ELSEVIER

Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms

Bo Tang, Gang Cheng, Jian-Chun Gu and Cai-Hong Xu

School of Pharmacy, P.O. Box 32, Shenyang Pharmaceutical University, 103 WenHua Road, Shenyang City 110016, Liaoning Province, PR China

Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. 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 gives an overview of the recent advances in the study of S-SEDDS, especially the related solidification techniques and the development of solid SE dosage forms. Finally, the existing problems and the possible future research directions in this field are pointed out.

Introduction

In drug discovery, about 40% of new drug candidates display low solubility in water, which leads to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality. Furthermore, oral delivery of numerous drugs is hindered owing to their high hydrophobicity [1,2]. Therefore, producing suitable formulations is very important to improve the solubility and bioavailability of such drugs.

One of the most popular and commercially viable formulation approaches for solving these problems is self-emulsifying drug delivery systems (SEDDS). SEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and lipophilic drugs [3]. Traditional preparation of SEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents. However, SE formulations are normally prepared as liquids that produce some disadvantages, for example, high production costs, low stability and portability, low drug loading and few choices of dosage forms. Irreversible drugs/excipients precipitation may also be problematic [4]. More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation.

Corresponding authors: Cheng, Tang, B. (tangbobox@126.com), G. (chenggang63@hotmail.com)

To address these problems, S-SEDDS have been investigated, as alternative approaches. Such systems require the solidification of liquid self-emulsifying (SE) ingredients into powders/nanoparticles to create various solid dosage forms (SE tablets [5,6] and SE pellets [7,8], and so on). Thus, S-SEDDS combine the advantages of SEDDS (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance.).

To date, there have been some studies that mainly focus on the preparation and characterization of a single, solid SE dosage form, yet relatively few that introduce S-SEDDS in a systemic way, especially with respect to dosage form development and preparation techniques.

Self-emulsifying drug delivery systems

SEDDS belong to lipid-based formulations. Lipid formulations can be oils, surfactant dispersions, emulsions, SEDDS, solid lipid nanoparticles and liposomes.

SEDDS are isotropic mixtures of drug, oil/lipid, surfactant, and/or cosurfactant, which form fine emulsion/lipid droplets, ranging in size from approximately 100 nm (SEDDS) to less than 50 nm for self-microemulsifying drug delivery systems (SMEDDS), on dilution with physiological fluid. The drug, therefore, remains in solution in the gut, avoiding the dissolution step that frequently

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2008.04.006

limits the absorption rate of hydrophobic drugs from the crystalline state [9].

Excipient selection

The oily/lipid component is generally a fatty acid ester or a medium/long chain saturated, partially unsaturated or unsaturated hydrocarbon, in liquid, semisolid or solid form at room temperature. Examples include mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil, fatty acids, fatty alcohols, and mono-/di-/tri-glycerides [10].

The most widely recommended surfactants are non-ionic surfactants with a relatively high hydrophilic–lipophilic balance (HLB) value. The surfactant concentration ranges between 30% and 60% (w/w) in order to form stable SEDDS [3]. More detailed descriptions are given elsewhere [3,11], which can serve as a useful guide for excipient selection.

Biopharmaceutical issues

It is important to note that lipids (e.g. triglycerides) affect the oral bioavailability of drugs by changing biopharmaceutical properties, such as increasing dissolution rate and solubility in the intestinal fluid, protecting the drug from chemical as well as enzymatic degradation in the oil droplets and the formation of lipoproteins promoting lymphatic transport of highly lipophilic drugs [12]. The absorption profile and the blood/lymph distribution of the drug depend on the chain length of the triglyceride, saturation degree, and volume of the lipid administered. Drugs processed by the intestinal lymph are generally transported to the systemic circulation in association with the lipid core of lipoproteins. In addition to the stimulation of lymphatic transport, administration of lipophilic drugs with lipids may enhance drug absorption into the portal blood compared with non-lipid formulations [13].

