

SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS): FORMULATION DEVELOPMENT, CHARACTERIZATION, AND APPLICATIONS

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ABSTRACT

Self-emulsifying drug delivery systems (SEDDS) possess unparalleled potential in improving oral bioavailability of poorly water-soluble drugs. Following their oral administration, these systems rapidly disperse in gastrointestinal fluids, yielding micro- or nanoemulsions containing the solubilized drug. Owing to its miniscule globule size, the micro/nanoemulsified drug can easily be absorbed through lymphatic pathways, bypassing the hepatic first-pass effect. We present an exhaustive and updated account of numerous literature reports and patents on diverse types of self-emulsifying drug formulations, with emphasis on their formulation, characterization, and systematic optimization strategies. Recent advancements in various methodologies employed to characterize their globule size and shape, ability to encapsulate the drug, gastrointestinal and thermodynamic stability, rheological characteristics, and so forth, are discussed comprehensively to guide the formulator in preparing an effective and robust SEDDS formulation. Also, this exhaustive review offers an explicit discussion on vital applications of the SEDDS in bioavailability enhancement of various drugs, outlining an overview on myriad *in vitro*, *in situ*, and *ex vivo* techniques to assess the absorption and/ or permeation potential of drugs incorporated in the SEDDS in animal and cell line models, and the subsequent absorption pathways followed by them. In short, the current article furnishes an updated compilation of wide-ranging information on all the requisite vistas of the self-emulsifying formulations, thus paving the way for accelerated progress into the SEDDS application in pharmaceutical research.

KEYWORDS: Self-emulsifying formulation, bioavailability enhancement, SNEDDS, SMEDDS, hepatic first-pass effect, lipid-based drug delivery.

I. INTRODUCTION

Oral intake has been the most sought-after route of drug delivery by both patients and drug Manufacturers for the treatment of most pathological states. Despite tremendous strides made in novel non oral drug delivery systems (DDS) to date, the majority of the drugs available commercially are oral formulations.¹ Nevertheless, with oral delivery, over one-half of the drug compounds are diminished in the gastrointestinal (GI) tract because of their high lipophilicity and consequently poor aqueous solubility. Oral bioavailability of such drugs, being primarily a function of their solubility and dissolution, ^{2,3} tends to exhibit inadequate magnitude with high intra- and inter subject variability. Further, oral bioavailability also depends upon a multitude of other drug factors such as stability in GI fluids, ^{2,3} intestinal permeability,⁴ resistance to metabolism by cytochrome P450 family of enzymes present in gut enterocytes and liver hep tocytes,^{5,6} and

interactions with efflux transporter systems such as P-glycoprotein (P-gp). ^{7,8} Figure 1 illustrates the mechanisms of the physiological pathways through which the bioavailability of a drug from the conventional formulations tends to get impeded.

Several approaches have been employed to improve the oral bioavailability of diverse drugs during formulation. Among these, oral lipid-based drug-delivery systems (DDS) have shown immense potential in improving the poor and inconsistent drug absorption of many poorly water-soluble drugs, especially following their administration after meals.^{9, 10} These approaches include various types of lipid suspensions, solutions, and emulsions.¹¹⁻¹⁴ With applications in specific domains, lipidic formulations have therefore gained a significant niche in oral drug delivery systems. Self-Emulsifying Drug Delivery Systems.

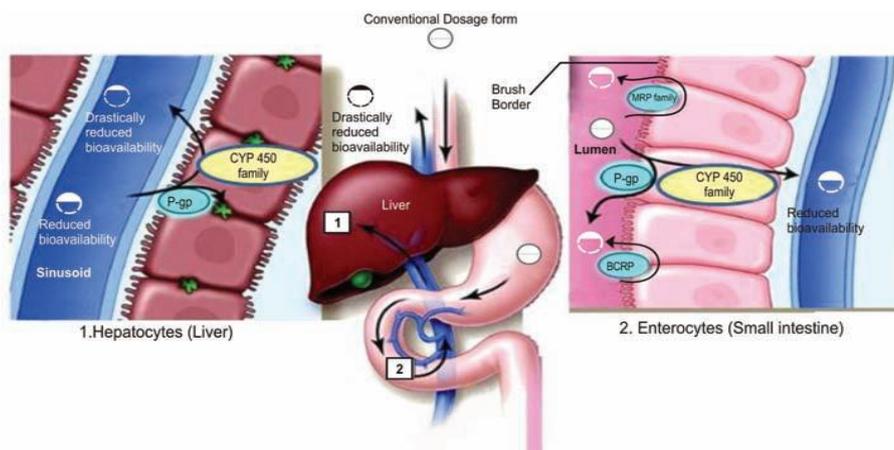


Figure 1: Physiological pathways leading to reduction in drug bioavailability through oral conventional dosage Forms.

