Recent Advances in Self-Emulsifying Drug Delivery Systems

Amol S. Deshmukh*

Department of Pharmaceutics, S.M.B.T. College of Pharmacy, Nandi Hills, Dhamangaon, Nashik, India.

ABSTRACT

Oral route has always been preferred route for formulators and has dominated over other routes of administrations. But major problem encountered in oral formulations (as estimated more than 50% of oral formulations are found to be poorly aqueous soluble), is low bioavailability, giving rise to further problems like, high inter and intra subject variability, lack of dose uniformity and finally leading to therapeutic failure. Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. Particularly for BCS class II substances, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. The newer and novel technologies developed in recent year for troubleshooting such above problems. This review describes an overview of SEDDS as a capable approach to effectively capture the problem of poorly soluble molecules and give the novel approaches for evaluation of the SEDDS. Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers.

KEYWORDS: Self-emulsifying delivery system; solvent; surfactant; cosurfactant.

Introduction

The oral route is the preferred route for chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties. For this class of compounds, defined by Amidon et al., as low solubility/high permeability class II, dissolution in the environmental lumen is the rate controlling step in the absorption process. Efforts are ongoing to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles, such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposomes, with every formulation approach having its special advantages and limitations. Self-emulsifying drug delivery systems (SEDDS) 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 aqueous phase under gentle agitation (Patel et al., 2008). Poor aqueous solubility of lipophilic drugs creates problems in formulation as well as in oral administration. Various approaches have been developed to resolve poor aqueous solubility of lipophilic drugs. As oral route for drug administration is most commonly used among all the routes of administration due to its convenience, non-invasiveness and cost effectiveness it become necessary that drug should have some aqueous as well as some lipid solubility for their absorption (Goyal et al., 2012). The most popular approach is the incorporation of the active lipophilic component into inert lipid vehicles, such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposomes, with every formulation approach having its special advantages and limitations. Efficacy of lipophilic drug is often hindered due to their poor aqueous solubility leading to low absorption after in vivo administration (Sharma et al., 2013). The spontaneous formation of emulsion advantageously presents the drug in a dissolved form, and the resultant small droplet size provides a large interfacial surface area. These characteristics result in faster drug release from emulsion in a reproducible manner. Both system, SEDDS (droplet sizes of 200 nm – 5 mm) and SMEDDS (droplet size <100 nm) are associated with the generation of large surface area dispersions that provide optimum conditions for the increased absorption of poorly soluble drugs (Bhupindar et al., 2013). These systems form homogeneous, transparent/translucent, isotropic and thermodynamically stable microemulsion upon dispersion in aqueous media with oil droplet sizes of less than 50 nm (Ingle et al., 2013). When the mixture of drug, oil and a surfactant comes in contact with the aqueous environment in GIT they form an emulsion under gentle agitation provided by digestive motility of stomach and intestine which is necessary for self-emulsification in-vivo. Once an emulsion is formed then the drug is quickly distributed throughout the GIT as fine droplets, due to this dispersion and large surface area of fine droplets the bioavailability of drug enhanced. Presence of surfactant also influences absorption due to membrane induced permeation changes. The mechanism of self-emulsification is specific for parameters like, pair
of oil and surfactant, type and concentration of surfactant, oil:surfactant ratio, and temperature at which self-emulsification occur. Since the drug delivery should be biocompatible so the selection of excipient used in formulation is very important (Gupta et al., 2009; Kyatanwar et al., 2010).

**Biopharmaceutical Classification System**

Drug bioavailability prediction relies on the principles originally laid down in the Biopharmaceutical Classification Scheme. In the initial phase, combinations of solubility testing and *in-vitro* transport studies are typically employed as a prognostic tool to predict oral absorption. At later stages *in vitro* dissolution testing as well as other permeation approaches are often added to the tool-box (Buckley et al., 2013). The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. When combined with the *in vitro* dissolution characteristics of the drug product, the BCS takes into account three major factors: solubility, intestinal permeability and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid oral-dosage forms. It classifies drugs into four classes (Fig. 1).

<table>
<thead>
<tr>
<th>Permeability</th>
<th>Solubility</th>
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<td>High</td>
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<td>Low</td>
<td>II</td>
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![Fig. 1 Biopharmaceutical classification system.](image)

Poorly water soluble drug candidates often emerge from contemporary drug discovery programs, and present formulators with considerable technical challenges (Goldberg et al., 1966; Deshmukh et al., 2014). A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption.

**Advantages**

1. Enhanced oral bioavailability enabling reduction in dose.
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. Protective of sensitive drug substances.
8. High drug payloads.
9. Liquid or solid dosage forms (Asija et al., 2014).

**Advantages of SEDDS over conventional drug delivery system**

Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these system can form fine oil in water (o/w) emulsion or microemulsion (S(M)EDDS). Fine oil droplets would pass rapidly wide distribution of the drug through the stomach and promote wide distribution of the drug throughout the GI tract, there by minimizing the irritation frequently encounter red during extended contact between bulk drug substance and the gut wall.

Emulsions are sensitive and metastable dispersed forms while S(M)EDDS are physically stable formulation those are easy to manufacture.

As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water (Bhupindar et al., 2013).

**Why SEDDS are needed**

SEDDS are promising approach for oral delivery of poorly water-soluble compounds. It can be achieved by pre-dissolving the compound in a suitable solvent and fill the formulation into capsules. The oral drug delivery of hydrophobic drugs can be made possible by SEDDS. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g., polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets (Amidon et al., 1995).

**Composition of SEDDS**

The self-emulsifying process is depends on:

1. The nature of the oil-surfactant pair
2. The surfactant concentration

**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, ketocnazole, mefanimic acid, carbamazepine, glibenclamide, cyclosporine-A, ritonavir etc. (Asija et al., 2014).

