INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Review Article

OPTIMIZING ORAL DRUG DELIVERY USING LIPID BASED FORMULATIONS

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Article Received on: 21/05/14 Revised on: 12/06/14 Approved for publication: 09/07/14

DOI: 10.7897/2230-8407.0507105

ABSTRACT
A great challenge facing the pharmaceutical scientists is transforming the new pharmacologically active lipophilic compounds that are poorly water soluble into orally administered medications with sufficient bioavailability. Lipid-based drug delivery systems has shown a great potential in the oral delivery of poorly water-soluble drugs, primarily for lipophilic drugs, with several successfully marketed products. Oral lipid-based formulations comprises of a broad range of oils, surfactants, and co-solvents. This review provides a comprehensive summary of the development, characterization, and utilization of oral lipid-based formulations, from both physicochemical and biopharmaceutical perspectives. The properties of the various lipid excipients are discussed and the criteria for selection of excipients for lipid-based formulations are identified. Finally the future prospects of this technique have been addressed to expand the utility of lipid based drug delivery systems.
Keywords: lipid based formulations, lipid excipients, bioavailability, Characterization.

INTRODUCTION

Oral route is the most preferred route for drug administration due to greater convenience, less pain, high patient compliance, reduced risk of cross-infection and needle stick injuries.[1] However, oral administration is limited by problems associated with physicochemical properties of the drug such as poor solubility, low permeability, instability and rapid metabolism all of which decrease oral bioavailability and potency of the drug. A drug with low solubility leads to low dissolution rate and limits oral absorption. This poor solubility not only gives low oral bioavailability but leads to high inter and intra subject variability and lack of dose proportionality.[2] Lipid based drug delivery systems gained much importance in the recent years due to their ability to improve the solubility and bioavailability of drugs with poor water solubility.[3] Oral lipid based formulation is developed for the improvement of oral bioavailability. Lipid based formulation may improve oral bioavailability via several mechanisms, enhancement of gastrointestinal solubilization possibly the most important method of absorption enhancement.[2] Lipid based formulations may also protect active compounds from biological degradation or transformation, that in turn can lead to an enhancement of drug potency. Lipid based formulation of drug delivery system have shown to reduce the toxicity of various drugs by changing the bio-distribution of the drug away from sensitive organs. The reduction in toxicity allows for more drugs to be administered and forms the basis for the current success of several marketed lipid based formulations of amphotericin B (Ambisome®, Abelcet ®) and doxorubicin (Doxil®, Mycet®)[4]. A water-insoluble drug can be formulated as a lipid-based formulation when the drug itself is an oil-like substance (e.g., ethyl icosapentate, tocopherol nicotinate etc) or when conventional formulation approaches like granulation or soluble liquids in capsules do not enhance the oral bioavailability.[5] A variety of lipid-based systems composed of simple oil solutions to complex mixtures of oils, co-solvents, surfactants and co-surfactants can be obtained based on the type of excipients and formulation variables.[6] The use of advanced lipid based drug delivery systems is a strategy to design pharmaceutical dosage forms with improved therapeutic benefits. Due to their stability at varying pH and moisture levels, lipids provide adequate protection from gastric or environmental conditions. They also provide a lipophilic environment to delay the release of the drug. This property is vastly used for designing drugs of sustained release, tablets, suspensions, implants or microcapsules. Their lipophilic property is used for masking the bitter taste of some drugs.[7] Drugs with low melting points or poor compression properties or low dosage form are all difficult to process using conventional approaches, so lipid based formulations can be used to fill them in hard or soft gelatin capsule.[8] Lipid based formulations eliminate the pre-absorption variability on the gastro-intestinal tract and help in improving the bioavailability of those drugs showing low therapeutic index. Lipoproteins when used as drug carriers offers many advantages, they are endogenous components and do not trigger immunological response. They have a relatively long half-life in the circulation. They have small particle size in the nanometer range allowing the diffusion from vascular to extravascular compartments. Lipoproteins can potentially serve as the carriers for targeted drug delivery through specific cellular receptors. Lipid core of lipoprotein provides a suitable compartment for carrying hydrophobic drugs.[9] Lipids open a wide array of different formulations for oral administration because they can be manufactured as solutions, suspensions, emulsions, self-emulsifying systems and micro-emulsions.[10] A list of commercially available oral lipid-based products is given in Table 1.