Specificity

Self-emulsification depends on the nature of the oil/surfactant pair, surfactant concentration and oil/surfactant ratio, and the temperature at which self-emulsification occurs. Only very specific pharmaceutical excipient combinations lead to efficient self-emulsifying systems (SES). The efficiency of drug incorporation into a SEDDS is dependant upon the particular physicochemical compatibility of the drug/system [3,11]. So, pre-formulation solubility and phase diagram studies are required in order to obtain an optimal formulation design.

Characterization

The very essence of SEDDS is self-emulsification, which is primarily assessed visually. The efficiency of self-emulsification can be estimated by determining the rate of emulsification and droplet size distribution. The charge on the oil droplets of SEDDS is another property that needs to be assessed [3]. Melting properties and polymorphism of lipid or drug in SES may be established by X-ray diffraction and differential scanning calorimetry.

Solid self-emulsifying 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. S-SEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/nanoarticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticle technology, and so on). Such powders/nanoparticles, which refer to SE nanoparticles [14]/dry emulsions/solid dispersions, are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipient.

To some extent, S-SEDDS are combinations of SEDDS and solid dosage forms, so many properties of S-SEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SEDDS and solid dosage forms. For instance, the characterizations of SE pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on.

In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres/nanoparticles and SE suppositories/implants.

Solidification techniques for transforming liquid/semisolid SEDDS to S-SEDDS

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 [15].

In parallel with the advances in capsule technology proceeding, liquid-Oros technology (Alza Corporation) has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SE formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pumps the drug formulation through an orifice in the hard or soft capsule [16,17].

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.* [18]. 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 solubilization of the mixture before spray drying. The solubilized

liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules.

The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.

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 [19].

Solid carriers can be microporous 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 cross-linked polymethyl methacrylate [20]. Cross-linked polymers create a favorable environment to sustain drug dissolution and also assist in slowing down drug reprecipitation [21]. Nanoparticle adsorbents comprise porous silicon dioxide (Sylysia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal [22].

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 as meltable binders. Thereinto, 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 [23]. 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 aluminometa silicate) [24,25].

Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%) [15], 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 [26]. 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 momogenious 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 [27]. Generally, the higher the water level, the longer the disintegration time [28]. 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 [29].

Applying extrusion–spheronization, SE pellets of diazepam and progesterone and bi-layered cohesive SE pellets have been prepared [7,30,31].

Dosage form development of S-SEDDS

Dry emulsions

Dry emulsions are powders from which emulsion spontaneously occurs *in vivo* or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules.

Dry emulsion formulations are typically prepared from oil/water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation [32], freeze-drying [33] or spray drying [34–36]. Myers and Shively obtained solid state glass emulsions in the form of dry 'foam' by rotary evaporation, with heavy mineral oil and sucrose. Such emulsifiable glasses have the advantage of not requiring surfactant [32]. In freeze-drying, a slow cooling rate and the addition of amorphous cryoprotectants have the best stabilizing effects, while heat treatment before thawing decreases the stabilizing effects [33]. The technique of spray drying is more frequently used in preparation of dry emulsions. The O/W emulsion was formulated and then spray-dried to remove the aqueous phase.

The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of a surfactant, a vegetable oil, and a pH-responsive polymer, with lyophilization used [37]. Recently, Cui *et al.* prepared dry emulsions by spreading liquid O/W emulsions on a flat glass, then dried and triturated to powders [38].

Self-emulsifying capsules

After administration of capsules containing conventional liquid SE formulations, microemulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the microemulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation [39]. With the similar purpose, the supersaturatable SEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state *in vivo*. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects [40,41].

Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers, and so on). As an example, a solid PEG matrix can be chosen. The presence of solid PEG neither interfered with the solubility of the drug, nor did it interfere with the process of self-microemulsification upon mixing with water [42,43].

Oral administration of SE capsules has been found to enhance patient compliance compared with the previously used parenteral route. For instance, low molecular weight heparin (LMWH) used for the treatment of venous thrombo-embolism was clinically available only via the parenteral route. So, oral LMWH therapy was investigated by formulating it in hard capsules. LMWH was dispersed in SMEDDS and thereafter the mixture was solidified to powders using three kinds of adsorbents: microporous calcium silicate (Florite™ RE); magnesium aluminum silicate (Neusilin™ US_2) and silicon dioxide (Sylysia™ 320). Eventually these solids were filled into hard capsules [44]. In another study, such adsorbents were also applied to prepare SE tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms [19].

