Lipid Based Self Emulsifying Formulations for Poorly Water Soluble Drugs-An Excellent Opportunity

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ABSTRACT

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Currently more than 50% of compounds identified are water insoluble and or poorly water soluble. These molecules are difficult to formulate using conventional approaches (for their poor aqueous solubility) and are associated with numerous formulation-related performance issues. Formulating these compounds using lipid based systems is one of the growing interest and suitable drug delivery strategies are applied to this class of molecules. The rapid growth and investment in the use of lipid based systems in product development is primarily due to the diversity and versatility of pharmaceutical grade lipid excipients and drug formulations and their compatibility with liquid, semi-solid and solid dosage forms. Lipid formulations such as self-emulsifying/ microemulsifying/ nanoemulsifying drug delivery systems have been attempted in many researches to improve the BA and dissolution rate for their better dispersion properties. One of the greatest advantages of incorporating the poorly soluble drug into such formulation products is their spontaneous emulsion and or micro emulsion/ nanoemulsion formation in aqueous media. The performance and ongoing advances in manufacturing technologies has rapidly introduced lipid-based drug formulations as commercial products into the marketplace with several others in clinical development. The goal of the current review is to present the characteristics feature, development and utilization of oral lipid based formulations within drug delivery region. The review also aims to provide an insight of the *in vitro* evaluation of lipid based systems and their potential limitations.

Keywords: Self-emulsifying formulations, oral drug delivery, solvent capacity, drug precipitation, LFCS

INTRODUCTION

Lipid based drug delivery systems (LBDDS) is one of the most notable findings over the past decade, and the number of publications related to lipid delivery systems increased exponentially. Structures and properties of lipid delivery systems have been the subject of research since the 1960s.[1] Various types of lipid-based formulations exist; from simple solutions or suspensions of drug in lipid, through to emulsions and more complex self-emulsifying/ microemulsifying/ nanoemulsifying (SEDDS /SMEDDS /SNEDDS) systems. The use of SEDDS to improve the bioavailability of poorly-water soluble drugs (PWSD) was first reported in 1982 by Pouton.[2] In his work, he identified an effective self-emulsifying system composed of Miglyol 812 (M812, medium chain triglyceride, MCT) and Tween 85 (T85, polyoxyethelene-20-sorbitan trioleate). Since then, SEDDS have attracted enormous interest from many researchers. Currently, SEDDS are formulated with mixtures of lipid vehicles and non-ionic surfactants in the absence of water, and are assumed to exist as transparent isotropic solutions. These systems have a unique property: they are able to self-emulsify rapidly in the GI fluids, forming fine oil-in-water (O/W) emulsions under the gentle agitation provided by gastro-intestinal motion and are suitable for oral delivery in soft and hard gelatin or hard hydroxypropylmethylcellulose (HPMC) capsules.

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Due to the limited solubility of some hydrophobic drugs in lipids and to increase formulation dispersibility, other components such as cosurfactants and cosolvents are frequently included in a lipid formulation. The need for higher solvent capacity led formulators to include more hydrophilic surfactants and cosolvents in formulations.[3] In addition, these systems are more recent approach to improve the dispersibility and reduce the particle size of dispersed systems, thus potentially increasing oral absorption for poorly water soluble drugs (PWSD).[4] These dispersed systems called SMEDDS are stable and show an acceptable shelf-life and can be post-developed into different types of dosage forms.

An example of a commercially available SMEDDS preparation is Neoral® (cyclosporine A). These formulations have the potential benefit of presenting the drug in a colloidal form without the need for digestion. However, the influence of these formulations on drug bioavailability may be influenced by digestion and other constituents of the intestine, which may vary according to diet and (patho)physiology.

