Development of Solid-Self Micron Emulsifying Drug Delivery Systems

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ABSTRACT
As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water-soluble and solubility is one of the most important parameter to achieve desired concentration of drug in systemic circulation for therapeutic response. It is a great challenge for pharmaceutical scientist to convert those molecules into orally administered formulation with sufficient bioavailability. Among the several approaches to improve oral bioavailability of these molecules, Self-micron emulsifying drug delivery system (SMEDDS) is one of the approaches usually used to improve the bioavailability of hydrophobic drugs. However, conventional SMEDDS are mostly prepared in a liquid form, which can have several disadvantages. Accordingly, solid SMEDDS (S-SMEDDS) prepared by solidification of liquid/semisolid self-micron emulsifying (SME) ingredients into powders have gained popularity. This article provides an overview of the recent advancements in S-SMEDDS such as methodology, techniques and future research directions.

KEYWORDS: Solid-Self Micron Emulsifying System, Solidification Techniques, Recent Advances and Future aspects.

Introduction
As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water-soluble. It is a great challenge for pharmaceutical scientists to convert those molecules into orally administered formulations with sufficient bioavailability. One of the most popular and commercially viable formulation approaches for solving these problems is self-micron emulsifying drug delivery systems (SMEDDS). SMEDDS have been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and lipophilic drugs (Palmer, 2003).

Traditional preparation of SMEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents. However, SME formulations are normally prepared as liquids that produce some disadvantages such as high production costs, low stability and portability, low drug loading, irreversible drugs/excipients precipitation and few choices of dosage forms. More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation.

To address these problems, S-SMEDDS have been investigated, as an alternative approach. These systems require the solidification of liquid self-micron emulsifying (SME) ingredients into powders/nanoparticles which can be converted to various solid dosage forms (SME tablets (Attama, 2003) and SME pellets (Abdalla, 2007) and so on. Thus, S-SMEDDS will have combined advantages of SMEDDS such as enhanced solubility and bioavailability and with those of solid dosage forms, such as low production cost, convenience of process control, high stability and reproducibility, better patient compliance. To date, there have been studies that mainly focused on the preparation and characterization of a single, solid SME dosage form, yet relatively few that introduce S-SMEDDS in a systematic way, especially with respect to the dosage form development and preparation techniques.

History of micron emulsions
The term microemulsion was first used by T. P. Hoar and J. H. Shulman in 1943. Alternative names for these systems are often used, such as transparent emulsion, swollen micelle, micellar solution, and solubilized oil. Microemulsions are formed when (i) The interfacial tension at the oil/water interface is
brought to a very low level and (ii) The interfacial layer is kept highly flexible and fluid. These two conditions are usually met by a careful and precise choice of the components and of their respective proportions, and by the use of a “co-surfactant” which brings flexibility to the oil/water interface. These conditions lead to a thermodynamically optimised structure, which is stable as opposed to conventional emulsions and does not require high input of energy (i.e. through agitation) to be formed. Because the size of the particles is much smaller than the wavelength of visible light, microemulsions are transparent and their structure cannot be observed through an optical microscope.

**Self-micron emulsifying drug delivery systems**

Self-micron emulsifying drug delivery systems (SMEDDS) are mixtures of oils, co-solvents and surfactants, which is isotropic in nature and which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. After per oral administration, these systems form fine emulsions (or micro emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility and it has a droplet size between 10–200 nm, transparent than those of conventional emulsions (1-20 μm) which is opaque shown in Fig. 1. These are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion and solubility effect of surfactants (Kreilgaard, 2002).

**Phase diagrams**

The microemulsion region is usually caracterized by constructing ternary-phase diagrams shown in Fig.2. Three components are the basic requirement to form a microemulsion: an oil phase, an aqueous phase and a surfactant. If a cosurfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single “pseudo-component”. The relative amounts of these three components can be represented in a ternary phase diagram. Gibbbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system. The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100 %. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally, according to the Gibbs’ phase rule) of one, two or three phases. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant temperature and pressure.