Table 1: Commercially Available Oral Lipid-based Products

Trade Name	Molecule	Therapeutic use	Company
Agenerase®	Amprenavir	HIV antiviral	Glaxo Smith Kline
Rocaltrol®	Calcitriol	Calcium regulator	Roche
Cipro®	Ciprofloxacin	Antibiotic	Bayer
Neoral®	Cyclosporin A/T	Immuno-suppressant	Novartis
Gengraf®	Cyclosporin A/III	Immuno-suppressant	Abott
Accutane®	Isotretinoin	Anti-comedogenic	Roche
Kaletra®	Lopinavir and Ritonavir	HIV antiviral	Abott
Norvir®	Ritonavir	HIV antiviral	Abott
Lamprene®	Clofazamine	Treatment of leprosy	Alliance laboratories
Sustiva®	Efavirenz	HIV antiviral	Bristol-Meyers
Fenogal®	Fenofibrate	Anti hyperlipoproteinomic	Genus
Restandol®	Testosterone undecanoate	Hormone replacement therapy	Organon laboratories
Convalex®	Valproic acid	Anti-epileptic	Pharmacia
Juvela®	Tocopherolnicotinate	Hypertension, hyperlipidemia	Eisai Co. [7]

Drug Absorption from Lipid Based Drug Delivery System

The two parameters that are of profound importance in case of oral drug delivery are the solubilization of the drug in GI tract digestive phase and the absorption phase through the intestinal barrier followed by circulatory uptake of the drug to allow its therapeutic action. The poor aqueous solubility of a drug leads to poor solubilization in gastrointestinal fluids, low and/or variable bioavailability and poor *in vitro*/*in vivo* correlation.[11] Lipid formulations can be obtained as a result of blending of excipients such as pure triglyceride oils, mixed glycerides, lipophilic surfactants, hydrophilic surfactants and water-soluble co-solvents.[12] These systems increase absorption from the gastrointestinal tract by accelerating the dissolution process, facilitating the formation of solubilized phases by reduction of particle size to the molecular level, yielding a solid-state solution within the carrier, changing drug uptake, efflux and disposition by altering enterocyte-based transport, and promoting drug transport to the systemic circulation via intestinal lymphatic system.[2,12,14] The bioavailability of some drugs is increased when co-administered with food. On contrary, many drug molecules have negligible interaction with food.[2] The lipid component of food primarily affects the absorption of lipophilic drugs, owing to the ability of lipids to stimulate biliary and pancreatic secretions, to decrease metabolism and efflux activity, to increase intestinal wall permeability, and to a prolongation of gastrointestinal tract (GIT) residence time and transport via lymphatic system, thus leading to enhanced oral bioavailability.[15] Triglycerides and long chain fatty acids play a major role in prolonging the GIT residence time. Moreover, a high fat meal increases the TG-rich lipoproteins which react with drug molecules and this association of lipoproteins with drug molecules promotes intestinal lymphatic transport and causes changes in drug disposition and finally changes the kinetics of the pharmacological actions of poorly soluble drugs.[16] Therefore the effect on drug absorption leads to a serious concern about the sub-therapeutic plasma drug concentration when co-administered without food. Such food effect is also a serious problem for drugs with a narrow therapeutic index, where increased bioavailability may lead to serious untoward effects. Formulating the drug as lipid based formulations can significantly reduce food-dependent bioavailability as lipid based dosage forms can increase the solubility and dissolution of lipophilic drugs and facilitate the formation of solubilized species, from which absorption occurs. Hence, lipid-based formulations can be used to reduce the dose of drug while simultaneously enhancing its oral bioavailability.[2,17]

Classification of Lipid Based Drug Delivery System

A lipid formulation classification system (LFCS) was introduced in 2000 by Pouton and this working model was further modified in 2006 by adding an extra type of formulation.[12,18] LFCS enables easy interpretation of the *in vivo* behavior of the formulations. With reference to the physico - chemical properties of specific drugs, the most suitable formulation can be identified through LFCS. Table 2 shows the various classes of LFCS and indicates the fundamental differences between the different types of formulations.[19] Most of the marketed products are Type III systems, which are diverse with a wide range of oil-and water- soluble substances. Therefore, this group has been further divided into Type III A that contains a significant proportion of oils and Type III B which are predominantly water-soluble.[2]

Table 2: Lipid Formulation Classification System (LFCS)

Formulation Type	Composition	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants (tri-di and mono glycerides)	Non-dispersing require digestion	Generally recognize as a safe status, simple excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water insoluble surfactants	SEDDS formed without water soluble components	Unlikely to lose solvent capacity on dispersion	Turbid oil-in-water dispersion
Type III A	Oils, surfactants, co solvents (both water-insoluble and water- soluble excipients)	SEDDS/SMEDDS formed with water soluble components. (fine emulsion)	Clear or almost clear dispersion, drug absorption without digestion	Possible loss of solvent capacity on dispersion, less easily digested
Type III B	Oils, surfactants, cosolvents (both water-insoluble and water- soluble excipients)	SEDDS/SMEDDS formed with water-soluble components and low oil content. (micro emulsion)	Clear or almost clear dispersion, drug absorption without digestion	Significant phase changes and potential loss of solvent capacity
Type IV	Water soluble surfactants and co-solvents	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion with limited digestion. [2,18]

