Self-Emulsifying Drug Delivery Systems: Strategy for Improving Oral Delivery of Poorly Soluble Drugs

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Abstract: Drugs are most often administered by the oral route. However, more than 40% of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Recently, much attention has been focused on self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly aqueous soluble drugs. SEDDS are isotropic mixtures of oil, surfactants, solvents and co-solvents/surfactants. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation following dilution by an aqueous phase. For lipophilic drugs, which display dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption.

This article gives an overview of the new excipients used in SEDDS and biopharmaceutical aspects of SEDDS. The application of SEDDS and closely related lipid-based systems as drug delivery vehicles is also introduced, with particular emphasis being placed on the application of SEDDS in traditional Chinese medicine (TCM).

Key Words: Self-emulsifying, self-microemulsifying, lipid-based systems, poorly soluble drugs, oral delivery, bioavailability.

1. INTRODUCTION

Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality [1]. To overcome these problems, various formulation strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronisation, salt formation, cyclodextrins, nanoparticles and solid dispersions [1, 2]. Recently, much attention has been paid to lipid-based formulations with particular emphasis on self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of lipophilic drugs [3, 4]. SEDDS or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/surfactants [5-9]. Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsions (SMEDDS). Fine oil droplets would pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substances and the gut wall. When compared with emulsions, which are sensitive and metastable dispersed forms, S(M)EDDS are physically stable formulations that are easy to manufacture. An additional advantage of SEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. Thus, for lipophilic drugs with dissolution-limited oral absorption, these systems may offer an improvement in the rate and extent of absorption and more reproducible plasma concentration profiles [9].

Several useful reviews of lipid-based systems as drug delivery vehicles have been published in recent years. Strategies for the formulation of self-emulsifying systems and the efforts made to understand their mechanisms of action have been reviewed by Pouton, Gursoy, Gershanik and Constantinides [4-6, 10]. The *in vitro* assessment of oral lipid-based formulations has been reviewed by Porter [11] while Humberstone, MacGregor and O'Driscoll have reviewed the biopharmaceutical aspects [3, 12, 13]. This article gives an overview of the new excipients used in SEDDS and biopharmaceutical aspects of SEDDS. The application of SEDDS and closely related lipid-based systems as drug delivery vehicles is also introduced, with particular emphasis being placed on the application of SEDDS to traditional Chinese medicine (TCM).

2. EXCIPIENTS USED IN SEDDS

We acknowledge that reviews have been presented earlier on excipients used in SEDDS [3-6], however there are some critical studies conducted since those reviews were prepared. Emphasis is placed on the new excipeints.

Polyglycolyzed glycerides (PGG) with varying fatty acid and polyethylene glycol (PEG) chain lengths giving them a varied hydrophile-lipophile balance (HLB) value, in combination with vegetable oils have been used to solubilise poorly water-soluble drugs and improve their bioavailability [7]. According to the manufacturer, these products are derived from selected, high purity, food-grade vegetable oils which are reacted with pharmaceutical grade PEG and therefore expected to be well tolerated by the body [10]. Recently, the emulsification and solubilisation properties of polyglycolyzed glyceride-based oils, Labrafils (Table **1**), in self-emulsifying formulations have been investigated using Tween 80 and Tween 20 as surfactants [14]. Danazol (a

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Table 1. Physicochemical Properties and Main Fatty Acid Composition of Labrifil Oils (Compiled from Gattefossé Specification Sheets) [14]

Oil (MW)	Main fatty acid (%)	PEG group	HLB	Water solubility at 20℃	Viscosity at 20℃ (m.Pa.s)
Labrasol (430)	Caprylic (C8) 50-80% Capric (C10) 20-50%	PEG 400	14	Soluble	80-110
Labrafac CM 10 (440)	Caprylic (C8) 50% Capric (C10) 50%	PEG 200	10	Dispersible	0-90
Labrafil WL 2609 BS (850)	Oleic (C18:1) 24-34% Linoleic (C18:2) 53-63%	PEG 400	6	Dispersible	80-120
Labrafil M 1944 CS (530)	Oleic (C18:1) 58-68% Linoleic (C18:2) 22-32%	PEG 8	4	Dispersible	75-95
Labrafil M 2125 CS (682)	Oleic (C18:1) 24-34% Linoleic (C18:2) 53-63%	PEG 6	4	Dispersible	70-90
Labrafac Lipophile WL 1349 (504)	Caprylic (C8) 50-80% Capric (C10) 20-50%	—	1	Insoluble	25-35

