ABSTRACT
Approximately more than 50% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. The bioavailability of these drugs (BCS class II) is rate-limited by its dissolution, so that even a small increase in dissolution rate sometimes results in a large increase in bioavailability. The rate and extent of absorption of class II compounds is highly dependent on the performance of the formulated product. Self-emulsifying drug delivery systems (SEDDS) are usually used to improve the bioavailability of hydrophobic drugs. Conventional SEDDS, however, are mostly prepared in a liquid form, which can produce some disadvantages. Accordingly, solid SEDDS (S-SEDDS), prepared by solidification of liquid/semisolid self-emulsifying (SE) ingredients into powders, have gained popularity. This article presents an account on types of self-emulsifying formulations with emphasis on formulation of solid dosage forms, characterization and in vitro analysis.

Key Words: Self-emulsifying drug delivery systems (SEDDS), Lipid formulation classification system.

INTRODUCTION
It has been estimated that around 50 to 70 percent of all new chemical entities (NCE) entering drug development programs possess insufficient aqueous solubility to allow consistent gastrointestinal absorption of a magnitude sufficient to ensure therapeutic efficacy. The poor and variable absorption afforded these compounds by conventional formulations can be complicated by a significant, positive food effect, potentially resulting in unexpected toxicity while making development more costly and difficult.

Solubilization of a drug in the gastrointestinal tract (GIT) is dependent upon the complex interplay of multiple factors, including the presence of food, and thus is an inherently variable phenomenon often resulting in erratic absorption of poorly soluble drugs.

The molecular characteristics of BCS class II drugs are identified as low solubility and high permeability. For instance, cyclosporine, griseofulvin and itraconazole are categorized into this class. Generally, the bioavailability of a BCS class II drug is rate-limited by its dissolution, so that even a small increase in dissolution rate sometimes results in a large increase in bioavailability. Therefore, an enhancement of the dissolution rate of the drug is thought to be a key factor for improving the bioavailability of BCS class II drugs. Several physicochemical factors control the dissolution rate of the drugs. According to the modification of the Noyes-Whitney equation, the factors affecting the drug dissolution rate are defined as the effective surface area, the diffusion coefficient, the diffusion layer thickness, the saturation solubility, the amount of dissolved drug, and the volume of dissolution media. Increases in the saturation solubility and the effective surface area have a positive impact on the dissolution rate of the drugs, and these factors could be increased by efforts of preformulation study and formulation design. Crystal modification, particle size reduction, pH modification and amorphization are considered to be effective for improving the dissolution behaviour of BCS class II drugs.

In recent years, much attention has been paid to self-emulsifying drug delivery systems (SEDDS). The Self-emulsifying drug delivery systems (SEDDS) are physically stable, isotropic mixtures of oil, surfactant, cosurfactant and solubilized drug substance that are suitable for oral delivery in soft and hard gelatin (or hard hydroxypropylmethylcellulose) capsules. Depending on the excipient selection and relative composition of the formulation, aqueous dilution will result in spontaneous formation of lipid droplets ranging in size from approximately 100 nm (SEDDS) to less than 50 nm (SMEDDS). However, traditional preparations of SEDDS are usually prepared in the liquid state. So the liquid SEDDS are generally enclosed by soft or hard capsules to facilitate oral administration but it produces some disadvantages, such as high production costs, low drug incompatibility and stability, drugs leakage and precipitation, capsule ageing. Then formulation of liquid SEDDS into a solid dosage form is compelling and desirable.
Advantages
Potential advantages of these systems (SEDDS) include
1. Enhanced oral bioavailability enabling reduction in dose.
3. Protection of drug(s) from the hostile environment in gut.
4. Control of delivery profiles.
5. Reduced variability including food effects.
7. Liquid or solid dosage forms.

LIPID FORMULATION CLASSIFICATION SYSTEM
The Lipid Formulation Classification System (LFCS) was introduced in 2000 and an extra type of formulation was added in 2006. 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.

Type I systems
Type I systems consist of formulations where the drug is in a solution of triglycerides and/or mixed glyceride sor in an oil-in-water emulsion stabilised by low concentrations of emulsifiers such as 1% w/v polysorbate 60 and 1.2% w/v lecithin. These systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase/co-lipase in the GIT to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I lipid formulations represent a relatively simple option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required “payload” dose. Although precipitation may sometimes be a problem, Type I formulations are an excellent option if the drug is sufficiently soluble in mixed glyceride oils.