Still there is low uptake of lipid-based formulations due to the large empirical development strategies, which include only few commercially successful drug products in the market.[5] However, these commercially successful drugs during the last decade have gained considerable attention from the pharmaceutical companies that wishing to improve patient compliance and convenience, as well as to reduce cost of drug products. There are a number of issues in relation to lipid-based systems which require further investigation including; an understanding of physicochemical properties of lipids and how lipids reduce the variability in plasma profile, lipid drug interactions and formulation classification systems, a better understanding of the versatility of lipid systems and standard methodologies by which the best formulation can be selected for each drug.[6] An extensive drug solubility database in lipid systems may also be useful for overcoming formulation and manufacturing problems caused by poor solubility.[7]

The core themes of this review article are, firstly, to identify a limited group of chemically-related excipients which can be used to classify lipid-based formulations into four types, with minimum change of components. Secondly the article aims to investigate the dynamic mechanism associated with the fate of dissolved drug after dispersion of formulations. And thirdly, to have better knowledge of some factors which could influence the fate of formulations during digestion. A number of non-ionic surfactants have already been shown to depress the rate of digestion, and this is one amongst the factors which may have an important effect on the precipitation of drugs in the intestine. The digestion products themselves are expected to play an important role in drug solubilization but the understanding of these processes is limited.[8] Thus more information is required to better explain the role of lipid digestion in enhancing bioavailability of PWSDs.

"Lipid formulations" for oral drug delivery

In the context of oral delivery the term lipid can be understood to mean one or more of a limited number of natural glyceride lipids and phospholipids, various synthetic and semi-synthetic lipids, surfactants and cosolvents. All of these are commonly included in LBDDS.

Lipid-based excipients may be used in simple, single component oily solutions of the drug substance or in more complex systems such as microemulsions or self-emulsifying drug delivery systems.[3] Simple oil excipients are generally composed of mono-, di-, or triglycerides or their derivatives and differ on the content of medium (C_6-C_{10} in chain length) or long chain (C_{12}-C_{24} in chain length) fatty acids. Glyceride esters are water-immiscible and their solvent characteristics for drug substances vary according to the chain length of the fatty acid content. Many of the surfactants and oils that are regarded as acceptable are food grade materials and therefore expected to be well-tolerated by the body.[9] These excipients have a history of use in a wide variety of pharmaceuticals.

In simple terms lipid formulations can be differentiated by the way in which they disperse in water and their digestibility.[10] The lipid formulation classification system (LFCS) which is described later on, is undoubtedly a useful advance in characterisation of what can seem a confusing and fairly empirical blend of excipients. The choice of lipid formulation has been largely empirical both in terms of the performance of the self-emulsifying lipid formulation and the solubilization of the drug in the anhydrous oil-surfactant mixture. Pouton in early 1985 reported that relatively small changes in the oil-surfactant ratio can affect the size distribution of the formed emulsions significantly.[11] Emulsion droplet size has been considered to be an important factor in the performance of self-emulsifying systems since particle size can determine the rate and extent of drug release *in vitro*. With small particle size, it might be expected to lead to drugs being released more rapidly from the vehicle.[12]

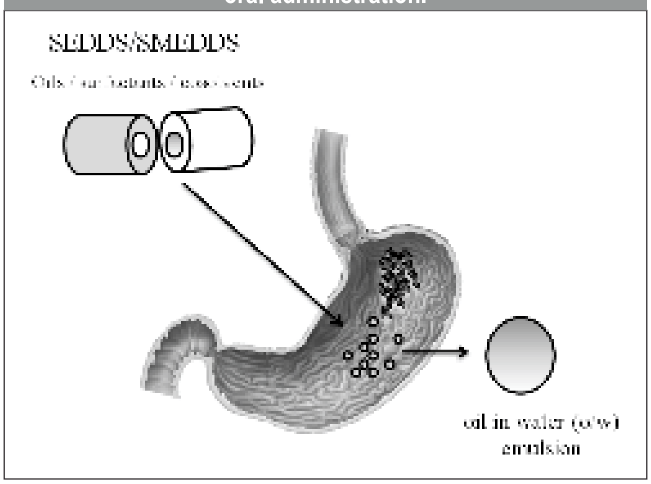
In 1995, when the first HIV protease inhibitor, saquinavir was launched initially in the market, as a mesylate salt formulation in a hard gelatin capsule (Invirase®), its bioavailability was only 4% and highly variable.[13] Later on, in 1997, saquinavir (Fortovase®) formulated with medium chain mono- and diglycerides, povidone, and α tocopherol increased bioavailability, up to three-fold against Invirase® in humans.[13, 14]