poorly water-soluble compound with an estimated aqueous solubility of <1 μg/mL and log *P* = 4.2) and mefenamic acid (a non-steroidal anti-inflammatory drug with an aqueous solubility of 40 μg/mL and log *P* = 5.3) were selected as the model drugs. The more hydrophilic oil-surfactant mixtures showed greater emulsification ability and a smaller particle size. A linear relationship was observed between the hydrophile-lipophile balance (HLB) of the mix and the solubility of both danazol and mefenamic acid, with more hydrophilic mixtures producing greater drug solubility (Fig. **1**) [14]. These results should serve as a useful guide to the proper selection of PGG for SEDDS.

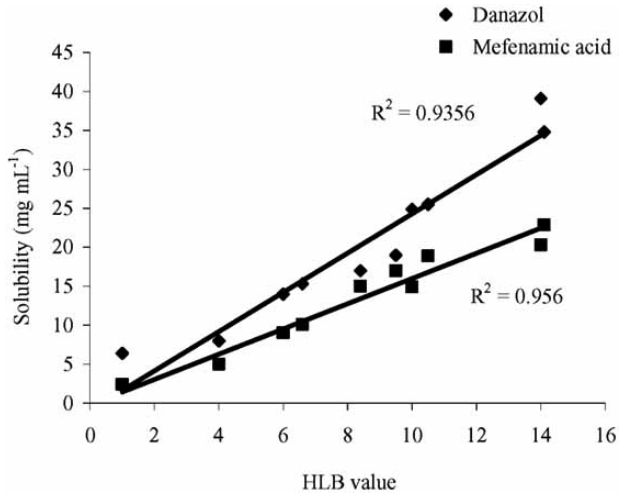

Fig. (1). Relationship between the solubility of mefenamic acid and danazol in Labrafils and Labrafil/surfactant mixes and HLB value of the solvent. Danazol (▲) and mefenamic acid (■) [14].

Galactolipids, which are polar lipids commonly found in the chloroplast membranes of green plants, and a natural part of the human diet, are the main surfactants in formulations of cyclosporine [15]. Similar to phospholipids, galactolipids have good emulsifying properties, but one major difference is that phospholipids are charged, while galactolipids are non-ionic and regarded as being safe for long-term use [15]. However, surfactants of natural origin usually have a limited self-emulsification capacity. The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80) [5]. Excipients in the formulation are usually selected from the Generally Recognized As Safe (GRAS) list of ingredients as published by the FDA. If compounds are not listed in GRAS, their potential toxicity is of the utmost importance.

A convenient and reliable model for evaluating cytotoxicity is the use of a human epithelial Caco-2 cell line. Palamakula *et al*. have developed a suitable method for evaluating the cytotoxicity of oils used in SEDDS using Coenzyme Q10 (Co Q10) as a model compound [16]. Three methods of sample preparation were tested, namely suspensions, homogenization, and oil nanoemulsions. The cytotoxicity of oils was found to be dependent on the method of sample preparation, nanoemulsions being the least cytotoxic. All evaluation methods showed that Myvacet 9-45, peanut oil and soybean oil were non-cytotoxic in emulsion form. Therefore, these oils are more suitable for SEDDS. Of the above three methods of sample preparations tested, homogenization and nanoemulsification provided a suitable tool to evaluate the cytotoxicity and permeability of many different compounds. Corn oil, Captex-200 and Captex-355 were found to be cytotoxic when used as suspensions or dispersions. However, all these oils were found to be non-cytotoxic when presented as homogenized or nanoemulsified particles [16]. Gursoy *et al*. developed a novel SEDDS devoid of cremophor for the i.v./oral delivery of paclitaxel and investigated the *in vitro* cytotoxicity of combined excipients including Triton WR-1339 (tyloxapol), sodium deoxycholate (DOC-

Na), and D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). The Caco-2 cell line was used to monitor the cytotoxicity of the excipients. An increase in the sodium deoxycholate excipient content led to an increase in physical stability but caused more chemical degradation of the drug and pronounced cytotoxicity [17].

