

**ABSTRACT:** The percentage of new chemical entities synthesised with low aqueous solubility and high therapeutic efficacy is growing, this presents a major challenge for the drug delivery. To overcome this challenge, different methods were developed for the improvement of oral bioavailability, but some have major disadvantages. Recently, 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 solubilisation remains arguably the most important method of absorption enhancement. This review discusses about lipid formulation, classification system (LFCS) based on different types of surfactants, like water-soluble and water-insoluble and different concentrations of the excipients those are generally recognized as safe (GRAS). Various parameters are mentioned for the evaluation of the lipid based formulation, like equilibrium phase behaviour, self dispersion and size dispersions, *in vitro* dispersion, droplet size and surface charge, *in vitro* release. In the USA, Japan and other countries, various poorly soluble drugs are commercially available as lipid-based formulations for oral administration.

**KEYWORDS:** Lipid based Formulation; Oral bioavailability; self- dispersion; *in vitro* release

## Introduction

It has been estimated that between 40% and 70% of all new chemical entities identified in drug discovery programs are insufficiently soluble in aqueous media to allow for their adequate and reproducible absorption from the gastrointestinal tract, following oral administration. Many individuals maintain that reliance on combinatorial chemistry is responsible for creating this solubility problem. Oral lipid-based formulations, which are by no means a recent technological innovation, have not only proven their utility for mitigating the poor and variable gastrointestinal absorption of poorly soluble, lipophilic drugs, but in many cases have shown the ability to reduce or eliminate the influence of food on the absorption of these drugs (Hauss et al, 2002).

Traditionally, the primary roles of formulation excipients were to bind and provide bulk to the dosage form, to facilitate or control drug release from the formulation, and to allow product manufacturing on high speed, automated production equipment. As such, excipients were regarded as largely inert and roles in absorption modification beyond the potential to facilitate disintegration or alter the kinetics of release were not considered.

## The Lipid Formulation Classification System

The Lipid Formulation Classification System (LFCS) was introduced as a working model in 2000 and an extra ‘type’ of formulation was added in 2006 (Pouton et al, 2006). 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.

Group III has been further divided into Type IIIA and Type IIIB, to distinguish between formulations which contain a significant proportion of oils (Type IIIA) and those which are predominantly water-soluble (Type IIIB). The distinction between Types IIIA and IIIB was based arbitrarily, as a starting point for discussion, on the proportions of typical excipients in formulations.
Table 1 indicates the fundamental differences between Type I, II, III and IV formulations. Whilst the defining properties of each Type are easy to understand, as yet there are few studies which link the LFCS with in vitro or in vivo performance. Table 2 shows typical composition of various types of lipid formulations.

At present the sub-classification of Types III formulations is ill-defined, particularly when one considers that a Type III formulation could contain 3–5 excipients, including water-insoluble and water-soluble surfactants, as well as water miscible co-solvents. In the immediate future it will be important to establish in vitro performance criteria which can be determined experimentally to distinguish between various Type III formulations, because this group is likely to contain formulations which have very different performance characteristics.

### Table 1

The Lipid Formulation Classification System: characteristic features, advantages and disadvantages of the four essential types of ‘lipid’ formulations.

<table>
<thead>
<tr>
<th>Formulation type</th>
<th>Materials</th>
<th>Characteristics</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Oils without surfactants (e.g. tri-, di- and monoglycerides)</td>
<td>Non-dispersing, requires digestion</td>
<td>Generally recognized as safe (GRAS) status; simple; excellent capsule compatibility</td>
<td>Formulation has poor solvent capacity unless drug is highly lipophilic</td>
</tr>
<tr>
<td>Type II</td>
<td>Oils and water-insoluble surfactants</td>
<td>SEDDS formed without water-soluble components</td>
<td>Unlikely to lose solvent capacity on dispersion</td>
<td>Turbid o/w dispersion (particle size 0.25–2 μm)</td>
</tr>
<tr>
<td>Type III</td>
<td>Oils, surfactants, co-solvents (both water-insoluble and water-soluble excipients)</td>
<td>SEDDS/SMEDDS formed with water-soluble components</td>
<td>Clear or almost clear dispersion; drug absorption without digestion</td>
<td>Possible loss of solvent capacity on dispersion; less easily digested.</td>
</tr>
<tr>
<td>Type IV</td>
<td>Water-soluble surfactants and co-solvents</td>
<td>Formulation disperses typically to form a micellar solution</td>
<td>Formulation has good solvent capacity for many drugs</td>
<td>Likely loss of solvent capacity on dispersion; may not be digestible</td>
</tr>
</tbody>
</table>