Lipid Excipients

Lipid is a necessary component of oral lipid based drug delivery system formulation. Lipid can easily solubilize vast amount of lipophilic drug and facilitate self-emulsification. It can also expand the fraction of drug transported via intestinal lymphatic system thereby increasing its absorption from the gastro-intestinal tract.[20] The factors that determine the choice of excipients for lipid based formulations include immiscibility, solvent capacity, self-dispersibility and ability to promote self-dispersion of the formulation, digestibility and fate of digested products, regulatory issues-irritancy, toxicity, purity, chemical stability, capsule compatibility, melting point and cost. For preparing lipid-based formulations, dietary oils composed of medium and long chain triglycerides, along with various solvents and surfactants are frequently chosen. Many lipids are amphiphilic in nature, having a lipophilic portion (fatty acid) and a hydrophilic portion. The melting point increases as the fatty acid chain length increases, but it decreases with the increase in the unsaturation of the fatty acid and also increases the susceptibility to oxidation.[2] A list of solubilizing agents used in lipid-based formulations is given in Table 3.

Table 3: Solubilizing Excipients used in commercially available Lipid-based oral formulations

Water- soluble excipients	Triglycerides	Surfactants
Bees wax	***Long chain triglycerides***	Polysorbate 20 (tween 20)
Oleic acid	Hydrogenated soyabean oil	Polysorbate 80 (Tween 80)
Soy fatty acids	Hydrogenated vegetable oil	Sorbitan monolaurate (Span20)
D-α-Tocopherol (vitamin E)	Corn oil	D-α-Tocopheryl PEG 1000 succinate (TPGS)
Corn oil mono-di-triglycerides	Olive oil	Glyceryl monooleate
Medium chain (C8/C10) mono and diglycerides	Soyabean oil Peanut oil Sesame oil	Polyoxyl 35 castor oil (cremophor EL)
Propylene glycol esters of fatty acids	***Medium chain triglycerides*** Caprylic/capric Triglycerides derived from coconut oil or palm seed oil	Polyoxyl 40 hydrogenated castor oil (cremophor RH40) Polyoxyl 60 hydrogenated castor oil (cremophor RH60) PEG 300 oleic glycerides (Labrafil® M-1944CS) PEG 300 linoelic glycerides (Labrafil® M-2125CS) PEG 400 caprylic/capric Glycerides (Labrasol®) PEG 1500 lauric glycerides (Gelucire® 44/14)[7]

Types of Lipid Excipients

Triglycerides

The most common excipients used in lipid based drug delivery are triglyceride vegetable oils as they do not present any safety issues, since they are fully digested and absorbed. Triglycerides can be divided into three types - long chain triglycerides, medium chain triglycerides and short chain triglycerides.[6] However, medium chain triglycerides have higher solvent capacity and less prone to oxidation.[2] Examples include corn oil, olive oil, peanut oil, sesame oil, soyabean oil, rapeseed oil, coconut oil and palm seed oil.[10] Oils from different vegetable sources have different proportions of each fatty acid. D-α-Tocopheryl polyethylene glycol 1000 succinate (Vitamin ETPGS) is derived from vegetable tocopherols. It is water soluble and acts as absorption enhancer for poorly water-soluble drugs.[2]

Mixed glycerides and polar oils

Partial hydrolysis of vegetable oils yields mixed glycerides such as hydrogenated vegetable oil and hydrogenated soybean oil. The starting material (triglyceride) and the extent of hydrolysis determine the chemical composition of the mixed glycerides produced. Medium chains mixed glycerides are not susceptible to oxidation, have greater solvent capacity and promote emulsification. An example of polar oils is Sorbitan trioleate (Span 85).[2]

Water-insoluble surfactants

A group of lipid excipients with intermediate hydrophilic-lipophilic balance (HLB of 8–12) are available which can form emulsions with application of shear but are unable to self-emulsify due to their insufficiently hydrophilic nature. Typical examples of water-insoluble surfactants are oleate esters such as polyoxyethylene - 20, sorbitan trioleate (Tween-85) and polyoxyethylene - 20 glyceryl trioleate (Tagot- TO) are whose HLB values are between 11 and 11.5.[21]

Water-soluble surfactants

These are the most commonly used surfactants for the formulation of self-emulsifying drug delivery systems that have HLB values of 12 and greater (i.e. they impart high hydrophilicity) and are capable of forming micellar solutions at very low concentrations.[5] They are synthesized by mixing polyethylene glycols (PEG) with hydrolyzed vegetable oils or by reacting alcohols with ethylene oxide to produce alkyl ether ethoxylate, which is a commonly used surfactant (e.g., cetostearyl alcohol ethoxylate 'cetomacrogol'). A reaction of sorbitan esters with ethylene oxide produces polysorbates (predominantly ether ethoxylates). Examples of this type include Cremophor RH40 and RH60 (ethoxylated hydrogenated castor oil) which are obtained from hydrogenation of materials derived from vegetable oils. Cremophor EL (ethoxylated castor oil), which is not hydrogenated is also widely used.[5]

