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Review Article

SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS): FUTURE ASPECTS

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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 through the gastrointestinal tract 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 various developments of SEDDS and biopharmaceutical aspects of SEDDS. The characterization of SEDDS and application of SEDDS is also introduced, with particular emphasis being placed on the developments of Solid self emulsifying delivery system and dosage form of SEDDS.

Keywords: Self emulsifying drug delivery systems (SEDDS), Self Micro-emulsifying drug delivery systems (SMEDDS), Solid Self emulsifying drug delivery systems (S-SEDDS).

INTRODUCTION

A. SELF EMULSIFYING AND SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM

The drugs are most often administered by oral route, but approximately 40% of new drug candidates have poor-water solubility and the oral delivery of such drugs is difficult because of their low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality. To overcome these problems, various strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles and solid dispersions [1,2].

There are a number of formulation strategies that could be used to improve the bioavailability of class II drugs, either by increasing the dissolution rate or by presenting the drug in solution and maintaining the drug in solution in the intestinal lumen.

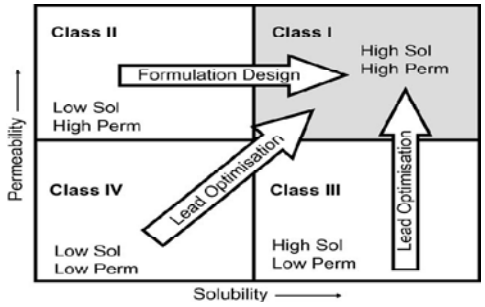

Fig. 1: A typical representation of the biopharmaceutical classification system

Figure 1 indicating that absorption of a class II drug can be markedly improved by attention to the formulation. Formulation may improve the bioavailability of class IV drugs but they are likely to be compromised by their poor membrane permeability. If a class II drug can be maintained in a solubilized state in the lumen of the gut one can achieve an absorption profile more like that of a class I drug. Formulation strategies can do little to improve the absorption of classes I and III drugs which are limited by poor membrane permeability.

Recently, due to good and reliable result, there is a great emphasis on self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of lipophilic drugs [3,4]. Self-emulsification is a phenomenon which has been exploited commercially for many years in formulations of emulsifiable concentrates of herbicides and pesticides [5]. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles [6], surfactant dispersions [7,8], self-emulsifying formulations [9], emulsions [10] and liposome [11] with every formulation approach having its special advantages and limitations. 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. There has been growing interest in the use of lipidic excipients in formulations and, in self-emulsifying lipid formulations (SELFs) because of their ability to solubilize poorly water-soluble 'lipophilic' drugs and overcome the problem of poor drug absorption and bioavailability.

Advantages

Potential advantages of these systems (SEDDS) include [12]

1. Enhanced oral bioavailability enabling reduction in dose.
2. More consistent temporal profiles of drug absorption.
3. Selective targeting of drug(s) toward specific absorption window in GIT
4. Protection of drug(s) from the hostile environment in gut.
5. Control of delivery profiles.
6. Reduced variability including food effects.
7. Protection of sensitive drug substances.
8. High drug payloads.
9. Liquid or solid dosage forms.

These formulations have attracted interest because they can improve the bioavailability of compounds that fall into Class II of the biopharmaceutical classification system (BCS). Class II compounds are poorly water soluble and highly permeable. This bioavailability enhancing property has been associated with a number of *in vivo* properties of lipidic formulation including:

1. The formation of fine dispersions and micellar suspensions to prevent precipitation and recrystallization of the drug compound.
2. The ability of certain lipid compounds and their metabolites to initiate changes in the gastrointestinal fluid to favour improved drug absorption.
3. The inhibition of cellular efflux mechanisms, which keep drugs out of the circulation.
4. Certain lipidic excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism in the liver.

The mechanisms by which lipids influence drug delivery, digestion and absorption are complex and not yet fully understood. Nevertheless, it is well known that lipidic excipients provide a safe and effective way of enhancing bioavailability, and offer an additional approach to 'mechanical' or 'chemical' strategies for dealing with poorly water-soluble compounds (i.e., techniques such as nano milling and altering the physicochemical properties of the compound).