### Table 2

The proposed lipid formulation classification system (LFCS) showing typical composition of various types of lipid formulations.

<table>
<thead>
<tr>
<th>Excipients in formulation</th>
<th>Content of formulation (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type I</td>
</tr>
<tr>
<td>Triglycerides or mixed mono and diglycerides</td>
<td>100</td>
</tr>
<tr>
<td>Water-insoluble surfactants (HLB &lt; 12)</td>
<td>–</td>
</tr>
<tr>
<td>Water-soluble surfactants (HLB &gt; 12)</td>
<td>–</td>
</tr>
<tr>
<td>Hydrophilic cosolvents (e.g. PEG, Propylene glycol, transcutol)</td>
<td>–</td>
</tr>
</tbody>
</table>
Excipients for Lipid Formulations

A wide range of triglycerides, partial glycerides, semi-synthetic oily esters, and semi-synthetic non-ionic surfactants esters are available from excipients suppliers. A recent book chapter by Gibson provides a detailed list of the most popular excipients used in lipid-based products for oral administration, concentrating on esters, which are preferred from a toxicological standpoint, and indicating the trade names, suppliers and differences between related excipients. Note that one popular group of surfactants, the Sorbian esters and their ethoxylated derivatives (polysorbates), is omitted (Gibson et al, 2008).

General selection criteria

Lists some of the factors which are affecting the choice of excipients. Several of these issues are discussed in the context of formulation.

Factors affecting the choice of excipients for lipid-based formulations

- Regulatory issues–irritancy, toxicity, knowledge and experience
- Solvent capacity
- Miscibility
- Morphology at room temperature (i.e. melting point)
- Self-dispersibility and role in promoting self-dispersion of the formulation
- Digestibility, and fate of digested products
- Capsule compatibility
- Purity, chemical stability
- Cost of goods

Toxicity is an independent issue, and is important with regard to the choice of surfactants. Water-insoluble surfactants penetrate and fluidize biological membranes and water-soluble surfactants have the potential to solubilise membrane components. All surfactants are potentially irritant or poorly tolerated as a result of these non-specific effects. There is a considerable literature on the interaction of surfactants with biological systems and published toxicity data gives an indication of differences between surfactants (Attwood et al, 1983). In general terms cationic surfactants are more toxic than anionic surfactants which in turn are more toxic than non-ionic surfactants. Lipid-based delivery systems usually only include non-ionic surfactants so it is pertinent to compare the toxicity of non-ionic surfactants. In general bulky surfactants such as polysorbates or polyethoxylated vegetable oils are less toxic than single-chain surfactants, and esters are less toxic than ethers (which are non-digestible). Non-ionic surfactants are generally considered to be acceptable for oral ingestion, and the emergence of several successful marketed products has given the industry confidence in lipid-based products. The oral and intravenous LD50 values for most non-ionic surfactants are in excess of 50 g/Kg and 5 g/Kg respectively, so 1 g surfactant in a formulation is well-tolerated for uses in acute oral drug administration. More careful consideration needs to be given to formulation of a product which is intended for chronic use, and it is noteworthy that marketed lipid products for chronic use generally do not include surfactants (Strickley, 2007).

Another practical consideration relates to the chemical complexity of excipients. The use of vegetable oils from different plants is an immediate source of diversity, and subsequent chemical derivation by hydrolysis and esterification introduces more diversity. Further processing is required to produce nonionic surfactants, usually esters of polyoxyethylene or polyglycerol, or products of reaction with ethylene oxide. The polyoxyethylene or polyglycerol chains are polymeric in nature, which means that a typical surfactant product based on mixed glycerides is comprised of dozens of separate chemical entities in different proportions (Jannin et al, 2008).