Cosolvents

Cosolvents increase the solvent capacity of the formulation for drugs and aid in the dispersion of systems which contain a high proportion of water soluble surfactants, thus enhancing the solubilizationprocess.[22] However, there are certain limitations to the use of solvent that include precipitation of the solubilized drug from the solvent due to loss of the solvent capacity following dilution, immiscibility of some cosolvents with oils and incompatibilities of low molecular weight solvents with capsule shells. The most widely used cosolvents are ethanol, glycerol, propylene glycol and polyethylene glycols 400 (PEG 400).[8,23]

Other excipients

Various lipid soluble anti-oxidants such as α-tocopherol, β-carotene, propyl gallate, butylated hydroxyl toluene (BHT) or butylated hydroxyl anisole (BHA) can be used in order to protect the formulation from oxidation.[5]

Design of Lipid Based Formulations

The design of lipid based drug delivery systems includes pre-selection of excipients based on their melting point, fatty acid composition, HLB value, digestibility and disposability; screening of selected excipients for solubility, dissolution/dispersion properties, stability and compatibility; identification of a formulation technique which is suitable for the intended dosage form; design of appropriate animal models to predict the *in vivo* performance of the chosen formulation; and optimization of the formulation considering the drug loading and dissolution profile.[2] Oral lipid-based formulations encompass a diverse group of formulations with very different physical appearance, ranging from simple triglyceride vehicles to more sophisticated formulations such as self-emulsifying drug delivery systems (SEDDS) which are summarized below.

Oily liquids

Drugs that are highly lipophilic and have solubility in oils only such as steroids have to be formulated as oily liquids by solubilizing the drug in oil. However, the quantity of oil required to dissolve a unit dose of drug is very high, which limits the usage of drug in oil formulations. Formulation of an oily solution of bupivacaine free base using a mixture of fractionated coconut oil and castor oil showed a prolonged local analgesic activity and reduced systemic toxicity when administered subcutaneously to male Wistar rats (Larsson et al, 2002).[24]

Mixed micelles

Mixed micelles represent a disc like structure and resemble a lipid bilayer that consists of more than one molecular species. Enhanced anti-tumor activity of methotrexate against multidrug resistant tumors was observed by Chen *et al* when conjugated with polymeric mixed micelles (composed of Pluronic F127 and P105).[25]

Self-emulsifying drug delivery systems (SEDDS)

Self-emulsifying drug delivery systems (SEDDS) are oral dosage forms consisting of drug, oils, surfactants and sometimes cosolvents.[13] On addition to water (or on introduction to the GI tract) and with gentle agitation the system will easily form an emulsion or micro emulsion. Self emulsification may be driven by several mechanisms. The probable mechanisms involved in dispersion of pharmaceutical formulations are "diffusion and stranding," those driven by osmotic pressure imbalances, phase transformations and changes owing to alteration of environmental conditions (e.g. pH). SEDDS are more practical for oral applications than ready-to-use emulsions due to volume considerations and ease of formulating them into a soft-gelatin capsule dosage form.[25] Depending upon the size of the emulsion particles, these systems can be further classified as self-micro emulsifying drug delivery systems (SMEDDS) or self-nano emulsifying drug delivery systems (SNEDDS). Kale and Patravale developed SEDDS for the poorly water-soluble calcium channel blocker, nimodipine to evaluate its potential to improve oral bioavailability of nimodipine by carrying out *in vivo* studies in rabbits and comparing it with nimodipine suspension, oily solution and micellar solution. Relative bioavailability of nimodipine in SEDDS was significantly higher than all the other formulations.[26]