![Fig. 1. Difference between Self-Emulsions and Self-Micron Emulsion.](image)

![Fig. 2. Ternary-Phase Diagram.](image)

The Gibbs phase diagram, however, is an empirical visual observation of the state of the system and may, or may not express the true number of phases within a given composition. Apparently clear single phase formulations can still consist of multiple iso-tropic phases (e.g. the apparently clear heptane/AOT/water microemulsions consists of multiple phases). Since these systems can be in equilibrium with other phases, many systems, especially those with high volume fractions of both the two immiscible phases, can be easily destabilised by anything that changes this equilibrium e.g. high or low temperature or addition of surface tension modifying agents. However, examples of relatively stable microemulsions can be found. It is believed that the mechanism for removing acid build up in car engine oils involves low water phase volume, water-in-oil (w/o) microemulsions. Theoretically, transport of the aqueous acid droplets through the engine oil to microdispersed calcium carbonate particles in the oil should be most efficient when the droplets are small enough to transport a single hydrogen ion (the smaller the droplets, the greater the number of droplets, the faster the neutralisation). Such microemulsions are probably very stable across a reasonably wide range of elevated temperatures (Turner, 1985).
Mechanism of self-micron emulsification

According to Reiss, the energy required to increase the surface area of the dispersion for self-emulsification process bear less importance when compared to the entropy change that favours dispersion. Self-micron emulsifying process is related to the free energy. That is free energy of the conventional emulsion is a direct function of the energy essential to create a new surface between the oil and water phases and can be described by the equation:

\[ DG = SN \pi r^2 s \]

Where, \( DG \) is the free energy related to the process, \( N \) is the number of droplets of radius \( r \) and \( s \) represents the interfacial energy. The emulsion is stabilized by emulsifying agents only after the two phases of emulsion is separated with respect to time to reduce the interfacial area. The emulsifying agent forms a monolayer of emulsion droplets, and hence reduces the interfacial energy, and providing a barrier to avoid coalescence. In the case of self-micron emulsifying systems, the free energy required to form the emulsion is either very low or positive, or negative (Prince 1974). Emulsification requires very little input energy involves destabilization through contraction of local interfacial regions and this mechanism was shown in Fig. 3.

Fig. 3. Mechanism of Self-Micron Emulsifying Drug Delivery System.

Excipients 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. 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 SMEDDS.

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 (Hausse, 1998). 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 (Caliph, 2000).

Specificity

Self-emulsification depends on the nature of the oil/surfactant pair, surfactant concentration and oil/surfactant ratio, and the temperature at which self-micron emulsification occurs. Only very specific pharmaceutical excipients combinations lead to efficient self-micron emulsifying systems (SMES). The efficiency of drug incorporation into a SMEDDS is dependent upon the particular physicochemical compatibility of the drug/system (Constantinides, 1995). So, pre-formulation solubility and phase diagram studies are required in order to obtain an optimal formulation design.

Characterization

The very essence of SMEDDS 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 SMEDDS is another property that needs to be assessed (Gursoy, 2004). Melting properties and polymorphism of lipid or drug in SMES may be established by X-ray diffraction and differential scanning calorimetry.

Solid self-micron emulsifying drug delivery system

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties. S-SMEDDS focus on the incorporation of liquid/semisolid SME 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 (Attama, 2006) dry emulsions/solid
dispersions, are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SME capsules). SME capsules also include those capsules into which liquid-semisolid SMEDDS are directly filled without any solidifying excipients. To some extent, S-SMEDDS are combinations of SMEDDS and solid dosage forms, so many properties of S-SMEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms. For instance, the characterizations of SME pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on. In the 1990s, S-SMEDDS were usually in the form of SME capsules, SME solid dispersions and dry emulsions, but other solid SME dosage forms have emerged in recent years, such as SME pellets/tablets, SME microspheres/nanoparticles and SME suppositories/implants.

**Advantages of S-SMEDDS**

- Spontaneous formation
- Ease of manufacture
- Thermodynamic stability and
- Improved solubilization of bioactive materials
- More consistent temporal profiles of drug absorption
- Greater bioavailability
- less drug need to be used
- For many drugs taken by mouth
- Faster release rates and it improve the drug acceptance by consumers
- Selective drug targeting toward a specific absorption window in the GI tract and
- Drug protection from the hostile environment in the gut
- 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
- This may lower cost.

**Solidification Techniques for Transforming Liquid/Semisolid SMEDDS to S-SMEDDS**

**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 (Jannin 2008). In parallel with the advances in capsule technology proceeding, liquid-erosos technology has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SME 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 (Dong, 2000). A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell. 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 (Tao, 2008).