Trace contaminants are an issue with lipid excipients and surfactants, particularly in relation to the chemical stability of the dissolved drug. Care should be taken to select excipients with low level of peroxides, aldehydes etc. and to find out at an early stage in preformulation studies whether the drug of interest is sensitive to the presence of particular trace contaminants. Chemical stability of drugs in lipid vehicles is poorly understood. Formulators should exercise caution but the prevalence of stability problems is not clear from the published literature. It would be useful if more well-conducted studies were published using representative formulations.

Triglycerides

Triglyceride vegetable oils have many advantages as the foundation of lipid-based delivery systems. They are commonly ingested in food, fully digested and absorbed, and therefore do not present any safety issues. Vegetable oils are glyceride esters of mixed unsaturated long-chain fatty acids, commonly known as long-chain triglycerides (LCT). Oils from different vegetable sources have different proportions of each fatty acid. Triglycerides are highly lipophilic and their solvent capacity for drugs is
commonly a function of the effective concentration of the ester groups, thus on a weight basis MCT generally has higher solvent capacity than LCT. In addition MCT is not subject to oxidation, so MCT is a popular choice for use in lipid-based products (Anderson et al, 1999, Cao et al, 2004).

Mixed glycerides and polar oils

Partial hydrolysis of triglycerides is used to produce a wide range of mixed glyceride excipients, containing various proportions of monoglycerides, diglycerides and triglycerides. The chemical composition of mixed glyceride products depends on the source of triglyceride starting material as well as the extent of hydrolysis induced. Care needs to be taken with excipients names. ‘Monoglyceride’ products often contain substantial quantities of diglycerides and triglycerides, so the manufacturer’s datasheet should be consulted in detail. ‘Glyceryl monooleate’ is a waxy material but its physical form will be very dependent on the di-and triglyceride content. Since waxes create technical challenges, mixed mono and diglycerides of long-chain fatty acids are a good option, allowing liquid formulations to be produced. Trace amounts of saturated monoglycerides sometimes produce a hazy product and steps have been taken by some manufacturers to overcome this formulation- dependent effect. Nevertheless mixed long-chain glycerides are popular excipients. They are usually much better solvents for drugs than triglycerides, unless the drug is highly lipophilic, and they are also useful components of Type II and Type III self-emulsifying systems, promoting mutual miscibility and emulsification. Medium-chain mixed glycerides have become popular excipients, having even greater solvent capacity, enhanced ability to promote emulsification, and lack of susceptibility to oxidation. However there are complications with medium-chain excipients in relation to digestion (Porter et al, 2004, Kaukonen et al, 2004).

In addition to mixed glycerides, there are a wide variety of related materials which may be useful, including esters of propylene glycol, and esters formed between fatty acids and fatty alcohols. The literature is not extensive enough to evaluate how useful these alternative esters are. Other more polar oily excipients are of interest to improve the solvent capacity and dispersibility of the formulation. Some excipients which are traditionally thought of as hydrophobic surfactants, such as sorbitan fatty acid esters (Spans), are very similar in physical properties to mixed glycerides or propylene glycol esters. The more lipophilic sorbitan fatty acid esters, such as sorbitan trioleate (Span 80) are alternative polar oils. Sorbitan monooleate (Span 80) which has more hydroxyl groups has also been used widely in pharmaceutical products. In the context of formulation and the desire to promote mutual miscibility, free fatty acids can be considered to belong to this general group of polar oils or ‘co-surfactants’. Oleic acid has been used in a number of marketed products, it can enhance the solubility of weak bases, though there is a risk of chemical reaction with free alcohols.