A number of examples are available at present to show how the composition of the different type of lipid-based formulation can significantly influence bioavailability. For instance, O'Driscoll and Griffin in 2008 showed that Cremophor and TPGS: Oleic acid mixed micellar systems can significantly improve the saquinavir solubility *in vitro*, and produce similar extent of intestinal lymphatic transport.[15] Cases such as saquinavir suggest more careful evaluation of intestinal solubility and/ permeability of lipid excipients and thus a lipid-based formulation must be designed on a case-by-case basis. Several other published [16, 17] and unpublished case studies have also established the significance of rational approach in designing SEDDS which can improve the *in vivo* absorption of the PWSD compound.

Designing SEDDS/SMEDDS/SNEDDS within LBDDS

A self-emulsifying/microemulsifying/nanoemulsifying drug delivery system (SEDDS/SMEDDS/SNEDDS) is a fairly similar lipid dosage form designed for oral delivery which comprises a mixture of oils, surfactants and possibly cosolvents that has the ability to form fine oil in water (o/w) emulsion or microemulsion or nanoemulsion upon mild agitation following dilution with an aqueous media. This property renders SEDDS/SMEDDS/SNEDDS as good candidates for oral delivery of PWSD with adequate solubility in oil or oil/surfactant blends.[18, 19] Upon dilution, SEDDS typically produce emulsion with droplet size between 100 and 300 nm, while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm.[20] Similar to microemulsions, nanoemulsions are also the dispersions of oil and water stabilized by surfactant/s and kinetically but not thermodynamically stable systems. However, like microemulsions, nanoemulsions also have generated high interest as drug delivery vehicles.[21] In comparison with many other drug delivery systems, these systems have the potential to increase the apparent solubility of PWSD, and also reduce the extent of efflux and even pre-systemic metabolism, all of which can enhance bioavailability and establish the desired reproducible pharmacokinetic profile of orally administered drugs.

Figure 1: The encapsulated SEDDS/SMEDDS designed for oral administration.



Micoemulsions, especially o/w microemulsion (Figure 1) is the most appropriate formulation if someone considers using efficient formulation for increasing the apparent aqueous solubility of PWSD. Such a system is attractive due to having an extra possible locus of solubilisation (oil core).

An important best known example is Sandimmune® which was the turning point for development of SEDDS in oral lipid-based formulations of PWSD. In 1981, Cyclosoprine A (CsA), which is an immunosuppressing agent marketed in a self-emulsifying formulation (Sandimmune®) containing Labrafil M 1944 CS (polyoxyethylated oleic glycerides), olive oil and ethanol.[22] In 1994 another new self-microemulsifying formulation (Sandimmune Neoral®) was introduced, which emulsifies spontaneously into a microemulsion with a particle size smaller than 100 nm. This formulation contains Cremophor RH40 (polyoxyl hydrogenated castor oil), corn oil glycerides, propylene glycol and ethanol.[22] This new formulation (Sandimmune Neoral®) resulted in a two-fold increase in the bioavailability compared to the earlier product Sandimmune®.[23]

Recently, SEDDS/SMEDDS have gained lots of interest as potential drug delivery vehicles largely due to their clarity, simplicity of preparation, thermodynamic stability and their abilities to be filtered and to incorporate a wide range of drugs of varying lipophilicity.[24, 25, 26]

Ingredients of SEDDS/SMEDDS/SNEDDS

The formulation of SEDDS is comparatively simple as the drug need to be incorporated into a suitable oil-surfactant mixture, which could be filled in a soft or hard gelatin capsules.