3. BIOPHARMACEUTICAL ASPECTS

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed and the interested reader is directed to these references for further details [3, 18]. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability *via* a number of potential mechanisms, including [11]:

a) Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution [11].

b) Increases in effective lumenal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilisation capacity [11].

c) Stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly, or indirectly *via* a reduction in first-pass metabolism [19-21].

d) Changes in the biochemical barrier function of the GI tract. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism [22-24].

e) Changes in the physical barrier function of the GI tract. Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability-enhancing properties [25, 26]. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs.

3.1. Enhanced Drug Absorption by Lymphatic Delivery

Charman *et al*. proposed that drug candidates for lymphatic transport should have a log *P* >5 and, in addition, a triglyceride solubility >50 mg/ml. The importance of lipid solubility was illustrated by a comparing the lymphatic transport of DDT (log *P* 6.19) with hexachlorobenzene (HCB, log *P* 6.53). While both compounds have similar log *P* values, the difference in lymphatic transport on administration in oleic acid, 33.5% of the dose in the case of DDT and 2.3% with HCB, was attributed to the 13-fold difference in triglyceride solubility [27]. However, combination of a high log *P* and high triglyceride solubility does not always guarantee significant lymphatic transport. Penclomedine, an experimental cytotoxic agent with a log *P* of 5.48 and a triglyceride solubility of 175 mg/ ml, was poorly transported in the intestinal lymph, ~3% of the dose [28]. Khoo *et al*. showed significant lymphatic transport of the poorly lipid soluble (~1 mg/ml) HCl salt of halofantrine (Hf-HCl), following oral post-prandial administration to dogs. The authors suggest that the high level of lymphatic transport of Hf-HCl (43.7% of dose), which was similar to that of the lipid soluble Hf base, was due to conversion of Hf-HCl in the intestinal lumen, during lipolysis, to the more lipophilic free base, which then becomes associated with chylomicron production [29].

Although enhanced lymphatic transport has been suggested as a potential mechanism of enhanced bioavailability, few studies have investigated the lymphotropic potential of SEDDS. However, one such study by Haus *et al*. investigated the effects of a range of lipid-based formulations on the bioavailability and lymphatic transport of ontazolast, following oral administration to conscious rats. This drug undergoes extensive hepatic first-pass metabolism and it has solubility in soybean oil of 55 mg/ml, and a log *P* of 4. The formulations of ontazolast investigated included a suspension (lipid-free control), a 20% soybean o/w emulsion, two SEDDS containing Gelucire 44/14 and Peceol in the ratios 50:50 and 80:20, respectively, and a solution of the drug in Peceol alone. All the lipid formulations increased the bioavailability of ontazolast relative to the control suspension, while the SEDDS promoted more rapid absorption. Maximum lymphatic transport occurred with the emulsion and the Peceol solution. The emulsion prolonged lymphatic transport and this may be related to the need for preabsorptive lipolysis of the triglyceride vehicle and an associated slower gastric emptying time. The Peceol solution provided the highest rate of lymphatic triglyceride transport thus resulting in greater partitioning of the drug into the lymph. The SEDDS formulations resulted in the highest concentration of ontazolast in the chylomicron triglyceride. The authors suggest that SEDDS, which promote more rapid absorption of ontazolast, could produce higher concentrations of the drug in the enterocytes during absorption and hence improve lymphatic drug transport by a concentration-partitioning phenomenon [30].

3.2. The Effect of Excipients on Efflux Transport

Drug efflux mediated by broad-specificity xenobiotic transporters present in the intestinal epithelium may be an important factor in the poor or variable absorption of orally administered drugs [31]. In the search for less toxic multidrug resistance (MDR) modulators, Lo *et al*. have shown that bile salts, fatty acids, phospholipids, and surfactants were potent absorption enhancers and efflux-reducing agents in Caco-2 cells and the rat intestine [32-34]. Other researchers also investigated the non-ionic surfactants, such as Tween 80, Pluronic P85, and Cremophor EL *in vitro* and *in vivo* in animals and in humans for their potential ability to reverse MDR caused by p-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRP) [35-37]. Recently,