Liposomes

Liposomes are phospholipid bilayers with an entrapped aqueous volume. On the basis of the number of layers (lamellarity) and diameter, liposomes are classified into multi lamellar vesicles (MLVs, diameter >200 nm), large unilamellar vesicles (diameter 100–400 nm), and small unilamellar vesicles (diameter <100 nm). They can be further classified into cationic, neutral, and anionic liposomes on the basis of surface charge (zeta potential).[27] The advantage of these systems is that hydrophilic substances can be embedded in the aqueous internal spaces of the globules, while hydrophobic drugs can be embedded within the inner fatty acid layers.[2] In addition, liposomes can be deliberately engineered to possess unique properties, such as long systemic circulation time, target cell specificity, pH and reductive environmental sensitivity, and temperature sensitivity. These are achieved by selecting the appropriate lipid composition and surface modification for the liposomes.[27] Several methods have been established for liposome preparation based on the scale of the preparation and other considerations, such as drug encapsulation efficiency. The first step in liposome preparation is to dissolve lipid ingredients in a suitable solvent; this is then followed by lipid hydration and particle size reduction. For example, lipids are first dissolved in chloroform/methanol and dried into a thin film on a rotary evaporator and are then hydrated in an aqueous buffer above the phase-transition temperature. This process will result in the formation of heterogeneous MLVs. The lamellarity of the MLVs can be reduced by repeated cycles of freezing and thawing. If phospholipids are dissolved in a water-miscible solvent such as ethanol and rapidly diluted into an aqueous buffer, liposomes with relative small particle sizes can be generated directly. This is then followed by removal of the solvent from the liposome preparation and/or further size- modifying steps.[27] Designing liposomes to achieve optimized properties can be done by considering the following factors: drug loading and control of the drug release rate by changing the content of liposome bilayer by incorporating cholesterol, overcoming the rapid clearance of liposomes by reducing vesicle size and opsonization and intracellular delivery of drugs (hydrophobic weak base drugs such as doxorubicin or vincristine can enter cells as free drugs by passive diffusion whereas small hydrophilic drugs e.g., cytosine arabinoside can use cell membrane transporters).[28] The application of liposomes as a drug-delivery system has become more popular over the last decades, because of their biocompatibility and versatility in carrying systemically administered drugs such as chemotherapeutics and antibiotics with narrow therapeutic windows. A variety of therapeutic agents have been incorporated into liposomes and several of them have reached clinical use. These include liposomal doxorubicin (Doxil™), daunorubicin (Daunoxome™), amphotericin B (Amphotec™, Ambisome™, and Abelcet™), cytarabine (Depocyte™), and verteporfin (Visudyne™). Numerous liposomal formulations are in clinical trial, including those for vincristine, all-*trans* retinoic acid, topotecan, and cationic liposome-based therapeutic gene transfer vectors. Liposomal delivery of anticancer drugs has been shown to greatly extend their systemic circulation time, reduce toxicity by lowering plasma free drug concentration, and facilitate preferential localization of drugs in solid tumors based on increased endothelial permeability and reduced lymphatic drainage, or enhanced permeability and retention (EPR) effect. For example, liposomal entrapment of

doxorubicin greatly reduces its dose-limiting cardiotoxicity.[29] Liposomes also present a platform for delivery of drug combinations. For example, Wang *et al.* co encapsulated doxorubicin and verapamil (a Pgp inhibitor) into liposomes and studied there *in vitro* cytotoxicity. The result demonstrated effective reversal of multidrug resistance in doxorubicin-resistant cell lines.[29]

Solid Lipid Nanoparticles

Solid lipid nanoparticles are nanoscale spherical particles (sizerange10 – 1000 nm) composed of lipids with a lipidic core matrix (stabilized by surfactants) that can solubilize lipophilic molecules.[27] Lipids mainly used include monoglycerides (e.g. glycerol monostearate), diglycerides (e.g. glycerolbehenate), triglycerides (e.g. tristearin), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol) and waxes (e.g. cetyl palmitate). These are suitable for delivery of lipophilic therapeutic agents. The molecule of interest can be formulated to lipid nanoparticle matrix through lipid phase dissolution.[2] Lipid nanoparticles can be synthesized by combining an oil phase (e.g., triolein) with phospholipids as emulsifiers. The oily core can be used to incorporate lipid-soluble drugs such as paclitaxel, hematoporphyrin, and lipid-conjugated pro drugs. They can be synthesized by similar methods as those used in liposomes, such as high-pressure homogenization. Similar to liposomes, these particles are cleared by RES, localized in tumors via EPR effect, and their circulation time can be prolonged by incorporation of PEGylated lipid.[27] Solid lipid nanoparticles have several advantages. They are physicochemically stable and can be produced easily on a large industrial scale, the raw materials and production costs are relatively low and the lipids used are similar to physiological lipids and therefore toxicity is reduced. Their most important limitation is that the drugs incorporated into solid lipid nanoparticles have to be sufficiently lipophilic to guarantee high entrapment efficiency.[30-32] Nevertheless; they have considerable utility as controlled and site-specific drug delivery system for drugs and vaccines.[27]

Semisolid Formulations

Lipid-based formulations can also be developed as semisolid formulations which may be encapsulated as hard gelatin capsules. Semisolid formulations can be defined as multiphase dispersions with a high proportion of solid mixed with liquid phase. In general, they are prepared by combining a solid lipid with other liquid components and filling into capsules in the molten state. Banding or sealing in usually required to prevent leakage. Another option is a thixotropic gel semisolid formulation wherein an agent such as colloidal silicon dioxide provides the matrix to prevent flow of the liquid vehicle. The advantages of semisolids in comparison to liquids are that they are more amenable to hard capsules and may provide greater stability and compatibility between the capsule shells and the fills.[29]