Table1: SEDDS/SMEDDS/SNEDDS for a PWSD contain following classes of excipients:

Oils	**Medium Chain Triglycerides:** Fractionated coconut oil, and palm seed oil, Triglycerides of caprylic/capric acid.[27] e.g., Miglyol 812, Captex 355.
	Long Chain Triglycerides: Vegetable oils are glyceride esters of mixed unsaturated long-chain fatty acids, commonly known as long-chain triglycerides. e.g., soybean, sesame, corn, olive, peanut, and rapeseed oils.
	Mixed mono, di- and triglycerides: Novel semisynthetic medium chain derivatives. Esters of propylene glycol and mixture of mono- and diglycerides of caprylic/capric acid. eg, Imwitor988, Imwitor 308, maisene 35-1
	Polar oil : Some excipients which are traditionally thought of as hydrophobic surfactants, such as sorbitan fatty acid esters (Span 80, 85s), are very similar in physical properties to mixed glycerides are alternative polar oils.
Surfactants	**Water-insoluble:** Oleate esters, such as polyoxyethylene (20) sorbitan trioloeate (polysorbate 85— ‘ Tween 85 ’) or polyoxyethylene (25) glyceryl trioleate (‘ Tagat TO ’) are commonly used in the pharmaceutical industries.
	Water-soluble: The popular castor oil derivatives with saturated alkyl chains resulting from hydrogenation of materials derived from a vegetable oil (eg. Cremophor RH40, Cremophor EL) Other examples include polysorbate 80 (T80) which are predominantly ether ethoxylates, Tween 20, poloxamer 407,

	various Labrasols, Labrafac Labrafils, and Gelucires and phospholipids (e.g., hydrogenated soy phosphatidylcholine, L-α-dimyristoylphosphatidylcholine etc)
Cosolvents	**The most popular cosolvents include:** PEG 400, propylene glycol, ethanol and glycerol. diethylene glycol monoethyl ether (transcutol), polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (glycofurol).
Other excipient	Oil soluble antioxidants include α-tocopherol, β-carotene, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate and ascorbyl palmitate.[28]

Table 2: Factors influencing the selection of lipid excipients for PWSDs
Safety issues—irritancy, toxicity etc
Solvent capacity of the lipid formulation on dispersion which could lead to precipitation of the drug
Miscibility of the excipients that affect self- emulsification
Morphology at room temperature (i.e. melting point of the formulation)
Self-dispersibility and role in promoting self- dispersion of the formulation
Digestibility of the excipients and fate of digested products
Purity of the lipid excipients and chemical stability, which could affect capsule compatibility
Cost of materials

Nanocarriers in LBDDS

Using nanocarriers as drug delivery vehicles is a promising strategy that incorporates or encapsulates the drug molecules and are biodegradable or biocompatible. The entrapped drug substances can be taken intact and protected against degradation by gastrointestinal fluids, while drug absorption through the gastrointestinal epithelium or lymphatic transport can be enhanced.[29] Possible mechanisms of transport of these nanocarriers across gastrointestinal mucosa are introduced. These focus on effects of size and surface properties of the nanocarriers on the non-specific or targeted uptake by enterocytes and/or M cells. Applications of various oral nanocarrier formulations, such as lipid nanoparticles and nanoemulsions, are reviewed in several recent publications.[30, 31] Within the scope of the current review, SMEDDS could exist as potential nanocarriers, which are much more stable thermodynamically. SMEDDS as drug carriers showed great potential for improving the bioavailability of orally administered drugs.

In a pure drug nanoparticle formulation, submicron size particles of drugs are stabilized in aqueous medium with generally regarded as safe (GRAS) listed excipients blend. Such formulation can be used for drugs with poor solubility in both water and oil, high melting point, high log P and high dose.

A recent "lipid formulation classification system"

The Lipid Formulation Classification System (LFCS, Table 3) is fairly new and was initially introduced as a working model in 2000[3] then further updated by including an extra type of formulation.[32] In recent years the LFCS has been discussed more widely within the pharmaceutical industry to seek a consensus which can be adopted as a framework for comparing the performance of lipid-based formulations. The main purpose of the LFCS is to enable *in vivo* studies to be interpreted more readily, and subsequently to facilitate the identification of the most appropriate formulations for specific drugs, i.e. with reference to their physicochemical properties.