Cremophor, Tween 80, and Solutol HS-15 have been proven to reverse the MDR phenotype in cultured cells at concentrations likely to be achieved clinically [37, 38]. TPGS (d-α-tocopheryl plyethylene glycol 1000 succinate) has been shown to be an effective inhibitor of P-gp mediated drug resistance and has been used to enhance the bioavailability of CsA in liver transplant patients as well as significantly improving absorption and reducing the daily drug cost [39]. Inhibition of MDR-related pumps by various excipients has been proposed to occur due to binding competition, ATP depletion, and membrane perturbation [37, 40]. For example, Tween 80 has been shown to modulate anthracycline and Vinca alkaloid resistance in MDR cells by inhibiting the binding of these drugs to P-gp [37, 40]. The ability of Pluronic copolymer, one poly (ethylene oxide) block copolymer, to antagonize P-gp and sensitize MDR cells appears to be a result of ATP depletion, and inhibition of P-gp and MRP drug efflux proteins [41]. Studies with MDR modifiers such as bile salts indicated that perturbations of the cell membrane structure may influence P-gp-mediated drug transport [33, 42, 43]. These modifiers may influence cytotoxic drug action by producing structural changes to the lipid domains in the plasma membrane. The membrane perturbation caused by pharmaceutical excipients, such as Tween 20, Tween 80, Brij 30, and Myrj 52, may result in a change in the fluidity of Caco-2 cell membranes, and thus inhibit the activity of membrane-spanning proteins, such as P-gp and MRPs which substantially reduce the basolateral to apical efflux of epirubicin across Caco-2 monolayers [44]. Tween 20, Tween 80, Brij 30, and Myrj 52 may also inhibit protein kinase C (PKC) activity, reduce phosphorylation of P-gp, and modulate P-gp mediated drug efflux [45].

Inhibition of the efflux and/or enterocyte-based metabolism will increase the concentration and residence time of the intact drug in the cell. This may result in increased drug available for partitioning into the lymphatics [13].

3.3. Role of Lipolysis

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 or pancreatic lipase [46]. Digestion of formulations will inevitably have a profound effect on the state of dispersion of the lipid formulation, and the fate of the drug [12]. Fortunately, the liberation of free fatty acid during lipolysis can be titrated using NaOH in a pH stat, allowing quantitative data about the kinetics of digestion to be obtained. The location of the drug can be assayed in various fractions after ultracentrifugation of the products of digestion, which allows investigation of the likely fate of the drug after lipolysis [47].

The inclusion of highly lipophilic compounds in SEDDS is often reported to result in strongly enhanced oral absorption although it is still controversial whether further lipolysis of the dispersed lipid material is required for final transfer to the enterocyte membranes. In order to assess the relative roles of lipid vehicle dispersion and vehicle digestibility in the oral absorption of penclomedine (Pcm), a series of formulations of Pcm in medium chain triglyceride (MCT)/ TPGS was developed having three sizes (160 nm, 720 nm, and mm-sized ('crude' oil)); with or without the inclusion of tetrahydrolipstatin (THL), a known lipase-inhibitor. Oral absorption of Pcm was studied after administration of small volumes of these formulations to conscious rats. Formulations with a particle size of 160 nm had the highest relative bioavailability (set at $F = 1$), whereas administration in particle 720 nm in size resulted in a slightly lower bioavailability ($F = 0.79$). Co-inclusion of THL yielded similar bioavailability for these two SEDDS. 'Crude' oil formulations had an $F = 0.62$ (without THL) and 0.25 (with THL). Only in the case of Pcm administered as undispersed MCT was the absorption more dependent on the action of lipase as the bioavailability was inhibited two-fold by the co-incorporation of THL [48].

A single-dose comparative bioavailability study was conducted to evaluate the bioavailability of tocotrienols from two self-emulsifying formulations, one of which produced an emulsion that readily lipolysed under *in vitro* conditions (SES-A), while the other produced a finer dispersion with negligible lipolysis (SES-B) in comparison with that of a non-self-emulsifying formulation in soya oil (NSES-C). The results showed that both SES-A and -B achieved a higher absorption than NSES-C. Both SES-A and -B also achieved a faster onset of absorption. However, SES-A and -B had comparable bioavailability, despite the fact that SES-B was able to form emulsions with a smaller droplet size. Thus, it appears that the droplet size as well as the rate and extent of lipolysis of the emulsion products formed are important for enhancing the bioavailability of tocotrienols from the self-emulsifying systems [49].