Liquid Solid Compacts and Dry Emulsions

Possible designs for solid dosage forms of oral lipid-based formulations include liquid solid compacts and dry emulsion. In the preparation of liquid-solid compacts, drug is dissolved in a non aqueous solvent and adsorbed onto a solid carrier and resulting solid can be compressed into tablets or filled into capsules.[22] An example is coenzyme Q_{10} self emulsifying mixture containing lemon oil, Cremophor EL and Capmul MCM adsorbed onto maltodextrin/Avicel carrier (Nazzal *et al*., 2002).[33] In case of dry emulsion or solid state emulsion, the drug is first dissolved in a lipophilic solvent, which is combined with an aqueous phase containing bulking agents (cryoprotectants) and homogenized to form an emulsion. Water is then removed by lyophilization, spray drying, or a similar drying method. The resulting dry powder can be filled into capsules or compressed into tablets.[21] Examples of drugs formulated by this approach include hydrochlorothiazide (Corvelyn and Remon, 1998), Vancomycin (Shively and Thompson, 1995), and theophylline (Chambin *et al*, 2000).[34-36] The advantages of this method of adsorption onto solid carrier include good content uniformity and high lipid exposure.[2] The disadvantage of this method is low drug loading due to the requirement for the solid carrier unless the drug itself is an oil (e.g. for Vitamin E) (Takeuchi *et al*, 1991) and valproic acid (Cannon 2005).[37,38]

Solid Dispersions

Alternative to liquid lipid based formulations are solid dispersions which can be defined as solid matrix (e.g. lipids or polymers) containing dispersed or dissolved drug. Relatively high loading can be achieved with solid dispersions but bioavailability will depend on whether dissolved or amorphous drug is required for absorption.[25] A bio study in humans for a Vitamin E solid dispersion in Gelucire 44/14 melt filled into hard gelatin capsules showed improved bioavailability compared to the commercial product (Barker *et al*, 2003).[39] Unlike liquids and semisolids, solid dispersions with high melting points have the potential to be compressed into tablets.[30,40] There are various solidification techniques for conversion of liquids and semisolids into solid particles (powders or granules), which can be filled into capsules or alternatively compressed into tablets by selecting suitable tableting excipients.[2] One such technique is spray congealing which is also known as spray cooling. In this method, molten lipid is sprayed into a cooling chamber and, on contact with the cool air, congeals into spherical solid particles. The solid particles are collected from the bottom of the chamber, which can be filled into hard gelatin capsules or compressed into tablets. Ultrasonic atomizers are frequently used to generate solid particles in this spray cooling process. The parameters to be considered are the melting point of the excipient, the viscosity of the formulation and the cooling air temperature inside the chamber to allow instant solidification of the droplets.[2] In a study by Cavallari *et al*, micro particles with narrow size distribution were obtained when stearoyl polyoxylglycerides (Gelucires 50/13) were used as an excipient and significantly enhanced the drug release of poorly water soluble drugs like diclofenac.[41] Spray drying is another method which is similar to spray drying but differs in the temperature of the air inside the atomizing chamber.[2] This technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.[42] In a study carried out by Yan *et al*, a novel liquid self-emulsifying drug delivery system (SEDDS)

containing curcumin was formulated and further developed into a solid form by a spray drying method using Aerosil 200 as the solid carrier. After oral administration to rats, curcumin in the solid SEDDS resulted in significant improvement in *in vivo* absorption compared with that of curcumin powder.[43] Another study by Balakrishnan *et al* was based on preparation of a solid form of lipid-based self-emulsifying drug delivery system (SEDDS) by spray drying liquid SEDDS with an inert solid carrier Aerosil 200 to improve the oral bioavailability of poorly water-soluble drug dexibuprofen. The solid SEDDS gave significantly higher bioavailability than did dexibuprofen powder. In particular, the area under curve of solid SEDDS was about twofold higher than that of dexibuprofen powder.[44] Melt granulation also known as pelletization can be used to obtain solid dispersions which transforms a powder mix (with drug) into granules or pellets. In this method a melt able binder (molten state) is sprayed onto the powder mix in presence of high-shear mixing or the melt able binder is blended with powder mix and due to the friction of particles (solid/semisolid) during the high-shear mixing, the binder melts. The melted binder forms liquid bridges between powder particles and forms small granules which transform into spheronized pellets under controlled conditions. Depending on the fineness of the powder, 15 % – 25 % of the lipid-based binder can be used. The parameters to be considered during the process are binder particle size, mixing time, impellar speed and viscosity of the binder on melting.[2] The dissolution rate of diazepam was improved by formulating melt agglomerates containing solid dispersions of diazepam by Seo *et al*.[45] Supercritical fluid based method can also be used to produce solid dispersions that involve coating of the drug particles with lipids. In this method, the drug and lipid-based excipients are dissolved in an organic solvent and then in supercritical fluid (carbon dioxide) by elevating the temperature and pressure.[46,47] The coating process is facilitated by a gradual reduction in pressure and temperature in order to reduce the solubility of the coating material in the fluid and hence precipitate onto the drug particles to form a coating.[48] The solubility of the formulation components in the supercritical fluid and stability of the substance during the process are important parameters that must be considered during application of this method. Sethia and Squillante have formulated solid dispersions of carbamazepine using supercritical carbon dioxide. Vitamin E TPGS and Gelucires 44/14 were successfully used with this technique (supercritical fluid processing) for enhancement of the bioavailability of carbamazepine. The solid dispersions formulated with TPGS showed enhanced bioavailability of drug when compared to formulations prepared with Gelucires 44/14 aslipidexcipient.[48,49]