Self-emulsifying sustained/controlled-release tablets

Combinations of lipids and surfactants have presented great potential of preparing SE tablets that have been widely researched. Nazzal and Khan evaluated the effect of some processing parameters (colloidal silicates—X_1, magnesium stearate mixing time—X_2, and compression force—X_3) on hardness and coenzymum Q_{10} (CoQ_{10}) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X_1 = 1.06%, X_2 = 2 min, X_3 = 1670 kg) were achieved by a face-centered cubic design [45].

In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed by Patil *et al*. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release [46].

SE tablets are of great utility in obviating adverse effect, as disclosed by Schwarz in a patent. Inclusion of indomethacin (or other hydrophobic NSAID), for example, into SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. In these studies, the SES was composed of glycerol monolaurate and Tyloxapol™ (a copolymer of alkylphenol and formaldehyde). Polyethylene oxide successfully illustrated its suitability for controlled-release matrices. The resultant SE tablets consistently maintained a higher active ingredient concentration in blood plasma over the same time frame compared with a non-emulsifying tablet [47].

The newest advance in the research field of SE tablet is the SE osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SES. This system has outstanding features such as stable plasma concentrations and controllable drug release rate, allowing a bioavailability of 156.78% relative to commercial carvedilol tablets [48].

Self-emulsifying sustained/controlled-release pellets

Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability [49]. Thus, it is very appealing to combine the advantages of pellets with those of SEDDS by SE pellets.

Serratoni *et al*. prepared SE controlled-release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release. Pellets were prepared by extrusion/spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained mono-diglycerides and Polysorbate 80. As shown in Figure 1, this research demonstrated that combinations of coating and SES could control *in vitro* drug release by providing a range of release rates; and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution [50]. There is another report that SE sustained-release matrix pellets could be successfully formulated with glyceryl palmito-stearate (Gelucire 54/02) and glyceryl behenate (Gelucire 70/02) [51].

Self-emulsifying solid dispersions

Although solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients [52,53]. These excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending before filling [9,54]. SE excipients like Gelucire® 44/14, Gelucire® 50/02, Labrasol®, Transcutol® and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field [52–55].

For example, Gupta *et al*. prepared SE solid dispersion granules using the hot-melt granulation method. Seven drugs, including four carboxylic acid containing drugs, a hydroxyl-containing drug, an amide-containing drug (phenacetin) and a drug with no proton-donating groups (progesterone) were chosen. Gelucire® 50/13 was used as the dispersion carrier, whereas Neusilin US2 was used as the surface adsorbent [25].

Self-emulsifying beads

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, Patil and Paradkar investigated