Type II-System
Type II lipid formulations, referred to as self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of lipids and lipophilic surfactants with HLB value less than 12 that self-emulsify to form fine oil-in-water emulsions in aqueous media. Self-emulsification is generally obtained at surfactant content above 25% w/w. However, at a surfactant content of 50-60% w/w, the emulsification process may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface. Poorly water-soluble drugs can be dissolved in SEDDS and encapsulated in hard or soft gelatin capsules to produce convenient in-gel unit dosage forms. Type II lipid-based formulation offer the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and, as described above, and they are able to generate large interfacial areas which in turn allow efficient partitioning of drug between the oil droplets and the aqueous phase from which absorption occurs.

Type III Systems
Type III lipid-based formulations, commonly referred to as self-micro emulsifying drug delivery systems (SMEDDS), and are defined by the inclusion of hydrophilic surfactants with HLB value more than 12 and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further divided into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems. In Type IIIB, the content of hydrophilic surfactants and cosolvents is increased and the lipid content is reduced. Type IIIB formulations typically achieve greater dispersion rates when compared with Type II A although the risk of drug precipitation on dispersion of the formulation is higher owing to the lower lipid content.

Type IV Systems
The type IV category was recently added to the Lipid Formulation Classification System. Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. Type IV systems are essentially pure surfactants or mixtures of surfactants and cosolvents. It is generally accepted that formulation of poorly water-soluble drugs in pure cosolvents 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. 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 irrant and poorly tolerated in the gastrointestinal tract. The blending of water-soluble surfactants with cosolvent says the dispersion of surfactant and reduces the loss of solvent capacity. The amprenavir capsule formulation (Agenerase, GSK) is a type IV formulation, a blend of tocopheryl polyethylene glycol 1000 succinate (TPGS), PEG 400 and propylene glycol. TPGS is an unusual surfactant that originated as a water dispersible form of vitamin E.
FORMULATION OF SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM

DRUG CANDIDATE SELECTION

The Biopharmaceutical Classification Scheme (BCS) implies that aqueous solubility and membrane permeability are two major factors limiting drug absorption. A drug is considered to be highly soluble when the highest dose strength is soluble in 250 ml or less over a pH range 1–7.5 at 37 °C. In contrast, if the drug solubility is less than 100 μg/ml or the dose to solubility ratio is greater than 250 ml then it is considered poorly soluble. Alternatively, Lipinski’s rule of five has been widely proposed as a qualitative predictive model for oral absorption trends. In the discovery setting the ‘rule of 5’ predicts that poor absorption or poor permeation is more likely when: there are more than 5 H-bond donors, there are more than 10 H-bond acceptors, the molecular weight more than 500, and the calculated LogP more than 5. Lipid-based formulations, self-emulsifying drug delivery systems (SEDDS) have been shown to enhance the absorption and bioavailability of poorly water soluble drugs. Selection of drug candidate for lipid based formulation can be done by assessing the drug lipophilicity (log P) and its solubility in pharmaceutically-acceptable lipid excipients. The solubility in lipid excipients should be sufficient to allow the entire dose of the drug to be administered in a single dosage unit. Lipophilic drugs with high logP value usually greater than 4, and low dose are desirable for development of lipidic systems\textsuperscript{6,15}.

EXCIPIENTS USED IN THE FORMULATION

Natural oils

A number of natural product oils, derived primarily from plant sources and processed to remove impurities or to isolate various fractions of the original product, are available and suitable for use in encapsulated oral formulation products. Naturally occurring oils and fats are comprised of mixtures of triglycerides which contain fatty acids of varying chain lengths and degrees of unsaturation. The melting point of particular oil increases in proportion to the fatty acid chain lengths and decreases with increasing degree of unsaturation, which also increases the relative susceptibility to oxidation. Triglycerides are classified as short (5 carbons), medium (6–12 carbons), or long chain (12 carbons) and may be synthetically hydrogenated to decrease the degree of unsaturation, thereby conferring resistance to oxidative degradation. Separation of natural product oils into their component glyceride fractions is used to prepare excipients that maximize desirable physical and drug absorption-promoting properties\textsuperscript{16-17} while minimizing such issues as susceptibility to oxidation.