3.4. Positively Charged SEDDS

Many physiological studies have proved that the apical potential of absorptive cells, as well as that of all other cells in the body, is negatively charged with respect to the mucosal solution in the lumen [50, 51]. A novel SEDDS, which results in positively charged dispersed oil droplets upon dilution with an aqueous phase, showed an increase in the oral bioavailability of progesterone in young female rats [52]. More recently, it has been shown that the enhanced electrostatic interactions of positively charged droplets with the mucosal surface of the everted rat intestine are mainly responsible for the preferential uptake of the model drug cyclosporine A (CsA) from positively charged droplets [53]. The Caco-2 cell model was used for the investigation of the charge-dependent interactions of the SEDDS with human intestinal epithelial cells. The positively charged emulsions affected the barrier properties of the cell monolayer at high concentrations and reduced the cell viability. However, at the dilution with aqueous phase used in the study (1:2000), the positively charged SEDDS did not produce any detectable cytotoxic effect. The binding of the fluorescent dye $DiIC_{18}(3)$ was much higher from the positively charged SEDDS, compared with the negatively charged formulation, suggesting increased adhesion of the droplets to the cell surface due to electrostatic attraction [54].

4. THE APPLICATION OF SEDDS

4.1. Supersaturable SEDDS (S-SEDDS)

The high surfactant level typically present in SEDDS formulations can lead to GI side-effects and a new class of supersaturable formulations, including supersaturable SEDDS

(S-SEDDS) formulations, have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs [55-57]. The S-SEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Surpersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier [57]. The S-SEDDS formulations contain a reduced level of surfactant and a polymeric precipitation inhibitor to yield and stabilize a drug in a temporarily supersaturated state. Hydroxypropyl methylcellulose (HPMC) and related cellulose polymers are well recognized for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time periods [58-63].

A supersaturable self-emulsifying drug delivery system (S-SEDDS) of paclitaxel was developed employing HPMC as a precipitation inhibitor with a conventional SEDDS formulation. *In vitro* dilution of the S-SEDDS formulation results in formation of a microemulsion, followed by slow crystallization of paclitaxel on standing. This result indicates that the system is supersaturated with respect to crystalline paclitaxel, and the supersaturated state is prolonged by HPMC in the formulation. In the absence of HPMC, the SEDDS formulation undergoes rapid precipitation, yielding a low paclitaxel solution concentration. A pharmacokinetic study showed that the paclitaxel S-SEDDS formulation produces approximately a 10-fold higher maximum concentration (C_{max}) and a 5-fold higher oral bioavailability ($F \approx$ 9.5%) compared with that of the orally administered Taxol formulation ($F \approx 2.0\%$) and the SEDDS formulation without HPMC ($F \approx 1\%$) [56].

A poorly soluble drug, PNU-91325, was formulated as a supersaturable SEDDS. The comparative *in vitro* studies indicated that the presence of a small amount HPMC in the formulation was critical to achieve a stabilized supersaturated state of PNU-91325 upon mixing with water. A S-SEDDS formulation composed of 30% w/w Cremophor (surfactant), 9% PEG 400, 5% DMA, 18% Pluronic L44, 20% HPMC, and other minor components had an oral bioavailability of ~ 76%, comparable with that of a neat Tween formulation (bioavailability: ~ 68%). Note that the weight ratio of drug to cremophor EL is 1:7.5 in the S-SEDDS formulation while the weight ratio of drug to Tween is 1:39 in the neat Tween formulation. Applying the supersaturable SEDDS approach, a reduced amount of surfactant is deliberately used with HPMC in order to produce a temporarily supersaturated state with reduced solubilisation. This is to obtain a high free drug concentration through generating and maintaining a supersaturated state *in vivo* and to increase the driving force for absorption [57].

It is worth emphasizing that the significantly reduced amount of surfactant used in the S-SEDDS formulation approach provides a better toxicity/safety profile than the conventional SEDDS formulations. However, the underlying mechanism of the inhibited crystal growth and stabilized supersaturation by means of these polymers is poorly understood even although several studies have been carried out to investigate this [56, 64-66].

