

Self-Emulsifying Drug Delivery Systems (SEDDS) for Oral Delivery of Lipid Based Formulations - A Review

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Abstract: More than 60% of drugs have lipophilic nature and exhibit poor water-solubility. The dissolution is the rate limiting step in their absorption and oral bioavailability. To overcome this problem one approach to enhance dissolution is Self-Dispersing Lipid Formulations (SDLFs). Generally, an emulsified dosage form is rapidly absorbable; therefore, it makes sure that a poorly water-soluble drug is rapidly transported into the circulation. SDLFs consist of a mixture of oil and surfactant, in which active drug moiety is incorporated. They get emulsified under conditions of gentle agitation, similar to those which would be encountered in the gastrointestinal tract on mixing with biological fluids. In this review article introduction, advantages and uses of SDLFs to enhance the dissolution and oral bioavailability are overviewed.

Key words: Self-Emulsifying Drug Delivery Systems • Poorly Water-Soluble Drugs • Bioavailability • Dissolution

INTRODUCTION

Oral delivery of solid dosage form of lipophilic drug compounds is obstructed due to their hydrophobicity [1- 3]. Therefore, generating proper formulations for such drugs is extremely important, that improves dissolution/solubility and oral bioavailability. One of the most famous and commercially viable formulation approaches to solve out these problems is SDLFs [4, 5]. SDLFs, surfactant dispersions, solid lipid nanoparticles, liposomes, emulsions and oils are various lipid based formulations. In various studies, it is reported that SDLFs improve the oral bioavailability of lipophilic and poorly water-soluble drugs [3]. There are two types of SDLFs which includes Self-Emulsifying Drug Delivery Systems (SEDDS) and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS). SEDDS are formulated by utilizing surfactants having HLB value less than 12 whereas SMEDDS are formed by surfactants of HLB greater than 12 [6]. Both formulations are stable preparations and promise to enhance the dissolution of drug, because more surface area is provided on dispersion. SEDDS are isotropic combination of drug, lipid/oil, cosolvents and surfactants [3, 7]. On dilution by an aqueous phase they form fine stable oil-in-water (o/w) emulsions or fine lipid

droplets which is the characteristic feature of these systems. When such a formulation is released into the lumen of the GIT, it disperses to form a fine emulsion generally o/w emulsion, so that the hydrophobic drug get remain in solution in the GIT which avoids the dissolution step. As we know dissolution step is the rate limiting step in the absorption of poorly water-soluble drugs [8]. Generally this can lead to enhanced bioavailability, so that an additional constant temporal profile of absorption from the gut. To achieve self-emulsification there is need of ultra-low oil-water interfacial tension. The mechanism of self-emulsification is specific to a particular oil and surfactant. Additionally, it also depends upon the amount of surfactant and oil and the temperature at which self-emulsification take place [6, 9- 11]. The factors on which self-emulsification depends include various related parameters, such as droplet size, charge, polarity of emulsion, temperature, type of oil/surfactant and their quantity. The amount of drug incorporated in SEDDS depends on compatibility of drug with excipients [3, 12]. SEDDS are generally formulated by triglyceride oils and ethoxylated nonionic surfactants. In general, the concentration of surfactant is greater than 25% in the formulation. The size of droplets ranges approximately less than 100 nm. SEDDS are prepared in two forms liquid

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and solid SEDDS (S-SEDDS). S-SEDDS are prepared by solidification of liquid self-emulsifying components into powder. This powder is then used to produce various solid dosage forms, for example self-emulsifying pellets, self-emulsifying tablets etc [13- 16]. S-SEDDS do not suffer with the problems like liquid SEDDS (L-SEDDS). It has the advantages like low manufacturing cost, more stability and is more patient compliance, because they are available as solid dosage form in tablets or pellet form. In many studies it have been reported that SEDDS are used for delivering and targeting hydrophobic drugs such as coenzyme Q10, halofantrine, vitamin E and cyclosporine-A [17-20]. Charman *et al.*, prepared a SEDDS of WIN 54954, a lipophilic compound. They used non-ionic surfactant and a medium chain triglyceride. They observed the formulation shown self- emulsification in aqueous medium (0.1 N HCl at 37°C). The droplet size of dispersion was less than 3 microns. They have also studied the various pharmacokinetic parameters for SEDDS [5]. Abdalla *et al.*, developed a pellet based SEDDS. They used selected progesterone as a model drug. They employed a mixture of medium chain glycerides and Solutol® HS 15 as lipids. The pellets were prepared from L-SEDDS by mixing with microcrystalline cellulose and finally passing through extrusion. They concluded that, extrusion is a suitable process to formulate S-SEDDS [21]. Tang *et al.*, prepared a microemulsion for silybin derivative. Silybin is a component of *Carduus marianus* and have low water solubility. They employed ethyl linoleate and Miglyol 812 as oils and tween 20 as surfactant. They also used co-surfactant (dimethyl isosorbide) and an anti-oxidant (D-tocopherol). The prepared formulation showed an increase in level of oral bioavailability of silybin as compared to the conventional formulations [22].

Advantages of SDLFS: There are the following advantages of SDLFs [5- 7]:

- It acts as substitute for traditional oral formulations of lipophilic drugs.
- It enhances the dissolution rate and hence, bioavailability of hydrophobic drugs.
- It provides better consistent temporal profiles of drug absorption.
- It helps in selective drug targeting toward a specific site in the GI tract.
- It protects drug molecule from the hostile environment of GIT.