FIGURE 1.

Physiological pathways leading to reduction in drug bioavailability through oral conventional dosage forms. Self-emulsifying drug delivery systems (SEDDS) are relatively newer, lipid-based technological innovations with immense promise in enhancing the oral bioavailability of drugs. These formulations have been shown to reduce the slow and incomplete dissolution of a drug, facilitate the formation of its solubilized phase, increase the extent of its transportation via the intestinal lymphatic system, and bypass the P-gp efflux, thereby augmenting drug absorption from the GI tract.^{15,16} Figure 2 illustrates the lymphatic pathways through which these self-emulsifying formulations are known to carry the drug from the GI mucosa to systemic circulation. Recently, there has been a dramatic increase in the reporting of such lipid-based formulations in both published and patent literature worldwide.¹⁷⁻²² A quick glance at these reports affirms both the high versatility and success rate of the novel technology of these systems. Self-emulsifying formulations are isotropic mixtures of drug, lipids (natural or synthetic oils), and

emulsifiers (solid or liquid), usually with one or more hydrophilic co-solvents/co-emulsifiers.^{17,23} SEDDS is a broad term encompassing emulsions with a droplet size ranging from a few nanometers to several microns. Depending upon the size of globules, these emulsions are characterized as concentrated microemulsions, nanoemulsions, or pre-concentrates.²⁴

FIGURE 2.

The self-emulsifying formulations enhancing the oral bioavailability of drugs through lymphatic pathways bypassing the hepatic first-pass effect. microemulsified drug delivery system (SMEDDS) are formulations forming transparent microemulsions with an oil droplet size ranging between 100 and 250 nm. Self-nanoemulsified drug delivery system (SNEDDS) is relatively a recent term indicating formulations with a globule size less than 100 nm. Although several reviews have been written previously on the subject,^{23,25-29} the diversity of SEDDS and the number of drugs encapsulated in these carriers have since been augmented significantly, and this calls for an updated review.

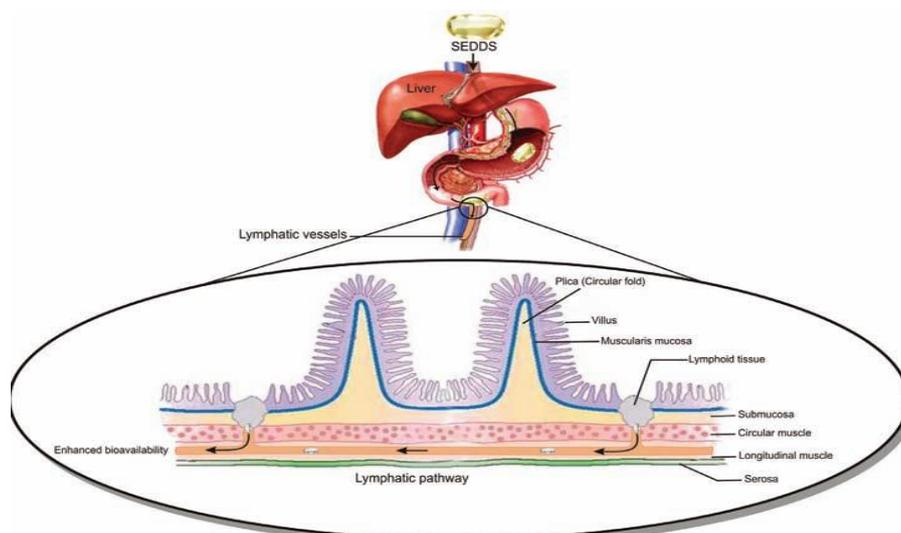


Figure 2: The self-emulsifying formulations enhancing the oral bioavailability of drugs through lymphatic pathways bypassing the hepatic first-pass effect.