Water-insoluble surfactants

Non-ionic esters which are not polyethoxylated or polyglycerylated can be considered to be polar oils. In the context of oral lipid-based formulations we refer to a group of excipients of intermediate HLB (8–12), which adsorb strongly at oil–water interfaces, as ‘water-insoluble surfactants’. These materials are insufficiently hydrophilic to dissolve in water and form micelles but nevertheless are sufficiently hydrophilic to be capable of driving self-emulsification. The constituents of water-insoluble surfactants will have a finite solubility in water depending on their degree of ethoxylation, but solubility is generally very low. These surfactants are sometimes described as ‘dispersible’ in water, meaning that they can form an emulsion if subjected to shear. These materials typically are predominantly oleate esters, such as polyoxyethylene (20) sorbitan trioleate (polysorbate 85—‘Tween 85’) or polyoxyethylene (25) glyceryl trioleate (‘Tagat TO’). These two examples have HLB values between 11 and 11.5 and are particularly useful for formulation of Type II systems It should be noted that the properties of these surfactants cannot necessarily be recreated by blending materials of different HLB values (Pouton et al, 2008).

Water-soluble surfactants

The most commonly used surfactants for formulation of SEDDS or SMEDDS are water-soluble, though by definition these materials can only be used in Type III or Type IV formulations. Above their critical micelle concentration these materials dissolve in pure water at low concentrations to form micelles solutions. This implies an HLB value of approximately 12 or greater. The fatty acid components can be either unsaturated or saturated this is a function of their proven safety profile rather than particular advantages they offer in physicochemical performance calculated HLB values or preferably the cloud point (which is easily determined by experiment) are useful for comparison and alignment of the physical properties of non-ionic surfactants.
However there are differences in the heterogeneity and chemistry of surfactant products which result from the source of starting materials and the methods used for synthesis. Many materials are synthesized by reacting polyethylene glycol (PEG) with hydrolysed vegetable oils. This results in fatty acid mono and di-esters of PEG combined with partial glycerides and some free (i.e.unreacted) PEG. An alternative method for surfactant synthesis involves the reaction of an alcohol with ethylene oxide to produce alkyl ether ethoxylates, which are a commonly used class of surfactants for example in cream formulation (e.g. cetostearyl alcohol ethoxylate, 'cetomacrogol'). Polysorbates are predominantly ether ethoxylates, produced by reaction of sorbitan esters with ethylene oxide. Polysorbate surfactants depend on the fatty acid ester groups for their amphiphilic character so they are inactivated as surfactants following digestion to give fatty acids and sorbitan ethoxylates. When vegetable oils are reacted with ethylene oxide the products contain predominantly esterified glyceryl ethoxylates, as well as glyceryl mono and diester ethoxylates. Chemically, these are very distinct from the PEGylated partial glycerides described above (Hauss et al, 2007).

Co-solvents

Several marketed lipid-based products contain water soluble co-solvents. The most popular materials have been PEG 400, propylene glycol, ethanol and glycerol, though other approved co-solvents have been used in experimental studies. There are at least three reasons why co-solvents have been included in lipid-based formulations. Ethanol was used in early cyclosporine formulations at a low concentration to aid dissolution of the drug during manufacture. More commonly it has been assumed that co-solvents could be included to increase the solvent capacity of the formulation for drugs which dissolve freely in co-solvents.

However, to enhance the solvent capacity significantly the co-solvent must be present at high concentration and this is associated with the risk of drug precipitation when the formulation is dispersed in water. Co-solvents lose their solvent capacity quickly following dilution. A third reason for inclusion of co-solvents is to aid dispersion of systems which contain a high proportion of water-soluble surfactants. There are practical limits on the concentrations of co-solvents which can be used, governed by issues of immiscibility with oil components and also possible incompatibilities of low molecular weight co-solvents with capsule shells (Cole et al, 2008).

Additives

Lipid-soluble antioxidants such as α-tocopherol, β-carotene, butylated hydroxy toluene (BHT), butylated hydroxyl anisole (BHA) or propyl gallate could potentially be included in formulations to protect either unsaturated fatty acid chains or drugs from oxidation.