Semi-synthetic lipid excipients

Several semi-synthetic liquid and thermo-softening (semisolid) excipients, most commonly prepared by chemically combining medium-chain saturated fatty acids or glycerides derived from natural product plant oils, with one or more hydrophilic chemical entities are currently available as pharmaceutical excipients for oral formulation development\textsuperscript{12,14}. These excipients find application as drug-solubilizing vehicles, surfactants and wetting agents and as emulsifiers and co-emulsifiers in SEDDS and self-micro emulsifying drug delivery systems (SMEDDS). They are generally well-suited for filling into both soft and hard gelatin or into HPMC capsules. Thermo-softening excipients, which melt in the range of 26–70 °C and exist as waxy semi-solids at ambient room temperatures, are typically filled into capsules in the molten state.

Synthetic Excipients

A number of fully-synthetic, monomeric and polymeric liquid and semi-solid excipients, most of which are glycolic in nature and relatively non-toxic, are used as solvents for formulating poorly water-soluble drugs. These excipients can be used alone or in combination with other lipid excipients to improve the overall solubilizing power of the formulation. However, their pronounced water miscibility can compromise formulation performance due to uncontrolled precipitation of the drug substance following dilution in the aqueous contents of the GIT. This typically results in dose-dependent bioavailability enhancement. A few examples of the most commonly applied excipients in this class and their applications follows. Among the polymeric glycol-based excipients finding pharmaceutical application, the polyethylene glycols (PEGs) are a versatile, well-characterized and widely applied class of solubilizers which are available as both liquids and thermo-softening semi-solids. The physical state of these excipients at ambient room temperature is determined by their molecular weights\textsuperscript{15}. PEGs ranging from 200 to 600 in molecular weight are liquid at ambient room temperature whereas those possessing molecular weights of 1000 or greater exist as thermo-softening semi-solids. In comparison to natural product oils, PEGs have the following disadvantages: they tend to be more chemically reactive; they can be more irritating to the GI mucosa than oils. PEGs are also known to contain varying levels of peroxide impurities and secondary products formed by auto-oxidation, which can contribute to chemical instability of the incorporated drug substance. These excipients are widely used in soft gelatin capsule formulations but find limited use in conjunction with hard gelatin capsules due to their hygroscopicity and resultant
effects on gelatin moisture content, which can compromise capsule physical integrity. Propylene glycol, a pharmaceutically-acceptable, monomeric solvent possessing humectant and plasticizing properties, finds application for soft gelatin capsule formulations of poorly water-soluble drugs. The polyoxymers, which are co-polymers of polyoxyethylene and polyoxypropylene, possess both solvent and surfactant properties and thus find application in the oral delivery of poorly water-soluble drugs. As with the PEGs, they are available in a range of molecular weights which control the physical state of the excipient at room temperature. In addition to improving the bioavailability of poorly water-soluble drugs, they have found application in modified release formulations.

**Surfactants**

Various non-ionic surfactants such as the polysorbates (e.g., Tween® 80) and poloxyls (e.g., Cremophor® EL), which cover the HLB range from 2 to 18, may be used in combination with lipid excipients to promote self-emulsification or microemulsification. The acceptable quantities for use of these surfactants are limited primarily by their tendency, at high concentrations, to cause brittleness of hard and soft gelatin capsules due to their dehydrating effects on capsule gelatin and the amount of water-miscible surfactant necessary to promote the self-emulsification of these formulations can occasionally be problematic in that it results in drug precipitation upon dilution in vivo.

**Co-solvents**

The production of an optimum SEDDS requires more than 30% w/w of surfactants. Organic solvents such as, ethanol, propylene glycol, and polyethylene glycol, glycerin are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. These solvents can even act as co-surfactants in micro emulsion systems. On the other hand, alcohols and other volatile co-solvents have the disadvantage of evaporating into the shells of the soft gelatin, or hard, sealed gelatine capsules in conventional SEDDS leading to drug precipitation.