I.A. Formulation Aspects

The SEDDS formulation forms a clear dispersion instantaneously in the GI tract that remains stable on dilution.³⁰ Such dispersions are either micro- or nanoemulsions, depending upon the globule size of the SEDDS formulation. A typical SEDDS formulation basically constitutes apt lipidic and emulsifying excipients having an inherent ability to solubilize the drug.³¹ As the release of a drug compound from SEDDS takes place in the GI tract, the hydrophobic agent should remain solubilized for at least the time period relevant

during GI absorption. Therefore, a typical SEDDS formulation also contains a co-emulsifier in addition to the essential lipid and emulsifier.³²⁻³⁴ Figure 3 illustrates the usual methodology pathways to prepare SEDDS formulations and the eventual formation of the micro-/nano emulsions following their dilution. These SEDDS have to be ultimately formulated as an oral solution in soft gelatin capsules or as solid dosage forms in hard gelatin capsules, depending on the final physical nature of the system as liquid or semisolid/solid, respectively.

FIGURE 3.

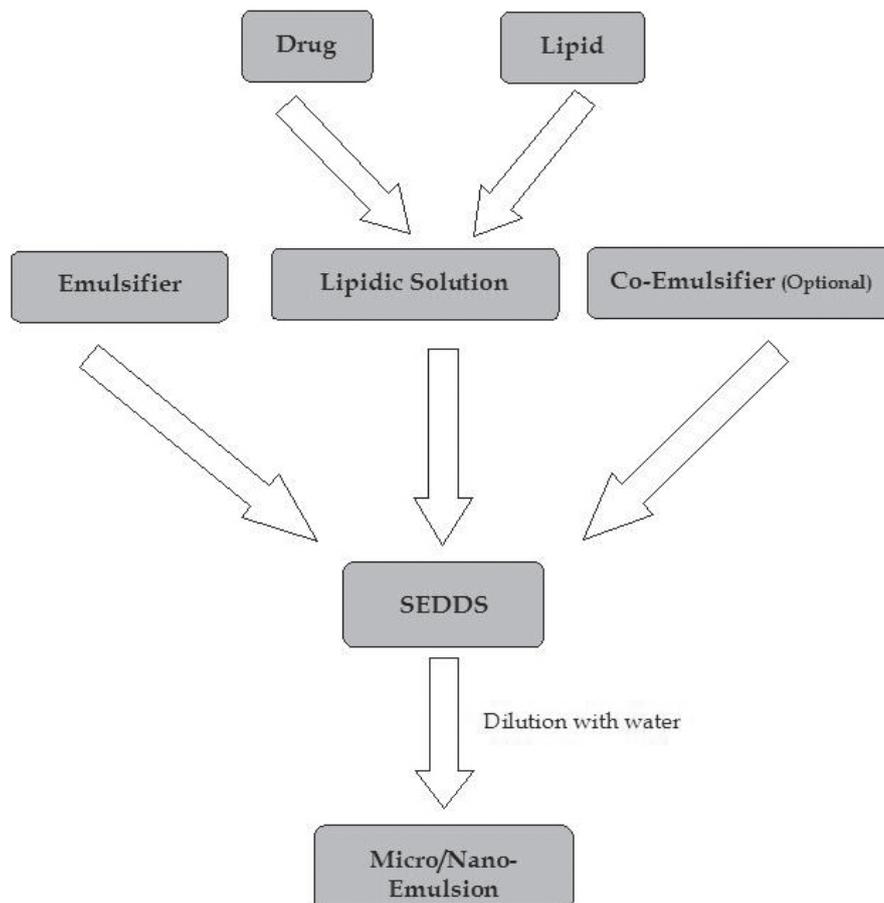


Figure 3: Schematic flowchart on the general strategy of formulating self-emulsifying systems and their subsequent conversion to micro/nano emulsions.