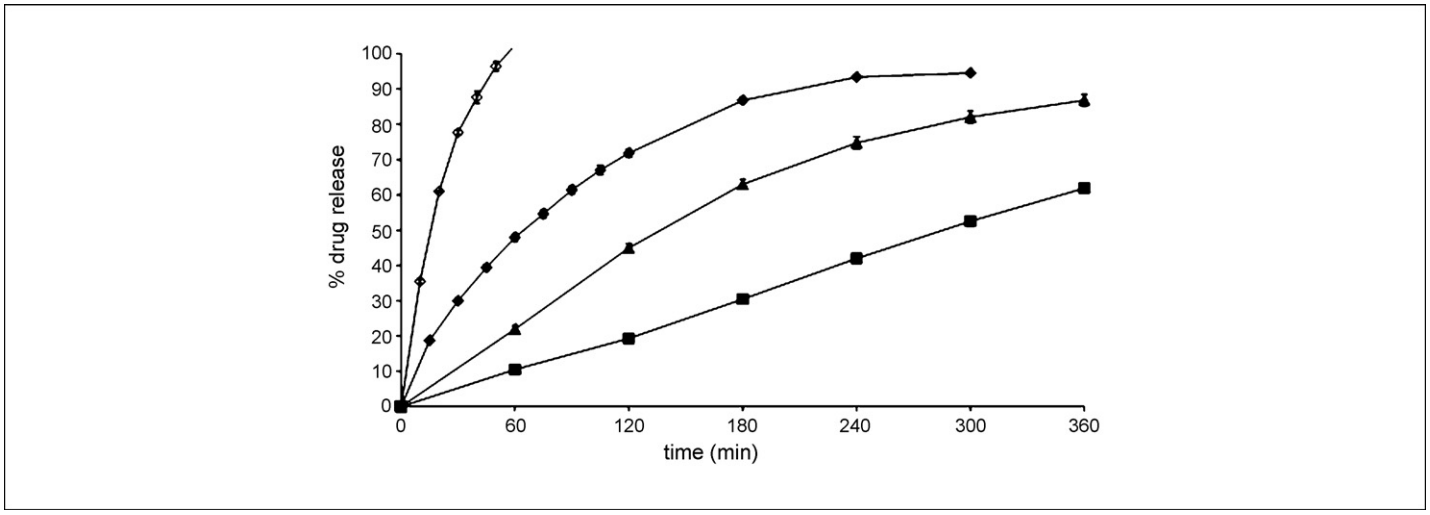

FIGURE 1

Drug release from pellet formulations containing methyl parabens and SES uncoated ◇ and coated 7.5 ◆, 12 ▲ and 20% ■ weight gain of ethyl cellulose.

loading SES into the microchannels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structures are typically produced by copolymerizing styrene and divinyl benzene. They are inert, stable over a wide pH range and to extreme conditions of temperature and humidity. This research concluded that PPB were potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and *in vitro* drug release from SES-loaded PPB [56].

Self-emulsifying sustained-release microspheres

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions including tumor suppressive, antibacterial, and antithrombotic activity. With ZTO as the oil phase, You *et al.* prepared solid SE sustained-release microspheres using the quasi-emulsion–solvent-diffusion method of the spherical crystallization technique. ZTO release behavior could be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration–time profiles (Figure 2) were achieved after oral administration of such microspheres to rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS [57].