**Stability of Excipients**

Oxidative instability is a concern mainly associated with lipids that consist of unsaturated fatty acids and or which possess sensitive bonds (PEG for example). Oxidative risks increase significantly with exposure to external factors such as heat, aeration, humidity, and light. Such risks can be controlled by preventive measures like addition of anti-oxidants, working under vacuum and or nitrogen blanketing to protect the sensitive bonds. Chelating agents (e.g. EDTA) may be useful in removing metallic oxidation catalysts. Simple routine testing for Acid Value, peroxide level, and water content can help assess oxidative changes after critical steps in processing and after formulation. Since lipid-based excipients are generally multi-component systems, there is potential for stratification of their molecular components during storage and or transport. To obtain a sample that is representative of the batch, it is therefore important to ensure homogeneity by: i) melting the entire content in the case of semi-solid excipients and ii) stirring the contents gently. Each time a portion is withdrawn, nitrogen flushing of the created headspace is necessary before rescaling the container. In short, adequate handling and processing conditions and preventive measures for oxidative risk control are essential to the success of lipid-based formulations. Lipid oxidation can be controlled by limiting (when possible) the use of unsaturated lipids, by inclusion of appropriate antioxidants.

**Safety of Excipients**

Surfactant, cosurfactants and oil are employed for the design of self-emulsifying systems, the most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). 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. The marketed HIV protease inhibitors products, such as Agenerase, Kaletra and Norvir, contain a considerable mass of surfactants in each capsule, and several capsules are administered 2–4 times daily, so that patients are ingesting 2–3 g Cremophor or TPGS daily.

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Table 1: Details of Each Excipient to be used in the Investigation

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Class</th>
<th>chemical description</th>
<th>HLB value</th>
<th>Physical form</th>
<th>Regulatory status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labrasol</td>
<td>Surfactant</td>
<td>Caprylocaproyl macrogolglycerides</td>
<td>14</td>
<td>Liquid</td>
<td>USP-NF/EP/IIG</td>
</tr>
<tr>
<td>Gelucire50/13</td>
<td>surfactant</td>
<td>Stearyl macrogolglycerides</td>
<td>13</td>
<td>Semisolid (M.P. 50°C)</td>
<td>USP-NF/EP/IIG</td>
</tr>
<tr>
<td>Vitamin E TGPS</td>
<td>surfactant</td>
<td>D-alpha tocopherol polyethylene glycol 1000 succinate</td>
<td>13.2</td>
<td>Yellowish powder 47°C</td>
<td>USP-NF, Included in the FDA Inactive Ingredients</td>
</tr>
<tr>
<td>Solutol</td>
<td>Surfactant</td>
<td>Macrogol 15 Hydroxystearate</td>
<td>14-16</td>
<td>yellowish-white, waxy mass</td>
<td>BP, PhEur</td>
</tr>
<tr>
<td>Maisine 35-1</td>
<td>Co-surfactant</td>
<td>Glycerol monolinolete EP</td>
<td>4</td>
<td>Liquid</td>
<td>FCC / GRAS / E471 / JFSA</td>
</tr>
<tr>
<td>Lauroglycol 90</td>
<td>Co-surfactant</td>
<td>Propylene glycol monolaurate (type I) EP</td>
<td>5</td>
<td>Liquid</td>
<td>USP-NF/EP</td>
</tr>
<tr>
<td>labrafil M2125CS</td>
<td>Co-surfactant</td>
<td>Linoleoyl macrogol-6 glycerides EP /</td>
<td>4</td>
<td>Liquid</td>
<td>USP-NF/EP</td>
</tr>
<tr>
<td>Capryol™ 90</td>
<td>Co-surfactant</td>
<td>Propylene glycol monocaprylate</td>
<td>6</td>
<td>Liquid</td>
<td>USP-NF/EP/USFA E477/JFSA</td>
</tr>
<tr>
<td>Labrafac™ PG</td>
<td>Oil vehicle</td>
<td>Propylene glycol dicaproylcaprate</td>
<td>2</td>
<td>Liquid</td>
<td>USP-NF/EP/USFA E477/JFSA</td>
</tr>
<tr>
<td>Hydrogenated vegetable</td>
<td>Oil vehicle</td>
<td>----------------------------</td>
<td>61 -66°C</td>
<td>Liquid</td>
<td>BP, USP-NF, Included in the FDA Inactive Ingredients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>


The following(s) should be considered in the formulation of a SEDDS:

1. The solubility of the drug in different oil, surfactants and surfactant/co-solvents.
2. The selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram.
3. The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and surfactant/co-solvents.
4. The addition of a drug to a SEDDS is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil–surfactant ratio. So, the design of an optimal SEDDS requires preformulation-solubility and phase- diagram studies.