Depending upon the relative proportions of lipidic triglycerides, water-soluble or water-insoluble surfactant emulsifiers, and hydrophobic co-emulsifiers or co-solvents, the SEDDS have been classified as Type I, II, IIIA, IIIB, and IV.²⁷ Barring Type I, which contains B. Singh et al. only mixtures of lipidic constituents, but without surfactants and co-surfactants, all of the SEDDS formulations tend to result in globule size in the nanometer ranges. While Type I is devoid of surfactants and co-surfactants, all of the rest of the categories contain different percentages of each of these constituents. Table 1 outlines the key features of each type of SEDDS. As is evident from the table, Type I SEDDS have been found to be of limited utility, as the

rate-governing phenomenon in determining their efficacy is lipid digestibility. This is particularly true when Type I SEDDS employ long-chain fatty acids. Type II to IV SEDDS are therefore better suited for the formulation of various kinds of drugs.

1. Lipids

Lipid is an essential component of SEDDS formulations. Not only can lipids solubilize marked amounts of lipophilic drugs and facilitate self-emulsification, but they also have the propensity to augment the fraction of drug transported via intestinal lymphatic system, thereby increasing its absorption from the GI tract.³⁵ Natural edible oils, comprised of medium-chain triglycerides are

not usually used owing to their poor ability to dissolve large amounts of lipophilic drugs. Modified long- and medium-chain triglyceride oils, with varying degrees of saturation or hydrolysis, have widely been used for the design and development of SEDDS formulations. These oils offer distinct formulative and physiological advantages, as their degradation products resemble that of the natural end-products of intestinal digestion.^{23,36,37} Of the vast list of these modified triglycerides, a list of the most important hydrogenated vegetable oils is presented in Table 2, along with their fatty acid composition and molecular structural features. Most of the mono-, di-, and triglycerides and their mixtures in varying proportions, with or without the fatty acid esters of propylene glycol, are available commercially in the purified form. Both unsaturated and saturated fatty acids have been widely employed in the formulation of lipidic systems. However, the SEDDS in particular are comprised of saturated fatty acids such as caproic, caprylic, capric, lauric, and myristic acid. One can make the appropriate choice of these by examining their composition, potential utilities, physical state, and hydrophilic-lipophilic balance (HLB). Table 3 provides a comprehensive account of most of such lipidic constituents, along with their characteristics, as gathered from various literature resources from journals and patents.⁴²⁻⁴⁴ These amphiphilic excipients are progressively and effectively replacing the conventional

2. Emulsifiers

Next to the lipids, the other most vital component of the SEDDS is an emulsifier. An emulsifier, invariably a surfactant, is obligatory to provide the essential emulsifying characteristics. Surfactants, being amphiphilic in nature, can dissolve (or solubilize) relatively high amounts of hydrophobic drug compounds. Emulsifiers from natural sources are regarded as much safer than synthetic ones. However, as the former possess only limited self-emulsification capacities, these are seldom employed for the formulation of SEDDS. The twin issues that govern the selection of a surfactant are its HLB and safety. The HLB of a surfactant provides important information on its potential utility in the formation of SEDDS. For imparting high self-emulsifying properties to the SEDDS formulation, the emulsifier should have a relatively high HLB (i.e., high hydrophilicity) for immediate formation of o/w droplets, and/or rapid spreading of the formulation in the aqueous media.^{26,49-51} This will keep the drug at the site of absorption for a relatively prolonged period of time for effective absorption, because the precipitation of drug compound within the GI lumen can be prevented.

The most widely recommended emulsifiers, which include nonionic surfactants with relatively high HLB values such as solid or liquid ethoxylated polyglycolized glycerides, polyoxyethylene (20) sorbitan monooleate (i.e., Tween 80), and poly(ethylene oxide)-poly(propylene oxide), block copolymers such as Pluronic F127 Nonionic surfactants are also considered

to be safer than the ionic ones. Nonetheless, the former may cause reversible change(s) in the permeability of intestinal lumen. Following the selection of safe and effective surfactants, it becomes important to explore their

3. Co-solvents

Co-solvents, such as ethanol, propylene glycol, and PEG, are also commonly required to enable the dissolution of a large quantity of hydrophilic surfactant(s) in SEDDS. Table 5 lists co-emulsifiers/ co-solvents commonly employed in SEDDS formulations. Lipid mixtures with higher surfactant/oil or co-surfactant/oil ratios lead to the formation of SMEDDS.^{45,66} However, co-solvents have a serious limitation of becoming evaporated from the shells of sealed gelatin capsules, leading eventually to the precipitation of drug inside the shell. Newer co-solvents such as Transcutol™ and Glycofurol™ have several stellar advantages over traditional ones, including better stability and less volatility.