4.2. Solid SEDDS

SEDDS are normally prepared as liquid dosage forms that can be administrated in soft gelatine capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SEDDS has been prepared by the process of extrusion/spheronization to provide a good *in vitro* drug release (100% within 30 min, $T_{50\%}$ at 13 min). The same dose of progesterone (16 mg) in pellets and in the SEDDS liquid formulation resulted in similar AUC, C_{max} and T_{max} values [67]. A method of producing self-emulsifying pellets by wet granulation of a powder mixture composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and di-glycerides, polisorbate 80 and water has been investigated. The pellets produced with oil to surfactant ratio of 1:4 (w/w) showed improved performance in permeation experiments [68]. Attama *et al*. used goat fat and Tween 65 admixtures to formulate self-emulsifying tablets containing diclofenac by pour-moulding using a plastic mould. The tablets showed good release profiles, as well as acceptable tablet properties. Under mild agitation, such as occurs under gastrointestinal conditions, the release rates are comparable with those of conventional tablets [69]. Encapsulating the emulsion lipid droplets in HPMC by spray-drying has been demonstrated to produce an improved bioavailability following release of the lipid droplets from the powder *in vivo*. Tue *et al*. [70] have investigated the oral bioavailability of a directly compressible dry emulsion as a tablet and compared it with an HPMC dry emulsion powder and a simple lipid solution. Four female Beagle dogs received a single dose of each formulation containing the same amount of MCT and model drug, Lu 28-179. Cyclodextrin solutions administered orally and intravenously were used as references. The absolute bioavailability decreased in the order: cyclodextrin solution (0.14) > HPMC dry emulsion (0.11) > technically improved dry emulsion (0.10) > MCT solution (0.06). The directly compressible dry emulsion tablets were concluded to be comparable with the HPMC dry emulsion powder in terms of bioavailability [70].

4.3. SEDDS for TCM

Silybin, the principal component of a *Carduus marianus* extract, is known to be very effective in protecting liver cells from harmful effects caused by smoking, drinking, overworking, environmental contaminants, stress or liver-damaging drugs. However, the bioavailability of orally administered silybin is very low due to its low solubility in water. Woo *et al*. discloses an oral microemulsion consisting of a *Carduus marianus* extract containing a major amount of silybin, or a silybin derivative as an active ingredient. The composition of the invention consists of Miglyol 812 and ethyl linoleate as oils, HCO 50 and Tween 20 as surfactant, dimethyl isosorbide as co-surfactant and D-α-tocopherol as an anti-oxidant. The formulation provides a greatly increased level of *in vivo* bioavailability of silybin, the level being at least 4-fold higher than that achievable by conventional formulations (Fig. (**2**)) [71].

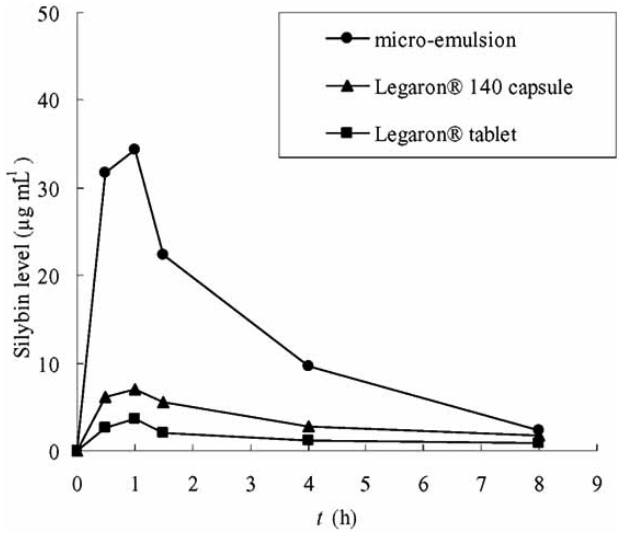

Fig. (2). Silybin plasma concentration-time curves of either microemulsion of *Carduus marianus* extract, Legaron® capsule or Legaron® tablet after oral administration of a single dose of 60 mg silybin/kg to rats. Microemulsion (●), Legaron® 140 capsule (▲) and Legaron® tablet (■) (n = 6) [71].