Drugs with low aqueous solubility present a major challenge during formulation as their high hydrophobicity prevents them from being dissolved in most approved solvents. The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The addition of solvents including ethanol, Propylene Glycol and Polyethylene glycol, also contribute to the improvement of drug solubility in the lipid vehicle. Examples of various drugs formulated using SEDDS and SMEDDS designed for oral delivery of lipophilic drugs are given in Table 2.

Table 2: Examples of SEDDS and SMEDDS designed for the oral delivery of lipophilic drugs

<table>
<thead>
<tr>
<th>Drug compound</th>
<th>Delivery system</th>
<th>Oil</th>
<th>Surfactant</th>
<th>solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontazolast [23]</td>
<td>SEDDS</td>
<td>A mixture of mono- and diglycerides of oleic acid</td>
<td>Solid, polyglycolyzed mono-, di- and triglycerides (HLB = 14), Tween 80 (HLB = 15)</td>
<td>--------</td>
</tr>
<tr>
<td>Progesterone[24]</td>
<td>SEDDS</td>
<td>Ethyl oleate</td>
<td>TWEEN 80</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Ritonavir*</td>
<td>SEDDS</td>
<td>Oleic acid</td>
<td>----------------------------------</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Saquingvir*</td>
<td>SEDDS</td>
<td>dl-alpha tocopherol</td>
<td>----------------------------------</td>
<td>Ethanol</td>
</tr>
<tr>
<td>CoQ10[53]</td>
<td>SEDDS</td>
<td>Myvacet 9:45 or</td>
<td>Labrasol (HLB = 14) or</td>
<td>--------</td>
</tr>
</tbody>
</table>
TECHNIQUES IN THE DEVELOPMENT OF SOLIDSELF EMULSIFIED DRUG DELIVERY SYSTEM

SEDDS can exist in either liquid or solid states. SEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SEDDS. From the perspective of dosage forms, S-SEDDS mean solid dosage forms with self-emulsification properties.

Capsule filling with liquid and semisolid self-emulsifying

Formulations Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process:

(i) Heating of the semisolid excipient to at least 20°C above its melting point;
(ii) Incorporation of the active substances (with stirring); (iii) Capsule filling with the molten mixture and (iv) Cooling to room temperature.

For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by microspray sealing. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. The liquid/semisolid lipophilic vehicles compatible with hard capsules were listed by Cole et al. The advantages of capsule filling are simplicity of manufacturing: suitability for low-dose highly potent drugs and high drug loading (up to 50% (w/w) potential.

Spray drying

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilisation 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.

Adsorption to solid carriers

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. Solid carriers can be micro porous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and crosslinked poly methyl methacrylate.

Melt granulation

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a ‘one-step’ operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied asmelttable binders. There into, Gelucire, a family of vehicles derived from the mixtures of mono-/di-/tri-glycerides and polyethylene glycols (PEG) esters of fatty acids, is able to further increase the dissolution rate compared with PEG usually used before, probably

owing to its SE property\textsuperscript{32}. Other lipid-based excipients evaluated for melt granulation to create solid SES include lecithin, partial glycerides, or polysorbates. The melt granulation process was usually used for adsorbing SES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium aluminometasilicate)\textsuperscript{32,33}.

**Melt Extrusion/Extrusion Spheronization**

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions\textsuperscript{34}. The size of the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion–spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids (pellets).

The extrusion–spheronization process requires the following steps: dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating (optional). In the wet masses comprising SES (polysorbate 80 and mono-di-glycerides), lactose, water and MCC, the relative quantities of SES and water had a significant effect on the extrusion force, size spread, disintegration time, and surface roughness of pellets. Studies suggested that the maximum quantity of this SES that can be solidified by extrusion spheronization occupies 42% of the dry pellet weight\textsuperscript{35}. Generally, the higher the water level, the longer the disintegration time\textsuperscript{36}. The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SES containing wet mass with a wide range of rheological characteristics can be processed, but a single rheological parameter cannot be used to provide complete characterization of how well it can be processed by extrusion–spheronization\textsuperscript{37}.