II. SPECIAL TYPES OF SEDDS FORMULATION

II.A. Supersaturable SEDDS

The high levels of surfactant typically present in SEDDS formulations can lead to severe GI side-effects. Therefore, a new class of SEDDS formulations, supersaturable SEDDS (S-SEDDS) has been designed to reduce the amount of surfactant by incorporating a water-soluble polymeric precipitation inhibitor (PPI).⁷⁴ Such formulations have been developed specifically to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs.⁷⁵⁻⁷⁷ The system is intended to generate and maintain a metastable supersaturated state *in vivo* by preventing or minimizing the precipitation of the drug through the use of a suitable PPI. Supersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit, resulting in an increased driving force for transit into and across the biological barrier.⁷⁸ The S-SEDDS formulations have been demonstrated to improve both the rate and extent of the oral absorption of poorly water-soluble drugs quite effectively.^{74,79,80} The inclusion of cellulosic polymers in the S-SEDDS formulation tends to effectively suppress the precipitation of drugs.⁷⁵ Various viscosity grades of hydroxypropyl methylcellulose (HPMC) are well-recognized for their ability to inhibit crystallization, and thereby their ability to generate and maintain their supersaturated state for extended time periods.⁸¹⁻⁸³ *In vitro* dilution of the S-SEDDS formulation results in the formation of a microemulsion, followed by slow crystallization of the drug on standing, indicating that the supersaturated state of the system is prolonged by HPMC in the formulations. In the absence of HPMC, the SEDDS formulation undergoes rapid precipitation, yielding a lower drug concentration.⁷⁴ The comparative *in vitro* studies¹⁵³ have indicated that the presence of a small amount HPMC in the formulation is critical to achieving a stabilized supersaturated state of drug upon mixing with water. Applying the S-SEDDS approach, a reduced amount of surfactant is deliberately

used with HPMC in order to produce a temporarily supersaturated state with reduced solubilization.⁷⁴ This is done to obtain a high free drug concentration through generating and maintaining a supersaturated state *in vivo* and to increase the driving force for absorption.⁷⁷ It is worth emphasizing that the significantly reduced amount of surfactant used in the S-SEDDS formulation approach significantly

I.B. Solid SEDDS

SEDDS are usually prepared in liquid form, and therefore have to be administered in a soft gelatin capsules, resulting in higher production costs and lower stability, lower portability, and lower drug loading.¹⁵⁷ This problem led to the development of solid SEDDS, which combine the advantages of conventional 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, and better patient compliance). The solid SEDDS focus on the incorporation of liquid/semisolid ingredients into powders, employing diverse solidification techniques such as spray drying,^{158,159} melt granulation,^{160,161} molding,¹⁰⁹ melt extrusion,^{162,163} and nanoparticle technology.¹²⁶ The Self-Emulsifying Drug Delivery Systems powders can then be formulated as solid dosage forms^{28,164} such as self-emulsifying tablets^{109,147,165} and self-emulsifying pellets.^{108,163,166} Alternative approaches for the development of solid SEDDS include adsorption by solid carriers such as microcrystalline cellulose,^{108,158} colloidal silica,¹⁶⁷ and various viscosity grades of HPMC,^{168,169} and the use of high-melting-point solid excipients such as Lutrol® and Gelucire®.⁴⁶ The idea of blending the advantages of SEDDS with those of pellets through the inclusion of a self-emulsifying mixture into micro crystalline cellulose, and the production of pellets using extrusion spherization, was first introduced by Newton et al. in 2001.¹⁷¹ Table 10 lists various studies on solid SEDDS formulations and their respective compositions. Postulating it as a platform technology for poorly soluble drugs, Bansal et al. in 2008¹⁷² highlighted various aspects of solid SEDDS, especially their formulation constituents. As melt extrusion/ extrusion spherization is a solvent-free process allowing high drug loading and content uniformity, it has been most extensively employed for solidification of SEDDS. Lesser used methods include spray drying and molding.