Self-emulsifying nanoparticles

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and

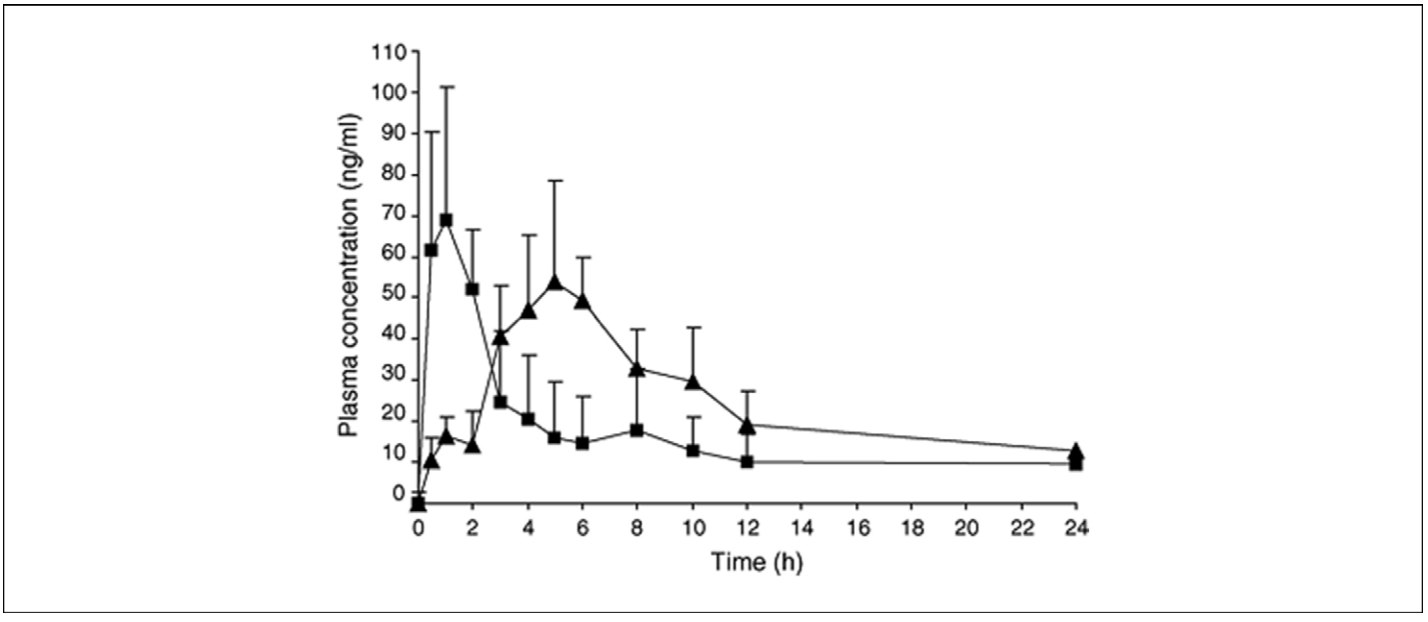

FIGURE 2

The mean plasma concentration–time profiles after oral administration (160 mg/kg ZTO dose) of the conventional SES (■) and the SE microspheres (▲). Each point represents the mean (+S.D.) ($n = 6$).

injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74% [58]. A second technique is that of sonication emulsion–diffusion–evaporation, by which co-loading 5-fluorouracil (5-FU) and antisense EGFR (epidermal growth factor receptor) plasmids in biodegradable PLGA/O-CMC nanoparticles was realized. The mixture of PLGA (poly-lactide-co-glycolide) and O-CMC (O-carboxmethyl-chitosan) had a SE effect, with no need to add another surfactant stabilizer. Eventually the 5-FU and plasmid encapsulation efficiencies were as high as 94.5% and 95.7%, respectively, and the 5-FU release activity from such nanoparticles could be sustained for as long as three weeks [59].

More recently, Trickler *et al.* developed a novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX). These chitosan/GMO nanoparticles, with bioadhesive properties and increased cellular association, were prepared by multiple emulsion (o/w/o) solvent evaporation methods. The SE property of GMO enhanced the solubility of PTX and provided a foundation for chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies of PTX. These advantages allow the use of lower doses of PTX to achieve an efficacious therapeutic window, thus minimizing the adverse side effects associated with chemotherapeutics like PTX [60].

Self-emulsifying suppositories

Some investigators proved that S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption [61].

Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C_6–C_{18} fatty acid glycerol ester and a C_6–C_{18} fatty acid macrogol ester [62].

Self-emulsifying implants

Research into SE implants has greatly enhanced the utility and application of S-SEDDS. As an example, 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. However, its effectiveness was hindered by its short half-life. In order to enhance its stability compared with that released from poly (d,l-lactide-co-glycolide) (PLGA) wafer implants, SES was formulated with tributyrin, Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil 1944 (polyglycolyzed glyceride). Then the self-emulsified BCNU was fabricated into wafers with flat and smooth surface by compression molding. Ultimately, SES increased *in vitro* half-life of BCNU up to 130 min contrasted with 45 min of intact BCNU. *In vitro* release of BCNU from SE PLGA wafers were prolonged up to 7 days. Such wafers had higher *in vitro* antitumor activity and were less susceptible to hydrolysis than those wafers devoid of SES [63].

Loomis invented copolymers having a bioresorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses [64].

Conclusion

As mentioned above, numerous studies have confirmed that S-SEDDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water-soluble drugs. As improvements or alternatives of conventional liquid SEDDS, S-SEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Most importantly, S-SEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable.

There is still a long way to go, however, before more solid SE dosage forms (except for SE capsules) appear on the market. Because there exist some fields of S-SEDDS to be further exploited, such as studies about human bioavailability and correlation of *in vitro*/*in vivo*. Moreover, the researches of S-SEDDS lose their balance, that is, SE implants/suppositories/microspheres have not been as extensively studied as SE tablets/pellets/capsules. It is also worth pointing out some issues to which much attention should be paid, for example physical aging phenomenon associated with glyceride, oxidation of vegetable oil [65], and interaction between drugs and excipients [66]. Selection of suitable excipients is the main hurdle of developing S-SEDDS [53]. Thus, these aspects should represent the major future working directions for S-SEDDS.