**CHARACTERIZATION OF SELF EMULSIFIED DRUG DELIVERY SYSTEMS**

**Chemical analysis**

The exact composition of lipid-based excipients in terms of esters, ethers and fatty acid distribution can be assayed by established HPLC and GC methods. Also, quick tests for excipient characterization are available as chemical indices like: Saponification Value relating to the molecular weight of the fatty acid chains; Iodine Value as a measure of the saturation of hydrocarbon chains; Hydroxyl Value to determine the quantity of free hydroxyl groups from free glycerol, mono- and di-glycerides combined; Peroxide Value to quantify and monitor oxidative changes; and Acid Value for measuring the quantity of free (un-esterified) fatty acids. Regular testing for Peroxide Value and Acid value can help assess oxidative stability and potential for hydrolysis of the sensitive bonds in storage or during processing. Analysis for moisture content may also be considered especially for hygroscopic/high HLB excipients.

**Physical analysis**

Since lipid based excipients are often processed near or above their melting points, analysis of their thermal behaviour at varying stages of formulation is of prime importance. Lipids possess complex chemical compositions that lead to broad melting ranges as opposed to a single melting point.

**Differential Scanning Calorimetry (DSC)**

DSC permits study of the thermal behaviour of excipients: melting, crystallization, solid-to-solid transition temperatures and determination of the solid fat content of the excipient versus temperature (which can also be assessed by Nuclear Magnetic Resonance, NMR). DSC allows also repeating heating/cooling cycles close to the thermal treatment the excipients are exposed to during processing. In addition, microscopic methods such as hot-stage microscopy (HSM) can be used to assess the organization of the lipid excipients during heating or cooling. Nearly all lipid excipients exist under various polymorphs. For glycerides the main crystalline structures determined by X-Ray Diffraction (XRD) are hexagonal (α), orthorhombic (β\textsuperscript{′}) and triclinic (β). These structures differ by their thermal properties (transition and melting temperature for example), and depend on the thermal history of the excipient. As a rule, polymorphic changes have little or no effect on the functionality of self-emulsifying systems that are readily dispersible in aqueous or physiological media. If on the other hand the formulation matrix is slow or incapable of erosion in the dissolution media, polymorphism can significantly affect the drug release properties\textsuperscript{38,42}. However, changes in lipid crystallinity can be controlled by adapted means: tempering at a temperature close to the melting point of the excipient, controlling the crystallization rate, adding some crystallization seeds to promote the crystallization of one chosen polymorph; or even by adding other excipients such as cellulose ethers, poloxamers or polysorbates to the lipid excipients\textsuperscript{43,44}. \textsuperscript{32,33}
Dissolution in bio-relevant media and dispersion testing

The conventional USP dissolution testing is required by the FDA as a quality control tool and is rarely an indication of the in vivo dissolution behaviour of lipid-based formulations. Lipids and lipid-based excipients are subject to digestive processes occurring in the gastrointestinal tract. Gastric and pancreatic lipases can lipolyze glycerides, as well as other esters of fatty acids and alcohols such as polyethylene glycol esters contained in polyoxylglycerides. Lipases may also impact the emulsification/dispersion properties of fatty acid esters, hence altering their solubilization capacity in vivo. Thus digestibility of the excipients should be taken into account during the development of lipid-based formulations.

Dissolution testing in biorelevant media can help the formulator to assess such effects and to predict the in vivo behaviour of lipid-based formulations. Dispersion testing, i.e. emulsification capacity and analysis of particle size distribution is often used to assess the effectiveness of self-emulsifying formulations. Emulsification capacity is generally evaluated visually and particle size distribution can be measured either by optical microscopy, laser light diffraction or Photon Correlation Spectroscopy (PCS) depending on the fineness of the dispersion.

CONCLUSION

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. Their efficacy is case specific, thus their proper characterization, composition of the SEDDS formulation should be determined very carefully. Since a relatively high concentration of surfactants is generally employed in the SEDDS formulation, toxicity of the surfactant being used should be taken into account. Effective in-vitro tests should be utilized which can predict in-vivo performance of this type of formulations. Formulation of SEDDS as solid dosage forms such as free flowing granules, pellets is compelling and desirable. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

ACKNOWLEDGEMENT

The author would like to acknowledge the Library facilities provided by King Saud bin Abdulaziz University for Health Sciences, Riyadh, Kingdom of Saudi Arabia, for collection of literature.

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