Provided the formulator succeeds in addressing the challenges of drug solubility and absorption, the next big challenge is the delivery of the drug in an acceptable dosage form. It is an undisputed fact that oral dosage forms are the preferred drug administration route, and lipid formulations offer versatility for oral dosage forms because they can be formulated as solutions, and semi-solid and solid forms. Within these oral dosage forms, lipids are formulated as simple emulsions, self-emulsifying and self-micro-emulsifying formulations. SELF systems comprise a defined mixture of lipid excipients, including simple oils, nonionic surfactants and cosurfactants. SELF systems act as carriers for drugs by forming fine emulsions, or micro-emulsions, under gentle stirring when diluted in water or physiological media with physiological motion. Drug molecules are either dissolved or suspended in the SELF system, which maintains the drug in very fine dispersion droplets inside the intestinal lumen, providing optimal conditions for absorption.

Two types of SELF systems exist: self-emulsifying drug delivery systems (SEDDSs) and self-micro-emulsifying drug delivery systems (SMEDDSs). Both SEDDSs and SMEDDSs have distinct features associated with improved drug delivery properties. SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SMEDDS requires the use of a co-surfactant to generate a micro-emulsion. SEDDS formulations are characterized by *in vitro* lipid droplet sizes of 200 nm–5 mm and the dispersion has a turbid appearance. SMEDDSs, however, have a smaller lipid droplet size (<200 nm) and the dispersion has an optically clear-to-translucent appearance. Both systems are associated with the generation of large surface area dispersions that provide optimum conditions for the increased absorption of poorly soluble drugs. The choice of whether a SEDDS or a SMEDDS is the preferred formulation option often depends on the interplay between the intrinsic properties of the drug compound and its solubility and dissolution profile during *in vitro* screening with a number of excipients.

In terms of dosage form, SELFs are principally liquid or semi-solid formulations and, therefore, ideal for soft or hard capsule filling. Currently, drugs that utilize SEDDs are exclusively developed in soft or hard gelatin capsules this is because, until recently, getting a SELF into tablet form was a formulation challenge because of the nature of excipients and formulation techniques. That is not to say that formulating for a solid dosage form that utilizes a SELF is impossible, but the starting point for such a formulation requires the use of semi-solid excipients. SELFs have been transformed into solid dosage forms using techniques such as melt granulation, where the lipid excipient acts as a binder and solid granules are produced on cooling. Solvents or supercritical fluids can be used with semi-solid excipients, which are solubilized and then the solvent evaporated to produce a waxy powder. Spraying techniques can be used to produce powder form formulations. These techniques enable the production of granules or powders that can then be compressed into a tablet form or filled into capsules. In all cases, the lipidic excipients used must be semi-solid at room temperature.

However, in many cases, because of the nature of lipidic excipients, the SELF system is a liquid-based formulation rather than a semi-solid formulation and, therefore, an alternative approach are required. The concept works by the adsorption/absorption of a liquid SELF onto a neutral carrier (i.e., neutral silicate). Although surprisingly straightforward, developing this solid dosage form technique has required extensive investigation of critical success parameters including:

1. Extensive screening of different neutral carriers to evaluate their ability to adsorb maximum levels of the liquid SELF.
2. Maximum loading value of the carrier and effect on tablet compression.
3. Absorption onto the carrier and effect on flowability — an essential feature for tablet compression.
4. Evaluation of the integrity of the system with a poorly soluble API to examine the effect of transforming a liquid into a powder on drug solubility and dissolution rate.

Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are isotropic mixtures of oils and surfactants [13], sometimes containing co-solvents, and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. SEDDSs emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation [14,15] SEDDS can be orally administered in soft or hard gelatin capsules and form fine, relatively stable oil-in-water emulsions upon aqueous dilution.

In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which leads to poor oral bioavailability, high intra- and inter-subject variability, and lack of dose proportionality. In the oral formulation of such compounds, a number of attempts—such as decreasing particle size, use of wetting agents, co precipitation, and preparation of solid dispersions have been made to modify the dissolution profile and thereby improve the absorption rate. Recently, much attention has focused on lipid-based formulations to improve the bioavailability of poorly water soluble drugs. Among many such delivery options, like incorporation of drugs in oils, surfactant dispersion, emulsions and liposomes, one of the most popular approaches are the self-emulsifying drug delivery systems (SEDDSs).

SEDDSs are mixtures of oils and surfactants, ideally isotropic and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation. Self-emulsifying formulations spread readily in the gastrointestinal (GI) tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self emulsification. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. When compared with emulsions, which are sensitive and meta-stable dispersed forms, SEDDSs are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles.