Acknowledgements

We are grateful to Dr. S.L. Carney for his support and edited work; we wish to thank Dr. J. Sun and Dr. C.F. Cai for their helpful opinions. This review is dedicated to Mrs. Y.Y. Lei on the occasion of her 50th birthday.

References

1 Lipinski, C. (2002) Poor aqueous solubility—an industry wide problem in drug discovery. *Am. Pharm. Rev.* 5, 82–85
2 Palmer, A.M. (2003) New horizons in drug metabolism, pharmacokinetics and drug discovery. *Drug News Perspect.* 16, 57–62
3 Gursoy, R.N. and Benita, S. (2004) Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. *Biomed. Pharmacother.* 58, 173–182
4 Prajapati, B.G. and Patel, M.M. (2007) Conventional and alternative pharmaceutical methods to improve oral bioavailability of lipophilic drugs. *Asian J. Pharm.* 1, 1–8
5 Attama, A.A. *et al.* (2003) The use of solid self-emulsifying systems in the delivery of diclofenac. *Int. J. Pharm.* 262, 23–28
6 Nazzal, S. *et al.* (2002) Optimization of a self-nanoemulsified tablet dosage form of ubiquinone using response surface methodology: effect of formulation ingredients. *Int. J. Pharm.* 240, 103–114
7 Abdalla, A. and Mader, K. (2007) Preparation and characterization of a self-emulsifying pellet formulation. *Eur. J. Pharm. Biopharm.* 66, 220–226
8 Franceschinis, E. *et al.* (2005) Self-emulsifying pellets prepared by wet granulation in high-shear mixer: influence of formulation variables and preliminary study on the *in vitro* absorption. *Int. J. Pharm.* 291, 87–97
9 Hauss, D.J. (2007) Oral lipid-based formulations. *Adv. Drug. Deliv. Rev.* 59, 667–676
10 Friedman, D. Non-aqueous compositions for oral delivery of insoluble bioactive agents. *US Pat 20070190080*

11 Constantinides, P.P. (1995) Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. *Pharm. Res.* 12, 1561–1572

12 Hauss, D.J. *et al.* (1998) Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB_4 inhibitor. *J. Pharm. Sci.* 87, 164–169

13 Caliph, S. *et al.* (2000) Effect of short-, medium- and long-chain fatty acid-based vehicles on the absolute oral bioavailability and intestinal lymphatic transport of halofantrine and assessment of mass balance in lymph-cannulated and non-cannulated rats. *J. Pharm. Sci.* 89, 1073–1084

14 Attama, A.A. and Mpamaugo, V.E. (2006) Pharmacodynamics of piroxicam from self-emulsifying lipospheres formulated with homolipids extracted from Capra hircus. *Drug. Deliv.* 13, 133–137

15 Jannin, V. *et al.* (2008) Approaches for the development of solid and semi-solid lipid-based formulations. *Adv. Drug. Deliv. Rev.* 60, 734–746

16 Dong, L. *et al.* (2000) A novel osmotic delivery system: L-OROS SOFTCAP. *Proceedings of the International Symposium on Controlled Release of Bioactive Materials*, July, Paris (CD ROM)

17 Dong, L. *et al.* (2001) L-OROS HARDCAP: a new osmotic delivery system for controlled release of liquid formulation. *Proceedings of the International Symposium on Controlled Release of Bioactive Materials*, June, San Diego (CD-ROM)

18 Cole, E.T. *et al.* (2008) Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. *Adv. Drug. Deliv. Rev.* 60, 747–756

19 Ito, Y. *et al.* (2005) Oral solid gentamicin preparation using emulsifier and adsorbent. *J. Control Release* 105, 23–31

20 Fabio, C. and Elisabetta, C. Pharmaceutical composition comprising a water/oil/water double microemulsion incorporated in a solid support. *WO2003/013421*

21 Boltri, L. *et al.* (1997) Enhancement and modification of etoposide release from crospovidone particles loaded with oil-surfactant blends. *Pharm. Dev. Technol.* 2, 373–381

22 Venkatesan, N. *et al.* (2005) Liquid filled nanoparticles as a drug delivery tool for protein therapeutics. *Biomaterials* 26, 7154–7163