**Adsorption to solid carriers**

Free flowing powders may be obtained from liquid SME 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. A formulation of Liquid SMEDDS which is converted to Solid SMEDDS using Maltodextrin as a solid carrier was represented in Fig.4. SMEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers (Ito, 2005). Solid carriers can be micro porous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked Polymers or Nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and cross linked polymethyl methacrylate. Cross-linked polymers create a favorable environment to sustain drug dissolution and also assist in slowing down drug reprecipitation. Nanoparticle adsorbents comprise porous silicon dioxide (Sylysia, 550), carbon nanotubes, carbon nanohorns, fullerene, and charcoal and bamboo charcoal (Venkatesan, 2005).
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 1, 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 SME property (Seo, 2003). Other lipid-based excipients evaluated for melt granulation to create solid SMES include lecithin, partial glycerides, or polysorbates. The melt granulation process was usually used for adsorbing SMES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium alumina metal silicate) (Gupta, 2001; Gupta, 2002).

Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions. The size of the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion-spheronization process is commonly used in the pharmaceutical industry to make uniformly sized spheroids (pellets). The extrusion–spheronization process requires the following steps: Dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating (optional). In the wet masses comprising SMES (Polysorbate 80 and mono-/di-glycerides), lactose, water and MCC, the relative quantities of SMES 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 SMES that can be solidified by extrusion spheronization occupies 42% of the dry pellet weight (Newton 2001). Generally, the higher the water level, the longer the disintegration time (Newton, 2005). The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SMES 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 (Newton, 2005). Applying extrusion-spheronization, SME pellets of diazepam and progesterone and bi-layered cohesive SME pellets have been prepared (Tuleu, 2004; Iosio, 2008).

Dosage form Development of S-SMEDDS

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 (Myers, 1992), freeze-drying (Bamba, 1995) or spray drying (Christensen, 2001; Hansen, 2004). 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 (Jang, 2006). 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.

**Self-micron emulsifying capsules**

After administration of capsules containing conventional liquid SME 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 SME formulation (Itoh, 2002). With the similar purpose, the supersaturatable SMEDDS 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 (Gao, 2006; Gao, 2003). Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semifluid 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 (Li, 2007). Oral administration of SME 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; magnesium aluminum silicate and silicon dioxide. Eventually these solids were filled into hard capsules (Ito, 2006). In another study, such adsorbents were also applied to prepare SME tablets of gentamicin that, in clinical use, was limited to administration as injectable or topical dosage forms.

**Self-micron emulsifying sustained/controlled-release tablets**

Combinations of lipids and surfactants have presented great potential of preparing SME tablets that have been widely researched. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SMEDDS has been developed, 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. SE tablets are of great utility in obviating adverse effect for example; SE tablets may increase its penetration efficacy through the GI mucosal membranes, potentially reducing GI bleeding. The resultant SME tablets consistently maintained a higher active ingredient concentration in blood plasma over the same time frame compared with a non-emulsifying tablet. The newest advance in the research field of SME tablet is the SME osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SMES. 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 (Wei, 2007).

**Self-micron 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 (Gandhi, 1999). Thus, it is very appealing to combine the advantages of pellets with those of SMEDDS by SME pellets.

**Self-micron emulsifying solid dispersions**

Although solid dispersions could increase the dissolution rate and bioavailability of poorly watersoluble drugs, some manufacturing difficulties and stability problems existed. 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. SME excipients like Gelucire1 44/14, Gelucire150/02, Labrasol1, Transcutol1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field (Serajuddin, 1999; Vasanthavada, 2007; Serajuddin, 1988 and Khoo, 2000).

**Self-micron emulsifying suppositories**

Some investigators proved that S-SMEDDS could increase not only GI adsorption but also rectal/vaginal absorption (Kim, 2000). For example Glyceryrrhizin, which is given by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory...
therapeutic levels for chronic hepatic diseases by either vaginal or rectal SME suppositories.

Self-micron emulsifying implants

Research into SME implants has greatly enhanced the utility and application of S-SMEDDS. As an example, 1,3-bis(2-chloroethyl)-1-nitrosourea 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, SMES was formulated. Such wafers had higher in vitro antitumor activity and were less susceptible to hydrolysis (Chae, 2005).

Conclusions

The oral delivery of hydrophobic drugs can be made possible by SMEDDS, which have been shown to substantially improve oral Bioavailability. As mentioned above, numerous studies have confirmed that SMEDDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water-soluble drugs. As improvements or alternatives of conventional liquid SMEDDS, S-SMEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Most importantly, S-SMEDDS 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 SME dosage forms (except for SME capsules) appear on the market. Because there exist some fields of S-SMEDDS to be further exploited, such as studies about human bioavailability and correlation of in vivo in vivo.

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