Curcuma zedoaria (Berg.) Rose. (Zingiberaceae), also called 'er-zhu' in Chinese, has long been used as a folk medicine. The essential oil, zedoary turmeric oil (ZTO), was extracted from the dry rhizome of *C. zedoaria*. A series of studies on ZTO indicated that it exhibits potent pharmacological actions including the suppression of tumors, antibacterial and antithrombotic activity, increased white blood cell count, and increased gastric motility [72]. To increase the *in vivo* absorption of zedoary turmeric oil (ZTO) and develop new formulations of a water-insoluble oily drug, Li formulated SEDDS using ZTO as the oil [73]. Recently, novel ZTO microspheres with self-emulsifying ability, called self-emulsifying microspheres, have been prepared in a liquid system by the quasi-emulsion solvent diffusion method. The microspheres containing hydroxypropyl methylcellulose acetate succinate (HPMCAS-LG), Talc and Aerosil 200 formed a stable surfactant-free emulsion when exposed to pH 6.8 phosphate buffer, and were significantly different from the conventional self-emulsifying systems. The release rates of ZTO and Germacrone from the microspheres were enhanced significantly with increasing amounts of dispersing agents, and the efficiency of self-emulsification closely related to the HPMCAS-LG/Aerosil 200 ratio. The emulsion droplets released from the microspheres were much smaller than those of the conventional SES. The microsphere bioavailability (F) compared with that of conventional SES for oral administration was 157.7% in rabbits. The method greatly improved the bioavailability of the water-insoluble oily drug from the self-emulsifying microspheres compared with the conventional SES and it is useful for producing solid preparations of the oily drug [72].

Pueraria lobata is a traditional Chinese medicinal herb. In China, its extract has been used for the treatment of hypertension, senile ischemic cerebrovascular disease and angina pectoris. Studies of its pharmacology and clinical applications have shown that the active constituents in the extract are isoflavones, mainly puerarin. It is known to dilate coronary arteries, reduce myocardial oxygen consumption and improve microcirculation in both animals and humans suffering from cardiovascular disease [74]. Yufengningxin tablets are a formulation of total isoflavones obtained from Pueraria lobata, and are available commercially in China. The dissolution rate of Yufengningxin tablets is very low and, therefore, a SMEDDS formulation of Pueraria lobata isoflavone was developed to improve the oral bioavailability. An optimized formulation consisted ethyl oleate, Tween 80 and transcutol P as cosurfactant. The dissolution of SMEDDS after 10 min was more than 90%, and the dissolution of Yufengningxin tablets at 60 min was less than 30% (Fig. (**3**)). The absorption of puerarin from the SMEDDS of Pueraria lobata isoflavone resulted in a 2.2-fold increase in bioavailability compared with Yufengningxin tablets (Fig. (**4**)) [75].

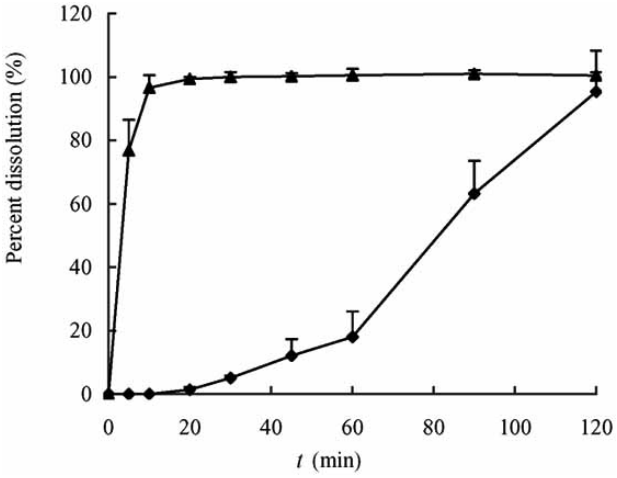

Fig. (3). Dissolution profiles of puerarin from SMEDDS (●) and Yufengningxin tablet formulartion (○) in water at 37°C (n = 6) [75].

Ginkgo biloba L., the last surviving member of a family of trees (Ginkgoaceae) that appeared more than 250 million years ago, has been mentioned in the Chinese Materia Medica for more than 2500 years. A standardized *Ginkgo biloba* extract (GBE) contains 5-7% terpene lactones (ginkgolides and bilobalide) and 22-27% ginkgo flavonol glycosides (eg., the flavones quercetin, kaempferol, and isorhamnetin) [76]. Many pharmacological and clinical studies have demonstrated that the extracts of Ginkgo biloba possess antioxidant, anti-ischemic, neuro-protective, cardiovascular and cerebrovascular activities, and have beneficial effects on cognitive deficits, including Alzheimer's-type and multi-infarct dementia, as well as peripheral vascular disease [77]. The dissolution and bioavailability of the active components from the oral solid preparations of different Ginkgo biloba brands were obviously different and irreproducible, due to the lower solubility of the active components [78]. The SEDDS formulation of GBE was accordingly developed to increase the dissolution rate and thus improve oral absorption and acquire the reproducible blood-time profiles of the active components of GBE. The prepared SEDDS was compared with the conventional GBE tablets following admini-