Drug release/dissolution from LBDDS

Characterization of *in vitro* drug release from emulsions, especially under sink condition, is technically difficult to achieve. Since solubility of the drug in sink phase may be poor, large volumes may be needed to maintain the sink conditions. Further, it is difficult to separate the oil droplets due to their smaller size from the dissolved or released drug in the sink solution levy.

The USP dissolution apparatus is suitable for the establishment of a dispersion test, but emphasis should be on precipitation rather than dissolution. Providing lipid formulation as a good self-emulsifying system, the drug will be rapidly dispersed in simulated gastric fluid in the vessel.[43] So, the question is whether the drug remains in solution and for how long.[32] More conventional Type II and Type IIIA lipid formulations disperse to produce o/w emulsions or microemulsions which would be expected to retain better solvent capacity. However, 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.[41]

In order to predict whether precipitation is likely to occur it is possible to examine the equilibrium solubility of the drug in components of the formulation after maximum dilution, also to carry out corresponding dynamic dispersion/precipitation tests, and then investigate correlations between the two experiments.[32] Care is needed in the design of lipid based formulations to ensure that the precipitation of the drug is minimized.

***In vitro* digestion (lipolysis)**

In vitro digestion tests are of critical importance to the formulator for predicting the fate of the drug in the intestinal

Table 3: Materials, characteristic features, advantages and disadvantages of the lipid formulation classification systems (LFCS)

Materials	Oils (e.g., MCT, LCT), surfactant free	Oils and water insoluble surfactants (HLB<12)[34]	Oils, Water soluble/insoluble surfactants and cosolvents[36]	Oils, Water soluble, surfactants and cosolvents (low oil proportion) [40]	Water soluble surfactant and cosolvents (oil free)
Characteristic features	Limited or no dispersion, requires digestion	SEDDS	SEDDS/SMEDDS	SMEDDS	SMEDDS/micellar solution [41]
Advantages	Stable and safe for oral ingestion, excellent capsule compatibility	Retain solvent capacity on dispersion,	Almost clear dispersion (particle size approx: 100-250nm),[37] drug absorption without digestion	Transparent dispersion, drug absorption without digestion	This system has good solvent capacity for many drugs
Disadvantages	Poor solvent capacity, mostly suitable for lipophilic drugs	Coarser emulsion (particle size: 0.2-2μm)[35]	Likely to lose solvent capacity on dispersion, less easily digested[38]	Likely to lose solvent capacity on dispersion, may cause partial drug precipitation, less easily digested	Likely loss of solvent capacity and ↑ risk of precipitation, may not be digestible and well-tolerated for chronic administration[32, 41]
Marketed products	Oil-soluble vitamins (A and D) [3] , Calcitriol (Rocaltrol ®) Roche [33]	Cyclosporin A as ‘ Sandimmune ® , Novartis [33]	Cyclosporin A as ‘ Neoral ® ’ Novartis [39]	HIV antiviral Tipranavir Aptivus ® Boehringer Ingelheim, US [40]	HIV protease inhibitor Ritonavir (Norvir®; Abbott), Amprenavir (Agenerase ® , GSK) [35, 42]

lumen prior to absorption. It is evident that the solvent capacity of the formulation can be lost on digestion, leading to drug precipitation.[38] Fortunately lipolysis can be carried out as an *in vitro* test using a pH-stat to maintain pH and using the lipase/co-lipase content of porcine pancreatin to serve as model for human pancreatic juice. Bile salt-lecithin mixed micelles are added to the reaction mixture to provide a sink for solubilization of degradation products.[32]

Lipolysis is allowed to proceed for a fixed time, the reaction is then subjected to ultracentrifugation, and further assay of drug in the various phases allows predicting whether the drug will remain solubilized in the intestinal lumen after digestion of the formulation. However, if the drug is partially precipitated then drug will be found in the pellet, which may be still in solution. This technique was used recently using LFCS Type I, Type II, and Type III formulations to predict the effect of formulation on the fate of a series of drug compounds [32] and given that surfactants are subjected to digestion, probably for Type IV formulations. Lipolysis experiments may play a vital role in the near future for establishing strong methods for *in vitro–in vivo* correlations.