Formulation (Pouton et al, 2008)

Formulation of Type I systems

Type I systems are mixtures of lipophilic materials which have little or no solubility in water. Typically they are blends of food glycerides derived from vegetable oils, which are safe for oral ingestion, rapidly digested, and absorbed completely from the intestine. Because Type I systems do not contain surfactant they have very limited ability to self-disperse in water. They depend on digestion to facilitate colloidal dispersion by solubilization of digestion products in mixed micelles. Both long chain triglycerides (LCT) and Medium chain triglycerides (MCT) are digested by pancreatic enzymes but in vitro lipolysis experiments reveal that there are fundamental differences in the processing of the digestion products, which are likely to have effects on the fate of drugs in the intestinal lumen. Bile is not necessary for digestion of MCT, which indicates that C8 and C10 fatty acids and monoglycerides can exist as separate dispersed or dissolved phases. In contrast LCT wills digestion in the presence of bile, which solubilizes fatty acids and 2-monoglycerides, stripping them from the surface of the partially degraded oil droplet. These recent publications suggest that Type I systems should be investigated using in vitro digestion tests to determine whether or not drug precipitation could occur in the intestine.

Although precipitation may sometimes be a problem, Type I formulations are an excellent option if the drug is sufficiently soluble in mixed glyceride oils. Bioavailability may be as good from Type I formulations as Type II and Type III formulations, and Type I formulations certainly have advantages, in relation to safety and drug stability.

Formulation of Type II systems

Type II systems are formulated with oils, polar oils and water-insoluble surfactants. Typical formulations are mixtures of MCT oil and polysorbate 85 or mixtures of MCT oil and Tagat TO. These systems have similar features which have been discussed previously. Self-emulsifying systems are formed when the surfactant concentration exceeds 25%w/w, the optimum
concentration range being 30–40% surfactant. Above 50% surfactant these systems emulsify slowly due to the formation of viscous liquid crystalline phases at the oil–water interface. Early phase studies suggested that the performance of these formulations as SEDDS relies on the formation of a dispersed lamellar liquid crystalline phase at low water contents (5–10%), which aids further of water causing interfacial disruption.

Digestion of Type II systems has not been studied adequately. The issues discussed in Type I systems relating to phase behaviour of digestion products of medium-chain glycerides would be expected to play a part in the fate of Type II systems in the intestine, though the influence of the surfactant component on phase behaviour remains to be examined. Indeed there are no comprehensive published studies which investigate the phases formed after digestion of more complex Type II and Type III SEDDS/SMEDDS formulations. Not surprisingly the effect of formulation on the fate of the dissolved drug is difficult to predict with confidence at present. These are complex issues and research is needed to build a more comprehensive understanding of digestion of these systems and their interaction with bile. Type II system can be formulated with long-chain glycerides, but these system produce coarser emulsions by self dispersion. It would be interesting to evaluate Type II systems formulated with long-chain glycerides against systems formulated with medium-chain glycerides, to explore the relative influences of particle size and digestion.

A Type II system has received limited attention and no marketed products have emerged. One reason may be that the most effective surfactants for Type II formulation do not appear on the FDA list of inactive ingredients.

Formulation of Type III systems

Sandimmune Neoral is an archetypal Type IIIA formulation, a SEDDS/SMEDDS formulation containing water-soluble surfactant and a significant mass of lipid components. Such formulations have the potential to disperse quickly to form fine submicron dispersions, often fine enough to form transparent dispersions. The key to successful formulation of Type III systems is to avoid formulations that are so hydrophilic that they lose a considerable proportion of their solvent capacity on dispersion.

Phase studies of Type III systems indicate why transparent dispersion are often produced, and can be used to optimize SMEDDS formulations.

**Formulation of Type IV systems**

Type IV systems are essentially pure surfactants or mixtures of surfactants and co-solvents. It is generally accepted that formulation of poorly water-soluble drugs in pure co-solvents is likely to result in precipitation of the drug. The only advantage that could be gained is the possibility that the drug precipitates as a suspension of very fine crystalline or amorphous particles. Reliability is likely to be problem with this strategy. At the other end of the spectrum formulation of the drug in pure water-soluble surfactant makes more sense with regard to the aim of avoiding precipitation, since loss of solvent capacity is less significant. There are two problems with using pure surfactants. The first is that surfactants often take a considerable time to dissolve, due to the formation of viscous liquid crystalline (or gel crystalline) phases at the surfactant-water interface. The second is the concern that pure surfactants can be irritant and poorly tolerated in the gastrointestinal tract. The adhesion of a partially dissolved viscous mass rich in surfactant to the wall of the stomach or intestine could do considerable local damage. The blending of water-soluble surfactants with co-solvents aids the dispersion of surfactant and reduces the loss of solvent capacity.