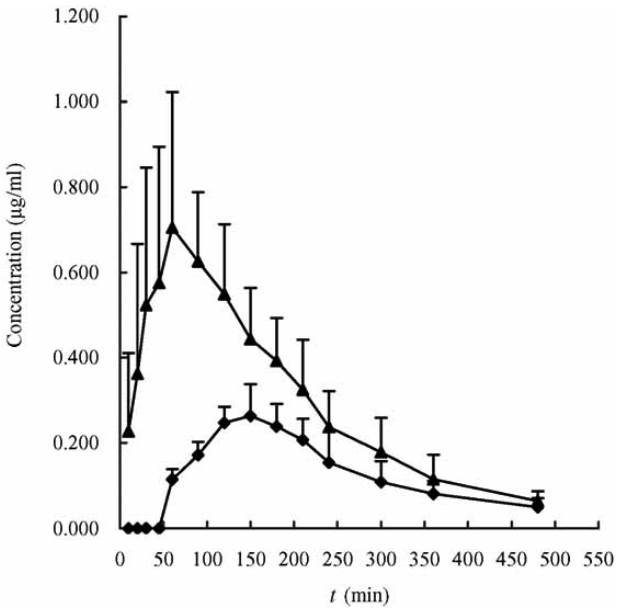

Fig. (4). Puerarin serum concentration-time profiles after oral administration of either SMEDDS (66 mg) or Yufengningxin tablets (65 mg) to dogs. SMEDDS (●) and Yufengningxin tablets (○). Each value is the mean ± SE (n = 6) [75].

stration to fasted dogs. The active components of GBE, terpene lactones, were determined using liquid chromatography with electrospray ionization mass spectrometric detection [79]. The relative bioavailability of SEDDS for ginkgolide A was 154%, compared with the reference tablets (Fig. **5**, unpublished results).

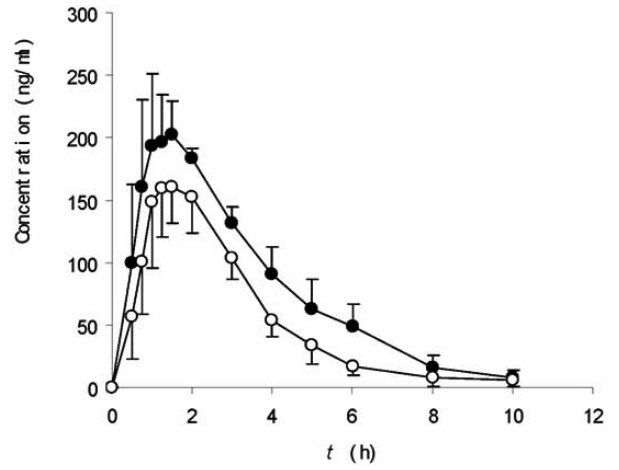

Fig. (5). Ginkgolide A plasma concentration-time profiles of either self-emulsifying soft capsules or tablets following oral administration of a single dose of 800 mg GBE to dogs. GBE self-emulsifying soft capsules (●) and tablets (○). Each value is the mean ± SE (n = 6).

5. FUTURE PROSPECTS

More than 40% of new drugs exhibit poor aqueous solubility and SEDDS are a promising approach for the formulation of these drugs. The development of SEDDS, however, is still largely empirical, and *in vitro* models that are predictive of oral bioavailability enhancement are lacking [11]. There is a need for *in vitro* methods for predicting the dynamic changes involving the drug in the gut in order to monitor the solubilisation state of the drug *in vivo*. Attention also needs to be paid to the interactions between lipid systems and the components of the capsule shells. The characteristics of various lipid formulations also need to be understood, so that guidelines can be established that allow identification of suitable candidate formulations at an early stage. Future research should involve human bioavailability studies, as well as more basic studies on the mechanisms of action of this fascinating and diverse group of formulations [47].

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