II.C. SEDDS for Traditional Herbal Medicine

Long well-accepted in the mainstream of medical care throughout the Asian continent, traditional herbal drugs are now considered as alternative medicines in much of the western world too. The concepts of herbal medicines are well-defined in "Ayurveda,"^{173,174} Chinese practice,^{175,176} and "Unani" systems of medicine. Nevertheless, the absorption of many active phytochemical constituents from these traditional herbs, such as *Cardus marianus* (silybin) and *Curcuma*

zedoaria (turmeric), have been reported to be ineffective. Therefore, several studies have been undertaken to formulate the self-emulsifying systems of vital constituents of such herbs to attain the desired objectives. Table 11 provides a brief account of these reports.

II.D. Positively Charged SEDDS

Many physiological studies have proven that the apical potential of absorptive cells, as well as that of all other cells in the body, is negatively charged with respect to the mucosal solution in the lumen.^{63,177-179} The drug exposure of the positively charged SEDDS has been found to be higher than conventional formulations, especially for bioavailability enhancement. More recently, it has been shown that

CONCLUSIONS

The prevalence of a strong relationship between the pharmacophore lipophilicity and its pharmacodynamic activity has led to the discovery of new chemical entities, most of which are inadequately soluble in aqueous fluids. Continued reliance on combinatorial chemistry and high-throughput processing is likely to bring forth majority of such new chemical entities, which fail on solubility and/or dissolution fronts. The standard formulation manipulations aiming at bioavailability enhancement, such as inclusion complexes, supersaturated systems, and micronization, have been usually found to be ineffective, not pragmatic, or inadequate for the purpose. Self-emulsifying formulations, which allow better formulation versatility and characterization of lipidic excipients, offer a viable alternative to serve the desired purpose through physicochemical and physiological mechanisms controlling drug absorption. In addition to enhancing the solubility of poorly soluble drugs, SEDDS also improve drug bioavailability by a number of other possible pathways; for example, bypassing the hepatic first-pass effect, inhibition of P-gp efflux, and resistance to metabolism by the cytochrome P450 family of enzymes within the gut and liver. The miniscule globule size of SEDDS, coupled with their surface activity, enables more efficient drug transport through the intestinal boundary layer and absorptive brush border membranes, resulting eventually in a more rapid onset and extended duration of therapeutic action. Further, less susceptibility of SEDDS to gastric emptying delays and lipolysis in the GI tract, as well as their high thermodynamic stability and robustness to dilution, thus keeping the drug in a solubilized state during the absorption phase, also reduces variability in bioavailability. To date, no other DDS can match the bioavailability enhancement potential of these self-emulsifying formulations.

Apart from the technological versatility of the SEDDS in employing different drugs, processes, and excipients, these formulations are also quite favorable for federal acceptance, because they qualify as GRAS excipients during their manufacture. Furthermore, the ease of their scale-up tends to reduce the burden of technology

transfer from laboratory to industry-sized batches. Like any other drug-delivery technology, there have been barriers to the practical applications of SEDDS formulations. Because of these barriers, the so-called “improved bioavailability” drug-delivery products that have been introduced into the market lately mostly consist of conventional products rather than SEDDS. No doubt, the number of publications, patents, and technologies on SEDDS are increasing at a steady pace. However, considerable skepticism and apathy tend to fuel the reluctance to undertake research into this relatively novel and more useful SEDDS approach. Now is the most opportune time to intensify research efforts on these promising drug delivery systems directed at surmounting the solubility and stability issues, improving production methodologies on industrial scale, and refinement of *in vitro* as well as *in vivo* models for more dependable prognosis of formulation performance in humans. This paper is an attempt by the authors to provide a holistic overview of all of the vital characteristics of these self-emulsifying formulations. It is hoped that this will provide the desired impetus to product development scientists, facilitating further evolution of SEDDS research and next-generation product launches. The day is not far off when the benefits of these self-emulsifying formulations will be realized and used by the drug industry and research groups to their fullest advantage.

ABBREVIATIONS

SEDDS

Self-emulsifying drug-delivery system S-SEDDS
supersaturable SEDDSB. Singh et al.

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