23 Seo, A. *et al.* (2003) The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. *Int. J. Pharm.* 259, 161–171

24 Gupta, M.K. *et al.* (2001) Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent. *Pharm. Dev. Technol.* 6, 563–572

25 Gupta, M.K. *et al.* (2002) Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. *Pharm. Res.* 19, 1663–1672

26 Verreck, G. and Brewster, M.E. (2004) Melt extrusion-based dosage forms: excipients and processing conditions for pharmaceutical formulations. *Bull. Tech. Gattefosse.* 97, 85–95

27 Newton, M. *et al.* (2001) The influence of formulation variables on the properties of pellets containing a self-emulsifying mixture. *J. Pharm. Sci.* 90, 987–995

28 Newton, J.M. *et al.* (2005) Formulation variables on pellets containing self-emulsifying systems. *Pharm. Tech. Eur.* 17, 29–33

29 Newton, J.M. *et al.* (2005) The rheological properties of self-emulsifying systems, water and microcrystalline cellulose. *Eur. J. Pharm. Sci.* 26, 176–183

30 Tuleu, C. *et al.* (2004) Comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension of progesterone. *J. Pharm. Sci.* 93, 1495–1502

31 Iosio, T. *et al.* (2008) Bi-layered self-emulsifying pellets prepared by co-extrusion and spheronization: influence of formulation variables and preliminary study on the *in vivo* absorption. *Eur. J. Pharm. Biopharm.* 10.1016/j.ejpb.2007.11.014

32 Myers, S.L. and Shively, M.L. (1992) Preparation and characterization of emulsifiable glasses: oil-in-water and water-in-oil-in-water emulsion. *J. Colloid Interface Sci.* 149, 271–278

33 Bamba, J. *et al.* (1995) Cryoprotection of emulsions in freeze-drying: freezing process analysis. *Drug. Dev. Ind. Pharm.* 21, 1749–1760

34 Christensen, K.L. *et al.* (2001) Technical optimization of redispersible dry emulsions. *Int. J. Pharm.* 212, 195–202

35 Hansen, T. *et al.* (2004) Process characteristics and compaction of spray-dried emulsions containing a drug dissolved in lipid. *Int. J. Pharm.* 287, 55–66

36 Jang, D.J. *et al.* (2006) Improvement of bioavailability and photostability of amlodipine using redispersible dry emulsion. *Eur. J. Pharm. Sci.* 28, 405–411

37 Toorisaka, E. *et al.* (2005) An enteric-coated dry emulsion formulation for oral insulin delivery. *J. Control Release* 107, 91–96

38 Cui, F.D. *et al.* (2007) Preparation of redispersible dry emulsion using Eudragit E100 as both solid carrier and unique emulsifier. *Colloid. Surf. A: Physicochem. Eng. Asp.* 307, 137–141

39 Itoh, K. *et al.* (2002) Improvement of physicochemical properties of N-4472 part I: formulation design by using self-microemulsifying system. *Int. J. Pharm.* 238, 153–160

40 Gao, P. and Morozowich, W. (2006) Development of supersaturatable self-emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs. *Expert. Opin. Drug. Discov.* 3, 97–110

41 Gao, P. *et al.* (2003) Development of a supersaturable SEDDS (S-SEDDS) formulation of paclitaxel with improved oral bioavailability. *J. Pharm. Sci.* 92, 2386–2398

42 Li, P. *et al.* (2007) Development and characterization of a solid microemulsion preconcentrate system for oral delivery of poorly water soluble drugs. *Controlled Release Society Annual Meeting, Long Beach*, CA, June

43 Li, P. *et al.* Novartis Pharmaceuticals Corp. Spontaneously dispersible pharmaceutical compositions. *WO2006/050123*

44 Ito, Y. *et al.* (2006) Preparation and evaluation of oral solid heparin using emulsifier and adsorbent for *in vitro* and *in vivo* studies. *Int. J. Pharm.* 317, 114–119

45 Nazzal, S. and Khan, M.A. (2006) Controlled release of a self-emulsifying formulation from a tablet dosage form: stability assessment and optimization of some processing parameters. *Int. J. Pharm.* 315, 110–121