Characterization of Lipid-based Formulations

Characterization of lipid based formulations is important since lipid excipients have complex chemical compositions that may lead to many problems in the formulations.[2]

Equilibrium phase behavior

Mechanism of dispersion of lipid based drug is done by studying the equilibrium phase behavior. The traditional method is to weigh out mixtures into glass tubes, seal the tubes, mix the components and store the tubes in a water bath until they reach equilibrium. Phase behavior for three component (oil, surfactant and water) systems is mapped out using a ternary diagram.[19] If more than two excipients are used then it is practical to combine groups of miscible excipients into two groups so that the influence of aqueous dilution of anhydrous formulations can be observed for a variety of formulations. Phase behavior is also valuable to assess the phases that form when formulations make contact with intestinal fluid containing bile.[21]

Self-dispersion and sizing of dispersions

Dispersion rate and particle size of lipid based formulations are necessary but no standards methods have been developed. Measuring the dispersion rate has no technical advantage in forming an accurate estimation of dispersion rate if a facile observation by eye can be used to verify that dispersion is sufficiently fast. Generally well formulated lipid based systems are dispersed within seconds under conditions of gentle stirring. Poor formulations can be distinguished with extended analysis by determining poly dispersity using a Fraunhofer diffraction sizer. Optimization of lipid based systems can be done using proton correlation sizer, but if a Fraunhofer instrument is available it is advisable to use this instrument to check that there are no particles larger than 1 um.[19]

***In vitro* dispersion and digestion tests**

Predicting the fate of the drug in the intestinal lumen is done with the *in vitro* dispersion and digestion tests which are critical to the formulator. Ideally the drug is dissolved in lipid based formulations. The case is not the same for semi solid waxy systems or suspensions and there is little evidence that suspending drug in a lipid formulation can reproducibly enhance bioavailability. Dispersion testing can be carried out using a standard dissolution apparatus but assuming that the drug is initially in solution in the anhydrous formulation, the emphasis should not be on dissolution but rather on detecting unwanted precipitation of the drug. Dispersion testing is vital for Type III and Type IV formulations, which may lose solvent capacity on dispersion due to migration of water-soluble components into the bulk aqueous phase. Digestion testing is of even greater importance because it offers the opportunity to predict the fate of the formulation and drug in the intestinal lumen prior to absorption.[19] *In vitro* assessments of the effects of lipolysis on the performance of lipid based systems have been developed (Porter and Chapman, 2001) and show promising correlations with *in vivo* performance (Kossena *et al*, 2005). A standard protocol does not yet exist with differences in digestion medium and specific techniques, but basically, the medium consist of a buffered solution containing calcium salts, bile salt and phosphatidylcholine with digestion by pancreatic lipase. The progress of digestion is monitored using a pH-stat titration to monitor fatty acid generation. The interest in monitoring the effects of digestion is to simulate the change in solubilization of the drug as the formulation undergoes chemical and physical (e.g. micelle, vesicle and liquid crystal) transformation. In order to do this, samples are digestion are centrifuged or undergo size exclusion chromatography to separate the various phases, and the drug concentration is measured in each.[23] These digestion tests are essential for evaluation of Type I, Type II, Type III formulations and given that surfactants are subject to digestion, probably for Type IV formulations as well.[19]

Appearance

The appearance in a graduated glass cylinder or transparent glass container is noted. At equilibrium, whether the color

and appearance of the formulation is uniform or not is noted.[50]

Color, Odor, and Taste

These characteristics are especially important in orally administered formulation. Variations in taste, especially of active constituents, can often be attributed to changes in particle size, crystal habit, and subsequent particle dissolution. Changes in color, odor and taste can also indicate chemical instability.[51]

Density

Specific gravity or density of the formulation is an important parameter. A decrease in density often indicates the presence of entrapped air within the structure of the formulation. Density measurements at a given temperature should be made using well-mixed, uniform formulation; precision hydrometers facilitate such measurements.[51]

pH value

The pH value of aqueous formulation should be taken at a given temperature and only after settling equilibrium has been reached, to minimize "pH drift" and electrode surface coating with suspended particles. Electrolyte should not be added to external phase of the formulation to stabilize the pH, because neutral electrolytes disturb the physical stability of the suspension.[51]

Droplet size and surface charge (zeta potential)

The droplet size distribution of micro emulsion vesicles can be determined by either light scattering technique or electron microscopy and recently being used is photon correlation spectroscopy (PCS). The surface charge is determined using a zeta potential analyzer by measuring the zeta potential (ZP) of the preparations. Zeta potential characterizes the surface charge of particles and thus it gives information about repulsive force between particles and droplets. Zeta potential should usually reach a value above 30 mV to obtain stable nanoemulsions by preventing flocculation and coalescence of nano-sized droplets.[51]