Mechanism of lipid digestion and drug absorption

Lipid metabolism

Following ingestion of a lipid-based dosage form (capsule/tablet), the formulation is initially dispersed in the stomach where the digestion of exogenous dietary/formulation lipid is initiated by the action of gastric lipase on the lipid-water interface. Gastric lipase releases about 15% of free fatty acids from lipids.[44] Within the small intestine, pancreatic lipase together with its co-factor co-lipase completes the breakdown of dietary glycerides to di-glyceride, monoglyceride and fatty acid.[45] The presence of exogenous lipids in the small intestine also stimulates secretion of endogenous biliary lipids including bile salt, phospholipid and cholesterol from the gallbladder. In the presence of raised bile salts concentrations, the products of lipid digestion are subsequently incorporated into a series of colloidal structures including multilamellar and unilammelar vesicles, bile salt mixed micelles and micelles.[46] Together these species significantly expand the solubilization capacity of the small intestine for both lipid digestion products and drugs.

The mixed micelles then transport these substances across the unstirred water layer and reach the vicinity of the aqueous-microvillus interface to allow for lipid absorption through the mucosal cells. During lipid absorption, some re-synthesis of triglycerides from the hydrolysis products must occur. Triglycerides complexes with proteins to form cylomicrons.[42]

Drug absorption

Several studies have reported increased absorption of PWSD when administered in lipid-based formulations including triglyceride emulsions, micellar systems and self-emulsifying formulations. Possible mechanisms for improving drug absorption include: (a) an increase in the membrane fluidity facilitating transcellular absorption, (b) larger surface area provided by the fine emulsion droplets and subsequent lipolysis and formation of mixed micelles, (c) opening of the tight junction to allow paracellular transport, mainly relavant for ionized drugs or hydrophilic macromolecules, (d) inhibition of P-gp and/or CYP450 to increase intracellular concentration and residence time, and (d) stimulation of lipoprotein/chylomicron production. The latter two mechanisms are potentially the most promising for intestinal lymphatic drug targeting using lipid-based vehicles.[47]

Digestion of dietary triglyceride in the small intestine is very rapid, and many other non-ionic esters, such as mixed glycerides and surfactants will be substrates for pancreatic lipase. Digestion of formulations will inevitably have a profound effect on the state of dispersion of the lipid formulation, and the fate of the drug. One possibility is that the drug will be solubilized in mixed micelles of bile salts and phospholipids. The capacity for solubilization of mixed micelles is dependent on the physical properties of the drug, but this can be studied relatively easily as a preformulation exercise. The natural process of digestion offers the possibility that very hydrophobic drugs could be taken up into the lymphatic system by partitioning into chylomicrons in the mesentery. This is expected to be a mechanism of absorption for drugs with log*P* values greater than 6, and has been demonstrated to be crucial for the absorption of the anti-malarial compound halofantrine.[3,48]

It is possible that digestion of a lipid formulation could reduce the solubility of the drug in the gut lumen, which would result in precipitation of the drug and a decrease in the absorption rate. More research is needed indeed to clearly understand drug precipitation during digestion.

The risk of precipitation

Triglycerides alone (Type I) are poor solvents for all but suitable for highly lipophilic compounds. If lipid-based formulations contain mixed glycerides, polar oils, surfactants and/or cosolvents ((Type I, II, III), it is likely to improve the solvent capacity of the formulation. Therefore, formulators are always preferred to add water-soluble surfactants and cosolvents at the expense of lipids, ultimately resulting in the complete exclusion of lipid excipients sometimes to produce lipid free formulations (Type IV). The formulator must balance the advantage of including cosolvents with the risk of inducing drug precipitation on dispersion. Several studies showed that small changes in formulation compositions are not expected to cause large changes in drug solubility but there could be a dramatic drop in solvent capacity upon dilution in water. Dilution of a cosolvent implies a substantial loss of solvent capacity, while the loss of solvent capacity suffered when a surfactant is diluted in water may be negligible. This is because the solubility of a solubilized drug is linearly related to the number of micelles present, and therefore to the surfactant concentration. Hence, increasing the solubility of a drug by including a cosolvent is generally a poor strategy than using a non-ionic surfactant.[32, 49]