46 Patil, P. *et al.* (2004) Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen. *AAPS Pharm. Sci. Tech.* 10.1208/pt050342 http://www.aapspharmscitech.org/articles/pt0503/pt050342/pt050342.pdf

47 Joseph, S. Solid self-emulsifying dosage form for improved delivery of poorly soluble hydrophobic compounds and the process for preparation thereof. *US Pat 20030072798*

48 Wei, L.L. *et al.* (2007) Investigations of a novel self-emulsifying osmotic pump tablet containing carvedilol. *Drug. Dev. Ind. Pharm.* 33, 990–998

49 Gandhi, R. *et al.* (1999) Extrusion and spheronization in the development of oral controlled-release dosage forms. *PSTT* 2, 160–170

50 Serratoni, M. *et al.* (2007) Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system. *Eur. J. Pharm. Biopharm.* 65, 94–98

51 Hamdani, J. *et al.* (2003) Physical and thermal characterizations of Precirol® and Compritol® as lipophilic glycerides used for the preparation of controlled-release matrix pellets. *Int. J. Pharm.* 260, 47–57

52 Serajuddin, A.T.M. (1999) Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* 88, 1058–1066

53 Vasanthavada, M. and Serajuddin, A.T.M. (2007) Lipid-based self-emulsifying solid dispersions. In *Oral Lipid-Based Formulations: Enhancing Bioavailability of Poorly Water-Soluble Drugs* (Hauss, D.J., ed.), pp. 149–184, Informa Healthcare

54 Serajuddin, A.T.M. *et al.* (1988) Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. *J. Pharm. Sci.* 77, 414–417

55 Khoo, S.M. *et al.* (2000) The formulation of halofantrine as either non-solubilising PEG 6000 or solubilising lipid based solid dispersions: physical stability and absolute bioavailability assessment. *Int. J. Pharm.* 205, 65–78

56 Patil, P. and Paradkar, A. (2006) porous polystyrene beads as carriers for self-emulsifying system containing loratadine. *AAPS Pharm. Sci. Tech.* 10.1208/pt070128 http://www.aapspharmscitech.org/articles/pt0701/pt070128/pt070128.pdf

57 You, J. *et al.* (2006) Study of the preparation of sustained-release microspheres containing zedoary turmeric oil by the emulsion–solvent-diffusion method and evaluation of the self-emulsification and bioavailability of the oil. *Colloid. Surf. B.* 48, 35–41

58 Attama, A.A. and Nkemnele, M.O. (2005) *In vitro* evaluation of drug release from self micro-emulsifying drug delivery systems using a biodegradable homolipid from Capra hircus. *Int. J. Pharm.* 304, 4–10

59 Hu, Y.X. *et al.* (2005) Preparation and evaluation of 5-FU/PLGA/gene nanoparticles. *Key Eng. Mat.* 288–289 147-150

60 Trickler, W.J. *et al.* (2008) A novel nanoparticle formulation for sustained paclitaxel delivery. *AAPS Pharm. Sci. Tech.* 10.1208/s12249-008-9063-7

61 Kim, J.Y. and Ku, Y.S. (2000) Enhanced absorption of indomethacin after oral or rectal administration of a self-emulsifying system containing indomethacin to rats. *Int. J. Pharm.* 194, 81–89

62 Takada, K. and Murakami, M. Glycyrrhizin preparations for transmucosal absorption. *US Pat 6890547*

63 Chae, G.S. *et al.* (2005) Enhancement of the stability of BCNU using self-emulsifying drug delivery systems (SEDDS) and *in vitro* antitumor activity of self-emulsified BCNU-loaded PLGA wafer. *Int. J. Pharm.* 301, 6–14

64 Loomis, G.L. Bioresorbable compositions for implantable prostheses. *US Pat 6403758*

65 Halbaut, L. *et al.* (1997) Oxidative stability of semi-solid excipient mixtures with corn oil and its implication in the degradation of vitamin A. *Int. J. Pharm.* 147, 31–40

66 Chambin, O. *et al.* (2004) Influence of cryogenic grinding on properties of a self-emulsifying formulation. *Int. J. Pharm.* 278, 79–89