**Characteristics of Formulation**

**Equilibrium phase behaviour**

Studies of equilibrium phase behaviour have been used since 1985 to explain the mechanisms of dispersion of SEDDS. The conventional approach is to weigh out mixtures into glass tubes, seal the tubes, mix the components and store the tubes in a water bath until they have equilibrated. Phase behaviour for three-component (oil, surfactant and water) systems is mapped out using a ternary diagram. If more than two excipients are used in the formulation it is sensible 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 behaviour for three-component (oil, surfactant and water) systems is mapped out using a ternary diagram. If more than two excipients are used in the formulation it is sensible 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 behaviour is also valuable to assess the phases that form when formulations make contact with intestinal fluid containing bile (Pouton et al, 1997).

**Self-dispersion and sizing of dispersions**

Assessment of the dispersion rate and resultant particle size of lipid-based systems is desirable but as yet standard methods have not emerged. Little attention has been given to measuring dispersion rate. This is perhaps because there is no technical advantage in establishing a
precise estimate of dispersion rate if a facile observation by eye can be used to verify that dispersion is sufficiently fast. Generally well-formulated SEDDS or SMEDDS are dispersed within seconds under conditions of gentle stirring, and visual.

Poor systems are the least important and do not merit extended analysis. Usually a poor formulation can be distinguished from an adequate formulation by determining polydispersity using a Fraunhofer diffraction sizer. Optimization of SEDDS and SMEDDS is more likely to be a job for a photon 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 $1 \mu m$.

**In vitro dispersion and digestion tests**

In vitro dispersion and digestion tests are of critical importance to the formulator with regard to predicting the fate of the drug in the intestinal lumen. As yet there are no standard pharmacopoeia methods for testing lipid-based formulations, but standard methods may emerge over the next few years. Ideally the drug is dissolved in lipid-based formulations. This may not always be the case if the anhydrous formulation is a semi-solid waxy system or if the drug is deliberately formulated as a suspension. But 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 significance because it offers the opportunity to predict the fate of the formulation and drug in the intestinal lumen prior to absorption.

It is becoming evident that solvent capacity can be lost on digestion, leading to drug precipitation. If the digestion experiment is followed by a centrifugation step, precipitated drug can be quantified by analysing the contents of the pellet which sediments during centrifugation (Cuine et al, 2007). Digestion tests are essential for evaluation of Type I, Type II, and Type III formulations, and given that surfactants are subject to digestion, probably for Type IV formulations as well. These aspects are addressed in detail elsewhere in this theme issue.

**Appearance**

The appearance in a graduated glass cylinder or transparent glass container is noted. The following questions were addressed: At equilibrium, is the color and appearance of the formulation uniform (Porter et al, 2001).

**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 (Wei et al, 2005).

**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 (Wei et al, 2005).

**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 the external phase of the formulation to stabilize the pH, because neutral electrolytes disturb the physical stability of the suspension (Wei et al, 2005).

**Droplet size and surface charge (zeta potential)**

The droplet size distribution of microemulsion vesicles can be determined by either light scattering technique or electron microscopy. The dynamic light-scattering measurements are taken at 90° in a dynamic light-scattering spectrophotometer which uses a neon laser of wavelength 632 nm. The data processing is done in the built-in computer with the instrument. Recently, with respect to the importance of particle size distribution in terms of particle characterization and product physical stability testing, there has been interest in newer light-scattering methods for particle detection called photon correlation spectroscopy (PCS).

The surface charge is determined using a Zeta potential analyzer by measuring the zeta potential (ZP) of the preparations. ZP characterizes the surface charge of particles and thus it gives information about repulsive
forces between particles and droplets. To obtain stable nanoemulsions by preventing flocculation and coalescence of the Nan droplets, ZP should usually reach a value above 30 mV (Wei et al, 2005).