Composition of SEDDSs

The self-emulsifying process depends on:

- The nature of the oil–surfactant pair
- The surfactant concentration
- The temperature at which self-emulsification occurs.

1. **Oils:** Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.

2. **Surfactant:** Nonionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules.

3. **Co-surfactant/Co-solvents:** Co-surfactant/Co-solvents like Spans, capyrol 90, Capmul, lauroglycol, diethylene glycol monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the cosurfactants in the microemulsion systems.

Formulation of SEDDSs

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble co-surfactant/co-solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions.

Table 1: Examples of oils, surfactants, co-surfactant and co-solvents used

Oils	Surfactants	Co-surfactants/Co-solvent
Cotton seed oil	Polysorbate 20 (Tween 20)	Span 20
Soybean oil	Polysorbate 80 (Tween 80)	Span 80
Corn oil	D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)	Capryol 90
Sunflower oil	Polyoxy-35-castor oil(Cremophor RH40)	Lauroglycol
Castor oil	Polyoxy-40- hydrogenated castor oil(Cremophor RH40)	Transcutol
Sesame oil	Labrasol	Capmul
Peanut oil		Ethanol
Labrafac		Polypylene glycol
Labrafil		Polyethylene glycol

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

1. The solubility of the drug in different oil, surfactants and co-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 co-surfactant/co-solvents.

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. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent.

Mechanism of self-emulsification

According to Reiss [16], self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation:

$$DG = S N_i p r_i 2s$$

Where, DG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r and s represents the interfacial energy. The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents,which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence.

In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing [17]. According to Wakerly et al [18], the addition of a binary mixture (oil/nonionic surfactant) to water results in interface formation between the oil and aqueous-continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface, this will occur until the solubilization limit is close to the interface.

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 [19,20]. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability *via* a number of potential mechanisms, including:

1. **Alterations (reduction) in gastric transit:** thereby slowing delivery to the absorption site and increasing the time available for dissolution [21].

2. **Increase in effective luminal 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 solubilization 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 solubilization capacity

3. **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 [22,23].

4. **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 [24,25].

5. **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 [26,27]. 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.

6. **Effect of oils on the absorption:** Such formulations form a fine oil-in-water emulsion with gentile agitation, which may be provided by gastrointestinal motility. A SES also improves the reproducibility of the plasma level–time profile. Various physiological mechanisms have been proposed to explain the effect of oils on the absorption of water-insoluble compounds, including altered gastrointestinal motility, increased bile flow and drug solubilization, increased mucosal permeability, enhanced mesenteric lymph flow, and increased lymphatic absorption of water insoluble drugs and bioavailability also increased of hydrophobic compound.

Characterization of SEDDSs

The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

1. **Visual assessment:** This may provide important information about the self emulsifying and microemulsifying property of the mixture and about the resulting dispersion.
2. **Turbidity measurement:** This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.
3. **Droplet size:** This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a coulter nanosizer are mainly used for the determination of the emulsion droplet size. The reduction of the droplet size below 50 μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions.
4. **Zeta potential measurement:** This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.
5. **Determination of emulsification time:** Self-emulsification time, dispersibility, appearance and flowability was observed and scored according to techniques described in H. Shen et al. used for the grading of formulations.

Application

SEDDS formulation is composed of lipids, surfactants, and co-solvents. The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation. SEDDSs present drugs in a small droplet size and well-proportioned distribution, and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the pre-systemic clearance in the GI mucosa and hepatic first-pass metabolism

B. SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM

Introduction

In recent years, self-emulsifying and self-microemulsifying drug delivery systems (SEDDS and SMEDDS) have shown a reasonable success in improving oral bioavailability of poorly water soluble and lipophilic drugs. SEDDS and SMEDDS are normally prepared either as liquids or encapsulated in soft gelatin capsules, which have some shortcomings especially in the manufacturing process, leading to high production costs. Moreover, these dosage forms may be inconvenient to use and incompatibility problems with the shells of the soft gelatin are usual. Incorporation of a liquid self-emulsifying formulation into a solid dosage form may combine the advantages of SEDDS with those of a solid dosage form and overcome the disadvantages of liquid formulations described above.