It is much more difficult to predict the fate of the drug on dispersion of a typical Type IIIA lipid formulation. The hydrophilic surfactant used in Type IIIA systems will be substantially separated from the oily components, forming a micellar solution in the continuous phase. Hence, one might question: does this system lower the overall solvent capacity for the drug or not? However, this may depend on the log*P* of the drug, and to what extent the surfactant was contributing to its solubilization within the formulation. At present there are no established techniques available to help formulators assessing the risk of precipitation. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in the solubilizing and colloidal stabilizing environment of the gut. In some cases, Type III formulations can take several days to reach equilibrium and the drug remain in a super-saturated state for up to 24 hrs time. It could be argued that such products are not likely to cause precipitation in the gut before the drug is absorbed, and the super-saturation may actually enhance absorption by increasing the thermodynamic activity of the drug.[3]

In vitro- In vivo correlation (*IVIVC*)

If there is a successful in *vitro-in vivo* correlation (*IVIVC*), confidence in the development of the pharmaceutical product and its quality are likely to increase, and the drug development time may be shortened.[50] However, there are only a few studies of *IVIVC* using lipid formulations. A recent study, reported by Dahan and Hoffman,[51] examined the impact of the different lipid-based formulations (LCT, MCT and SCT formulations) on the permeation of dexamethasone and griseofulvin through the gut wall, and attempted to correlate *in vitro* and *in vivo* data. An *in vitro* lipolysis and *ex vivo* intestinal permeability model was used to predict the corresponding *in vivo* oral bioavailability. The data illustrated that although the *in vivo* bioavailability of both drugs correlated well with the *in vitro* digestion data, the *ex vivo* permeation studies failed to predict the *in vivo* bioavailability.

Another study by Porter and colleagues [52] demonstrated a reliable correlation between the *in vitro* solubilization and digestion data and the *in vivo* data on relative oral bioavailability. This study investigated the fate of halofantrine using high or low masses of MCT and LCT *in vitro*, and suggested that the solubilization capacity of the lipid digestion products is highly dependent on the lipid concentration used in lipid digestion experiments. The *in vitro* digestion model is useful to optimize suitable oral lipid formulations for lipophilic drugs.[53, 54] It is clear that more robust *IVIVC* relationship is required using large number of model compounds and more human clinical data sets for complete characterisation of the *in vitro* and *in vivo* solubilization behaviour of PWSD formulated in lipid-vehicles.

Limitations and future research

It is still difficult to predict which factors are important in designing the suitable dosage forms. For example, questions regarding the importance of particle size to bioavailability and the necessity of presenting the drug as a solution rather than a fine suspension in the oil-surfactant mixture still have not been fully answered.

Another issue is that SEDDS/SMEDDS often require a cosolvent and/or cosurfactant to facilitate their low volume packaging and spontaneous formation. However, the use of SEDDS, SMEDDS and/or SNEDDS is limited by their drug loading capacity and the limited level of surfactants and cosolvents that can be used with no concern about safety. So, formulators need to develop systems with maximum drug loading capacity while using minimum possible amount of surfactants and/or cosolvents.[55]

Within a challenging pharmaceutical development environment, the sharing of knowledge and expertise, and combination of research efforts is a distinctive tool to advance science and address unmet needs, and can only result in novel and optimized therapies for healthcare professionals and the patients they serve. In future the formulation scientists need to consider more on the identification of LBDDS key performance criteria, the validation and publication of universal Standard Operating Procedures to assess performance, and the generation of *in vitro in vivo* correlations (*IVIVC*) and databases to predict the fate of drugs when administered in LBDDS. However, it is hypothesised that the closer the dissolution test conditions to the physiology, the better the chances of obtaining an *IVIVC*. Nonetheless, it is also required to establish the approved guidelines by the pharmaceutical regulatory bodies (EMEA, FDA) in the near future.

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