**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. The viscometer should be properly calibrated to measure the apparent viscosity of the suspension at equilibrium at a given temperature to establish suspension reproducibility. Apparent viscosity, like pH, is an exponential term, and therefore the log-apparent viscosity is an appropriate way of reporting the results (Wei et al, 2005).

**Effect of drug loading**

Especially for type-II and type-III formulation, in SEDDS or SENDDS (self-nanoemulsifying drug delivery systems) the increase or decrease in the amount of drug would influence the globule size of the resultant emulsion or nanoemulsions if drug participate at interface of emulsion or nanoemulsion. In order to investigate role of drug, various formulations are prepared containing varying amount of drug from 20 to 5% (w/w). SNEDDS, 50 mg, was diluted to 50 ml with different media viz and the mean globule size of resulting nanoemulsions was determined by PCS (photon correlation spectroscopy) (Wei et al, 2005).

**Characterizing Release from Lipid-Based Formulations**

Since lipid-based formulations are quite diverse in terms of composition and properties, attention must be paid to the specifics of a formulation in order to come up with an appropriate release method. In some cases, simple buffer media (perhaps with addition of a surfactant) might be adequate, in other cases the simulation of the conditions in the gastrointestinal tract must take into account wetting, solubilisation and digestion. Solubility of the API in the formulation, while obviously important, should not be the only criteria in selecting a formulation. Screening for dispersability of the formulation under a variety of conditions seems like a sensible next step for screening potential formulations. Provided the formulation disperses well, the next consideration is the release mechanism and how quickly this occurs. Depending on the type of formulation being contemplated, appropriate methodology should be selected. Following this approach should optimize the bioavailability of the formulation and provide a solid understanding of the behaviour of the formulation under a variety of dosing scenarios, as well as providing the basis for selection of quality control test methodology (Dressman et al, 2008).

**Other formulation tools**

Analysis of drug solubilization in bile salt–lecithin mixed micelles is a simple and effective diagnostic test. Drug solubilization can be analyzed directly by spectrophotometry in some cases or alternatively by HPLC. This technique offers a quick indication of whether a drug is likely to be solubilised in the gut lumen. The solubility enhancement ratio of steroids is a good illustration that solubilization cannot be predicted simply by octanol–water partition coefficient. Molecular dynamics modeling may become a useful formulation tool as available computing power increases. The structure of lipid formulations could be examined using similar techniques and studies of the partitioning (Naylor et al, 1995).

Assays for potency, preservative effectiveness, compatibility with primary container-closure system, off torque, simulated use testing, etc., should be handled in a manner similar to that used for conventional liquid solutions, with the provision that the container is well-mixed prior to sampling.

**Application of Lipid-based Systems for the Enhanced Delivery of Poorly Water Soluble Drug**

The utility of lipid based formulations to enhance the absorption of poorly water soluble, lipophilic drugs has been recognised for many years. The conversion of this potential into commercial products, however, has been until relatively recently, primarily limited to simple lipid solution formulations such as those commonly used to deliver fat soluble vitamins. Historically, the limited number of registered lipidic formulations most likely reflected a reticence to progress relatively more complex (non-solid dose) formulations, particularly when drug doses were commonly too high to allow development as a single unit dosage form and where both chemical and physical stability were often problematic.
Table 3  List of selected commercially available lipid-based formulations for oral administration.