**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 SEDDS owing to their formulation and physiological advantages. Novel semisynthetic medium-chain
triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride (Mishra and Srivastava, 2009).

Following are some frequently used oil ingredients for SEDDS formulation:

- Corn oil
- Mono, di, tri-glycerides
- DL-alpha-Tocopherol
- Fractionated triglyceride of coconut oil
- Fractionated triglyceride of palm seed oil
- Mixture of mono-and di-glycerides of caprylic/capric acid
- Medium chain mono-and di-glycerides
- Corn oil
- Olive oil
- Oleic acid
- Sesame oil
- Hydrogenated soyabean oil
- Hydrogenated vegetable oils
- Soyabean oil
- Peanut oil
- Beeswax (Patel et al., 2011).

**Surfactant**

Numerous compounds exhibiting surfactant properties might be working for the design of self-emulsifying systems, but the choice is limited at the same time as very few surfactants are orally suitable, because safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactant. The most extensively suggested ones being the non-ionic surfactants with a relatively high hydrophilic lipophilic balance (HLB) (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The strength of surfactant usually ranges between 30-60% w/w of the formulation for the formation of stable SEDDS. Surfactants contain high HLB and hydrophilicity, which assists the instantaneous formation of o/w droplets and fast dispersion of the formulation in the aqueous media. Amphiphilic surfactants can solubilize the high amounts of hydrophobic drug compounds. This can be able to prevent precipitation of the drug inside the GI lumen and for protracted continuation of drug molecules (Sunittha et al., 2011).

**Co-surfactant**

In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formation of micro emulsion (Bose and Kulkarni, 2002). Examples of co-surfactants are as mentioned below:

- Poly oxyethylated glycerides (Labrafil M 2125 Cs)
- Poly oxyethylated oleic glycerides (Labrafil M 1944 Cs)
- D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS).

**Co-solvent**

Organic solvents are suitable for oral administration. Examples are ethanol, propylene glycol and polyethylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid base. Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents act as co-solvents. Triacetin is suitable since it is miscible in the oil lipid phases and it can be used to solubilize a hydrophobic drug. Examples of co-solvents are:

- Ethanol
- Glycerin
- Polypropylene glycol
- Polyethylene glycol

**Consistency builder**

Additional material can be added to alter the consistency of the emulsions; such materials include tragacanth, cetyl alcohol, stearic acids and/or beeswax.

**Polymer**

Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionizable at physiological pH and being capable of forming matrix are used. Examples are hydroxy propyl methyl cellulose, ethyl cellulose, etc. (Asija et al., 2014; Patel et al., 2011).

**Formulation of SEDDS**

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble cosolvents, 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. The following should be considered in the formulation of a SEDDS: The solubility of the drug in different oil, surfactants and cosolvents. The selection of oil, surfactant and cosolvent based on the solubility of the drug and the preparation of the phase diagram. The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and cosolvent. 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 (Mishra and Srivastava, 2009).

**Mechanism of Self-Emulsification**

The theory of formation of emulsion shows that emulsification occurs when the entropy change for dispersion, is greater than energy required to increase the surface area of the dispersion and the free energy (AG) is negative (Muranishi et al., 1980). The free energy in the emulsion formation, is directly proportional to the
energy required to create new surface between the two desired phases and can be described by the equation (1) 

$$\Delta G = \sum N \pi r^2 \sigma \quad \text{(1)}$$

where, $\Delta G$ is the free energy associated with the process, $N$ is the number of droplets of radius $r$ and $\sigma$ represents the interfacial energy.

After a certain time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. To stabilize emulsions, emulsifying agents are added which reduces the interfacial energy, as well as provide a barrier to prevent coalescence (Dangi et al., 2011).

**Evaluation of SEDDS**

1. **Thermodynamic stability studies heating cooling cycle:** Six cycles between refrigerator temperature 4°C and 45°C with storage at each temperature of not less than 48 hr is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test. **Centrifugation:** Passed formulations are centrifuged thaw cycles between 21°C and 25°C with storage at each temperature for not less than 48 hr is done at 3500 rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze thaw stress test.

2. **Dispersibility test:** The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP dissolution apparatus II. One milliliter of each formulation is added to 500 mL of water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provides gentle agitation. The *in vitro* performance of the formulations is visually assessed using the following grading system:

   **Grade A:** Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

   **Grade B:** Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

   **Grade C:** Fine milky emulsion that formed within 2 min.

   **Grade D:** Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

   **Grade E:** Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

3. **Viscosity determination:** The rheological properties of the micro emulsion are evaluated by Brook field viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosities then it are w/o type of the system.

4. **Turbidimetric evaluation:** Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of self-emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter.

5. **Droplet size analysis particle size:** Measurements of the droplet size of the emulsions is determined by photon correlation spectroscopy using a Zeta sizer able to measure sizes between 10 and 5000 nm.

6. **Refractive index and percent transmittance:** Refractive index and percent transmittance proved the transparency of formulation. The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank.

7. **Drug content:** Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is analyzed by suitable analytical method against the standard solvent solution of drug (Bhupindar et al., 2013).

**Conclusions**

Self-emulsifying drug delivery system in solid dosage form has improved solubility/dissolution, absorption and bioavailability for poorly water soluble drug. This is the method suited for lipophilic drugs where resulting emulsification gives faster dissolution rates and absorption. SEDDS is superior to other colloidal vehicle in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance.

**References**


Address correspondence to: Amol S. Deshmukh, Department of Pharmaceutics, S.M.B.T. College of Pharmacy, Nandi Hills, Dhamangaon, Nashik, India. Mob: 9371393020, 9689313020. E-mail: meamoldeshmukh@rediffmail.com