Viscosity Measurement

The viscosity of lipid based formulations of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37 ± 0.2°C by a thermo bath, and the samples for the measurement are to be immersed in it before testing. Apparent viscosity, like pH, is an exponential term, and therefore the log-apparent viscosity is an appropriate way of reporting the results.[51]

Other analytical tools

Analysis of the thermal behavior of lipids during formulation is of primary importance, since lipid excipients have complex chemical compositions that lead to broad melting ranges. Various thermal properties of lipids including crystallization temperature, melting point, glass transition temperature and determination of solid fat content of the excipient versus temperature can be evaluated using differential scanning calorimetry (DSC). The organization of the lipid during heating or cooling can be assessed by hot-stage microscopy. Crystallinity of a lipid excipient can be confirmed by X-ray diffraction (XRD).[3] High performance liquid chromatography (HPLC) and gas chromatography (GC) can be used to determine the exact composition of ethers, esters and fatty acid distribution of the lipid excipients.[2]

Challenges with Formulation of Lipid Based Drug Delivery Systems

The most common challenge faced when preparing lipid based formulations is physical stability. A problem that is frequently encountered with liquid formulations is interaction with and leakage from the capsule shell. Liquid formulations contain hydrophilic components such as glycerol, propylene glycol, ethanol and water which may migrate between capsule shells and fills. The resulting change in shell composition can result in capsule brittleness or softening, impairing the capsule's physical integrity and potentially changing the dissolution profile of the product. In addition the change in fill contents could alter the solubility of the drug in the fill, potentially leading to precipitation of drug and loss of bioavailability. Additional challenges can arise with semisolid formulations as they are dynamic in nature and contain both liquid and solid phases. Crystallinity of the matrix must be considered which is highly dependent on lipid purity and chain length distribution as well as lipid polymorphism.[23] The two most important mechanisms that causes chemical instability of the components in lipid based formulations are hydrolysis (for those components containing ester bonds) and oxidation (for unsaturated lipids and oxygen labile co solvents and surfactants, for example PEG 400 and Labrafil® M2125 CS). The use of PEG based surfactants and unsaturated lipids in lipid-based formulations most likely cause lipid peroxidation that can cause drug instability and aldehyde products can react with gelatin shell of both hard and soft gelatin capsules leading to cross-linking that can retard dissolution. Therefore assay of aldehyde products and gelatin cross-linking should be considered for lipid based formulations.[23]

Future Prospects

There are several avenues of future research that will expand the utility of lipid based drug delivery systems. Although a number of excipients are available for preparing lipid based formulations, novel lipids and related substances for use in lipid formulations must be focused on. Desired attributes of new excipients would be enhanced solubilization of drugs candidates across a wide range of drug properties, favorable toxicological profiles, greater stability and ease of manufacture, availability of adequate specifications and controls on purity and compatibility with other lipids, surfactants and capsule shells. Improved methods of characterization of lipid-based formulations must be developed. At present there is a lack of suitable *in vitro* characterization methods to provide *in vitro* / *in vivo* correlations. Owing to the need for sink conditions in dissolution methods required for regulatory submission, surfactants must be added to the medium to achieve adequate drug solubility which may alter the dispersion behavior of the formulation but it does not predict the dispersion behavior *in vivo*. Therefore the dispersion behavior can be studied using other methods such as dissolution / Caco-II models or dialysis methods such as the rotating dialysis cell. Moreover, characterization of the fate of the drug on digestion of lipid based formulations should provide new insight for development of simpler *in vitro* methods. Further research has to be carried out in this field regarding the design of a proper *in vivo* model to correlate the data obtained *in vitro* studies to the actual *in vivo* experience.

CONCLUSION

Lipid-based formulations encompass a diverse group of formulations with very different physical appearance, ranging from simple triglyceride vehicles to more sophisticated formulations such as self-emulsifying drug delivery systems (SEDDS). Lipid-based drug delivery systems usually comprises of a broad range of oils, surfactants, and co-solvents. They represent one of the most popular approaches to overcome the absorption barriers and to improve the bioavailability of poorly water-soluble drugs. This review focused on the current trends in the field of lipid based drug delivery systems with respect to formulation approaches and their characterization. However, a few limitations of the technology such as the stability of lipid-based formulations, manufacturing methods, the lack of a database considering the solubility of drugs in lipids, indicate that development of proper regulatory guidelines for lipid-based formulations still need to be addressed in depth for advancement of the technology. Nevertheless, lipid based formulations is very promising in the field of drug delivery as a wide variety of lipid excipients are available and it is responsible for enhancement of solubilization, thus providing a major solution for overcoming the bioavailability problems associated with highly potent, but poorly water-soluble, drug candidates.

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Cite this article as:
Sheikh Zara, Morshed Nabila. Optimizing oral drug delivery using lipid based formulations. Int. Res. J. Pharm. 2014; 5(7):514-522 http://dx.doi.org/10.7897/2230-8407.0507105

Source of support: Nil, Conflict of interest: None Declared