<table>
<thead>
<tr>
<th>Molecules/Trade Name</th>
<th>Indication</th>
<th>Dose</th>
<th>Type of Formulation</th>
<th>Lipid Excipient &amp; Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol/Rocaltrol®</td>
<td>Calcium Regulator</td>
<td>Adult: 0.25-0.5µg q.d.</td>
<td>Soft gelatin capsule</td>
<td>Fractionated triglyceride of coconut oil</td>
</tr>
<tr>
<td>Cyclosporin/Nerol®</td>
<td>Immuno suppressant</td>
<td>2-10mg/kg/day b.i.d.</td>
<td>Soft gelatin capsule</td>
<td>Cremophor RH 40</td>
</tr>
<tr>
<td>Tretinoin/Vesanoid®</td>
<td>Antineo-plastic</td>
<td>45mg/m² subdivided</td>
<td>Soft gelatin capsule</td>
<td>Bees wax, hydrogenated soyabean oil</td>
</tr>
<tr>
<td>Valporic Acid/Depakene®</td>
<td>Antiepileptic</td>
<td>10-60 mg/kg/day</td>
<td>Soft gelatin capsule</td>
<td>Corn oil</td>
</tr>
<tr>
<td>Fenofibrate/Fenogal®</td>
<td>Antihyperlipoproteinemic</td>
<td>200 mg q.d</td>
<td>Hard gelatin capsule</td>
<td>Gelucire 44/4</td>
</tr>
<tr>
<td>Testosterone/Restandol®</td>
<td>Hormone replacement therapy</td>
<td>40-160 mg q.d.</td>
<td>Soft gelatin capsule</td>
<td>Oleic acid</td>
</tr>
</tbody>
</table>

Lipids are perhaps one of the most versatile excipients classes currently available, providing the formulator with many potential options for improving and controlling the absorption of poorly water-soluble drugs. These formulation options include lipid suspensions, solutions, emulsions, microemulsions, mixed micelles, SEDDS, SMEDDS, thixotropic vehicles, thermo-softening matrices, and liposomes. Lipid-based formulations, which are by no means a recent technological innovation, have not only proven their utility for mitigating the poor and variable gastrointestinal absorption of poorly soluble, lipophilic drugs, but in many cases have shown the ability to reduce or eliminate the influence of food on the absorption of these drugs. Despite these realities, marketed oral drug products employing lipid-based formulations are currently outnumbered 25 to 1 by conventional formulations. Table-3 shows list of selected commercially available lipid based formulation for oral administration.

Currently, lipid-based formulations occupy a small but successful niche for dealing with oral delivery of poorly soluble drugs. The majority of application and manufacturing expertise for these formulations is, not surprisingly, limited to smaller specialty companies. However, the services of these organizations are being leveraged with increasing frequency, which bodes well for more widespread acceptance of oral lipid-based formulations by the industry at large. Greater demand for this technology should drive increased research efforts directed at solving solubility and stability issues and refinement of in vitro and in vivo models for more reliable projection of formulation performance in humans. Increased regulatory acceptance of oral lipid-based formulations is expected to follow these anticipated developments.

Conclusion

Lipid-based drug delivery systems may include a broad range of oils, surfactants, and co-solvents. This diversity makes comparison of lipid-based formulations difficult. Although the relationship between formulation and drug absorption is understood at a conceptual level, performance in vivo cannot be predicted with confidence at present. The Lipid Formulation Classification System (LFCS) identifies the factors which are likely to affect performance in vivo. There is now a need to establish performance criteria which will facilitate in vitro–in vivo correlation studies.

We hope this commentary provides a useful stimulus that will encourage more pre-competitive research on aspects of lipid-based formulation. Most of the materials used for lipid based systems have been in use for many
years. As a result there is a considerable volume of prior art in the published literature. The scope for identifying commercially important new intellectual property in relation to lipid-based drug delivery is limited. On the other hand well-designed mechanistic studies which can be discussed in the public domain will be of great interest to formulators, who increasingly are faced with the challenge of formulating poorly water-soluble drugs.

**Future Prospects**

More attention needs to be paid to the characteristics of various lipid formulations available, so that guidelines and experimental methods can be established that allow identification of candidate formulations at an early stage. Methods need to be sought for tracking the solubilization state of the drug in vivo, and there is a need for in vitro methods for predicting the dynamic changes, which are expected to take place in the gut. Attention to the physical and chemical stability of drugs within lipid systems, and the interactions of lipid systems with the components of capsule shells will also be required. Whilst these present challenges there is a great potential in the use of lipid formulations. The priority for future research should be to conduct human bioavailability studies, and to conduct more basic studies on the mechanisms of action of this fascinating and diverse group of formulations.

**Reference**