Recently, increasing research has focused on this area. A solid state microemulsion for the delivery of cyclosporine was prepared by coating a pre-microemulsion with enteric coating materials. A eutectic-based self nanoemulsified drug delivery system of ubiquinone was incorporated into a tablet dosage form, using blends of maltodextrin, modified povidone and microcrystalline cellulose (MCC). The release of lipid formulations from this tablet dosage form could be controlled by the addition of MCC of finer particle size and colloidal silicates. Pellets containing self-emulsifying mixtures were prepared by extrusion/spheronization or wet granulation in high-shear mixer, with inclusion of MCC and lactose. The in vitro release of the drug from such pellets could be controlled by coating with a polymer film. However, these solid SEDDS were almost prepared by extrusion/spheronization, containing water-insoluble materials as solid carriers. There are a limited number of publications reporting the oral bioavailability of solid SEDDS. Additionally, few investigations on reconstitution properties of solid SEDDS have been performed. Spray drying has been employed to prepare dry emulsions by removing water from an ordinary emulsion containing a water soluble solid carrier. The initial emulsion mostly consisted of oil, water and an ordinary emulsifying agent, and the droplet size of reconstituted emulsions from dry emulsions was usually more than 1um.

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, solid self-micro emulsifying drug delivery system, 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/ nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticles technology, and so on). Such powders/nanoparticles, which refer to SE nanoparticles /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 micro-spheres/nanoparticles and SE suppositories/implants.

Developments of solid self emulsifying delivery system

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

1. 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:

a) Heating of the semisolid excipient to at least 20 °C above its melting point
b) Incorporation of the active substances (with stirring)
c) Capsule filling with the molten mixture and
d) Cooling to room temperature [28].

For *liquid formulations*, it involves two-step process:

a) Filling of the formulation into the capsules

b) Sealing of the body and cap of capsule, either by banding or by microspray sealing [29].

2. 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.

3. 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 [30]. 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 [31]. SEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. 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.

4. 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 [32]. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. The melt granulation process was usually used for adsorbing SES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium aluminometa silicate) [33-34].

5. Melt extrusion/extrusion spheronization: Melt extrusion is a solvent-free process that allows high drug loading (60%) [35], 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 [36]. 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:

a) Dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder

b) Extrusion into a spaghetti-like extrudate

c) Spheronization from the extrudate to spheroids of uniform size

d) Drying Sifting to achieve the desired size distribution and coating (optional) [37].

C. DOSAGE FORM DEVELOPMENT OF S-SEDDS

1. 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 [38], freeze-drying [39] or spray drying. 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. 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 . 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 [40]. Recently, Cui et al. prepared dry emulsions by spreading liquid O/W emulsions on a flat glass, then dried and triturated to powders [41].

2. 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 [42]. 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 [43,44]. 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-micro emulsification upon mixing with water [45,46].

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: micro porous calcium silicate (FloriteTM RE); magnesium aluminum silicate (NeusilinTM US2) and silicon dioxide (SylysiaTM 320). Eventually these solids were filled into hard capsules [47]. 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 [48].

3. 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—X1, magnesium stearate mixing time— X2, and compression force—X3) on hardness and coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X1 = 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face-centered cubic design [49]. 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 [50]. 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 TM (a copolymer of alkyl phenol and formaldehyde).

4. 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 [51].

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. 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) [52].

5. 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 [53,54]. 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 [55]. SE excipients like Gelucire1 44/14, Gelucire1 50/02, Labrasol1, Transcutol and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field [56].

6. Self-emulsifying beads: In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, Patil and Paradkar investigated loading SES into the micro-channels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structures is 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 was 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 [57].

7. 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 hydroxylpropyl methylcellulose acetate succinate to Aerosil 200 in the formulation. The plasma concentration– time profiles were achieved after oral administration of such microspheres to rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS [58].

8. 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 injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. These approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74% [59].

9. Self-emulsifying suppositories: Some investigators proved that S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption [60]. 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 C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester [61].

10. 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. 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 [62].

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. 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. Numerous studies have confirmed that 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 SEDDS to be further exploited, such as studies about human bioavailability and correlation of in vitro/in vivo. 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 , and interaction between drugs and excipients . Selection of suitable excipients is the main hurdle of developing S-SEDDS. Thus, these aspects should represent the major future working directions for S-SEDDS. Thus major breakthroughs are still required for proper development of sedds.

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