Disadvantages of SEDDS: The various disadvantages of SEDDS include [4-7]:

- Due to presence of high surfactant concentrations there may be chances of instabilities of drugs.
- Also the high content of surfactant in self-emulsifying formulations irritates the gastrointestinal tract. This problem may be avoided by utilizing optimum less amount of surfactants.
- Sometime co-solvents remain into the formulation and cause degradation of drugs.
- It may allow less drug loading.

A new class of supersaturable SEDDS formulations can be used to reduce the surfactant side-effects and to achieve rapid absorption of poorly water-soluble drugs. The supersaturable SEDDS formulations contain less amount of surfactant and a polymeric precipitation inhibitor to stabilize a drug in a temporarily supersaturated state. Hydroxypropyl methylcellulose (HPMC) and related cellulose polymers are used widely to inhibit crystallization and therefore, maintain the supersaturated state for long time [22].

Composition of SEDDS: The SEDDS is commonly composed of the following:

Drugs: Generally, SEDDS are prepared for drugs possessing poor water-solubility. BCS class II drugs are usually employed in preparation of SEDDS. Examples of drugs which belong to BCS class II include itraconazole, nifedipine, vitamin E, simvastatin, danazol, ketoconazole, mefenamic acid, naproxen, carbamazepine [23].

Surfactant: Surfactants are having amphiphilic character. They help in solubilisation of lipophilic drug compounds. In GI lumen, this prevents precipitation of drug. So that the drug exists in lumen for prolonged time. Nonionic surfactants possessing high HLB value are widely employed. The role of surfactant is to enhance absorption of drug, because of induction of permeation changes in biological membrane. It is reported that a cationic emulsion show greater absorption than an anionic emulsion. To form a stable SEDDS, 30-60% concentration of surfactant is used [4].

Lipid/Oils: Vegetable oil, mineral oil, lanolin, silicon oil, fatty acids, animal oil etc are utilized in SEDDS. Mono-/di-/tri-glycerides are widely used in SEDDS formulation because they enhance the dissolution rate of drug in the intestinal medium. It is also to be assumed that

this glyceride form a droplet which carry drug, so that the metabolism of drug is protected. Polyethylene glycol and polyglycolized glycerides in along with vegetable oils have been utilized to solubilise lipophilic drugs. Galactolipids show good emulsifying properties, similar to those of phospholipids. The main difference between phospholipids and galactolipids include the former possess charge, while later is non-ionic and regarded as being safe for long-term use [22].

Co-Solvents: Various organic solvents are used as co-solvents such as ethanol, propylene glycol and polyethylene glycol, which may help to dissolve large amounts of drug in liquid base. An aqueous solvent such as glyceryl triacetate or Triacetin, (an acetylated derivative of glycerol) act as co-solvent and is widely used.

Viscosity enhancers: The viscosity of the emulsions can be altered by the use of additional material such as acetyl alcohol, tragacanth, beeswax and stearic acids etc.

Polymers: Polymer matrix (inert) present in 5 to 40% w/w, which is not ionizable at physiological pH and able to form matrix. Examples are hydroxyl propyl methyl cellulose, ethyl cellulose, etc.

Evaluation Parameters: There are various evaluation parameters performed on SEDDS which include the following:

- Determination of particle size distributions in emulsions is done by using a laser diffraction sizer [5]. Size of the emulsion droplet is very important factor in self emulsification/dispersion performance; because the rate and extent of drug release is depend on it [24, 25]. For the determination of mean particle size for such system Coulter nanosizer, can be used. It provides a comparative measure of mean particle size. This technique is suitable for the systems having particle size range is less than 3µm [24].
- Visual detection provides information about the resulting dispersion [24, 26]. Measurement of turbidity by nephelometer is used to recognize the efficiency of self emulsifying ability of formulation [24].
- Polarity of droplet is important characteristics for an emulsion. Polarity of the oil droplets is determined by oil/water partition coefficient [24].

- *In vitro* dissolution studies are carried out for SEDDS. Determination of the enhanced dissolution rate is shown by the emulsion [24].

Techniques to convert L-SEDDS into S-SEDDS: There are various techniques used for this purpose and some of them are mention in given below this Table [4, 27- 30]:

Technique	Description	Benefits
Spray drying	Spray drying of mixture containing lipids, solid carriers, surfactants and drug.	Simple
Capsule filling	Liquids and semisolid self-emulsifying system are filled into the capsules.	Simple manufacturing and suitable for low-dose drugs
Direct adsorption on carrier	L-SEDDS adsorb on solid carrier	Provide good drug content uniformity and simpler approach
Melt extrusion	Raw material is forced through a die to produce a uniform shape product.	Allow high drug loading

CONCLUSION

SEDDS seems to be novel and hence its use can be followed in industry to fasten the oral bioavailability of the lipophilic drugs. Since the absorption of BCS class II drugs oral absorption is increased by applying SEDDS, we can suggest it as one of the methods for increasing oral bioavailability of drugs.

Future Prospective: SEDDS will be a promising approach for the formulation of lipophilic drugs. Since the development of SEDDS is hypothetical therefore, the *in vitro* models used for the determination of oral bioavailability enhancement have to be designed. Care has to be exercised to maintain the quality and stability of drugs inside lipid systems. Any incompatibility between the components of capsules shells and the lipid systems will have to be evaluated. Despite of these challenges there is great prospect in the use of lipid formulation. Conductance of human bioavailability studies should be the priority for future research and more emphasis should be given towards the studies on the mechanisms of action of this type of SEDDS formulations. *In vitro* procedures for finding the dynamic changes occurring with the drug in the gut the status of solubilisation state of the drug *in vivo* shall have to be monitored.

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