer drugs encapsulated into micelles prepared from polymer-lipid conjugates demonstrate an increased antitumor efficiency *in vitro* and *in vivo* compared to free drugs. Pharmaceutical polymer-lipid conjugate-based micelles and immuno-micelles can be used for the solubilization and enhanced delivery of poorly soluble drugs to tumors.

Microbubbles: Microbubbles are comprised of spherical voids or cavities filled by a gas and stabilized by coating materials such as phospholipid, surfactant, denatured human serum albumin or synthetic polymer. Since gas is less dense than liquids or solids, microbubbles have a number of potentially important medical applications like site-specific delivery, treatment of thrombosis and pulmonary delivery. One way of exploiting the diagnostic and therapeutic applications of microbubbles is with ultrasound.

In order to use microbubbles for intravascular applications, they must be smaller than erythrocytes. The microbubbles must be sufficiently stable, that after injection into the blood, they will circulate for a long enough period of time to reach the target site. Significant applications of lipid coated microbubbles are given in **Table 3**.

TABLE 3: IMPORTANT APPLICATIONS OF LIPID-COATED MICROBUBBLES

Application	Notes	References
Therapeutic imaging	Microbubbles enable visualization of blood flow.	54-58
Sonothrombolysis	Microbubbles accelerate clot lysis with ultrasound.	59-64
Drug delivery to brain	Transcranial application of therapeutic ultrasound with IV delivery of bubbles leads to reversible opening of blood–brain barrier potential to deliver macromolecules and low molecular weight therapeutics to CNS.	65-67
Gene delivery	Co-administration of microbubbles with plasmid DNA, antisense oligonucleotides, or other gene medicines.	68, 69
Targeted microbubbles	Incorporation of ligands onto surface of microbubbles enables targeting to cell-specific receptors.	70
Perflourocarbon nanoemulsions	Sub-micron-sized particles using liquid PFCs have enhanced fusogenic properties for gene and drug delivery.	71-73
Pulmonary delivery oxygen delivery	Low-density drug carrying microbubbles have good properties for delivery of materials deep into lung.	74

Marketed Formulations: An IV injectable ultrasound contrast agent, Perflutren (phospholipid- coated perfluoropropane filled microbubbles), is approved by the US FDA. In the US, "Definity" is approved for echocardiography and in Canada for both radiology and cardiology indications. The phospholipid coating in Definity is designed to stabilize bubbles of defined size. The lipid coating in Definity is composed of three different phospholipids, Dipalmitoylphosphatidyl choline (DPPC), Dipalmitoylphosphatidic acid (DPPA), and dipalmitolyphosphatidylethanolamine–PEG5000 (DPPE–PEG5000).

Lipoproteins: Lipoproteins are a class of complex macromolecules consisting of both lipid and protein subgroups. Its responsibility is to transport a number of hydrophobic nutrients throughout the systemic circulation, mainly lipids in an aqueous environment.

They are characterized by an insoluble core made of cholesteryl ester-triglyceride surrounded by a shell of amphipathic phospholipids and specialized proteins called apolipoproteins [75-76].

Plasma lipoproteins are primarily involved in the transport of lipids and proteins throughout systemic circulation. Lipoprotein's biological significance extends beyond transport of lipids and hydrophobic drugs.

Drugs such as halofantrine (Hf) amphotericin B (AmpB) and cyclosporine A (CsA) are specifically bound with lipoproteins. By understanding the mechanism of action of these lipoprotein bound drugs, which is taken up intracellularly may provide novel methods in drug targeting. There have been a number of studies suggesting that the LDL receptor and members of its super-family may be playing a role in cellular drug uptake, specifically, aminoglycosides, type-I ribosome-inactivating proteins (RIP), anionic liposomes and cyclosporine Administration of drugs such as CsA, Hf and amphotericin B lipid complex usually results in abnormal lipid levels secondary to the disease state.

Therefore, by understanding the mechanisms in which lipoproteins can bind to hydrophobic drugs, it can predict their therapeutic effects and/or their toxicities leading to improved administration and patient treatment of these drugs. An enhanced antiproliferative effect of CsA was observed when the drug was bound to LDL but was not evident when the drug was bound to either VLDL or HDL [77-78].

In addition, modification of the lipoprotein surface charge with an increased negative charge resulted in greater percentage of CsA recovered within the LDL subfraction after incubation in phosphatidylinositol treated rabbit plasma than control plasma[79]. Halofantrine is a therapeutic agent used in the effective treatment of malaria, particularly against *Plasmodium falciparum* and other multi-resistant strains [80-81].

The distribution of Hf between plasma lipoproteins is highly correlated with 0a0 polar core lipid of individual plasma lipoprotein fractions and binding of the Hf enantiomers to different plasma lipoprotein subclasses is stereoselective and species specific [82-83].

Taken together, these studies suggest that the bioavailability and clearance of Hf could be affected by its association to lipids [84]. Plasma distribution of free and liposomal nystatin in human plasma of various lipoprotein compositions revealed a majority of these formulations recovered in the HDL fraction. This preferential distribution of nystatin may be a function of the protein composition of the HDL particle [85-86].

Thus, lipoproteins can act as a natural drug delivery system for hydrophobic drugs or lipid-based formulations. By understanding the uptake mechanisms of these specific drug delivery systems, it can provide better therapeutic treatments and administration to patients who experience side effects or low efficacy.

CONCLUSION: Novel nanoparticulate carrier systems based on lipids could make an important impact on clinical practice for critical drugs such as in cancer chemotherapy, for diagnostic agents, DNA, and vaccines. In light of their physical chemical diversity and biocompatibility, lipid formulations are attractive candidates for improving drug solubility and for targeting specific tissues.

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