

## Review Article

# Solid Self Emulsifying Drug Delivery System: A Novel Approach

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### ABSTRACT

The new chemical entities discovered by the pharmaceutical industry up to 40% to 50% are poorly soluble or lipophilic compounds, which leads to poor oral bioavailability. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. Recently much attention has been paid to lipid based formulations with particular emphasis on self emulsifying drug delivery system (SEDDS), to improve the oral bioavailability of lipophilic drugs. Self emulsifying formulations are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsion when introduced into aqueous phase under conditions of gentle agitation. The present review examines the recent advances in Solid SEDDS (S-SEDDS) with regard to the selection of lipid systems for current formulations, solidification techniques by adsorbing agents and the development of solid SE (self-emulsifying) dosage forms and their related problem.

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## INTRODUCTION:

Most of the new chemical entities and existing drug candidates display low water solubility, which leads to poor bioavailability, high intrasubject/intersubject variability and lack of dose proportionality. Thus the oral delivery of these low soluble drugs is hindered where dissolution is rate limiting step. The various strategies such as solid dispersions, complexation with cyclodextrin, lipid based formulations and self emulsifying drug delivery systems (SEDDS) have been reported in literature.<sup>1</sup> SEDDS are described as isotropic mixtures of oil, surfactant, co-surfactant and lipophilic drug. They form fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation. These are able to self emulsify rapidly in the gastrointestinal fluids, forming O/W emulsion. In such a system, the lipophilic drug is present in solution, in small droplets of oil that leads to increase surface area and hence increased absorption.<sup>2</sup> Traditional preparations of SEDDS are usually prepared in liquid state. So, the liquid SEDDS are enclosed in hard or soft capsule to facilitate oral administration, but it produces some disadvantages such as stability, incompatibility, drug leakage, precipitation and capsule ageing. The incorporation of SEDDS into solid dosage form is desirable but challenging. Adsorption to solid carriers is one of the techniques to form solid SEDDS. Free flowing powders may be obtained from liquid SEDDS by adsorption to solid carriers. The adsorption process is simple and involved addition of liquid formulation to carriers by mixing in a blender. The resulting powder then filled directly into capsules. A significant benefit of adsorbent technique is good content uniformity. SEDDS can be adsorbed at high levels up to 70%W/W on to suitable carriers.<sup>3</sup> Lipid formulations however may interact with the capsule resulting in either brittleness or softness of the shell. To overcome this problem SEDDS need to convert into solid SEDDS. Numerous reports states that, the major techniques for converting SEDDS to S-SEDDS are spray cooling, spray drying, adsorption onto solid carriers, melt granulation, melt extrusion, super-critical fluid based methods and high pressure homogenization. Out of all these processes the physical adsorption process is simple.<sup>4</sup>

## Advantages:

- High stability and reproducibility.
- Spontaneous formation and thermodynamic stability.
- Selective drug targeting toward a specific absorption window in the GI tract.
- Drug protection from the hostile environment in the gut.
- These systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles.<sup>5,6</sup>
- Reduced variability including food effects.<sup>7</sup>

## Disadvantages:

- In vitro in vivo correlations are responsible for further development; therefore development of different prototype lipid based formulations and in vivo testing in a suitable animal model are necessary.
- This system has different drawbacks such as instabilities of drugs, high concentration of surfactants in formulations (30-60%) which causes GIT irritation.
- Before evaluating the strength of SEDDS in in-vitro model, development and validation are needed.<sup>8</sup>

## Design of S-SEDDS formulation:

A series of SEDDS formulations were prepared using various oil, surfactant and co surfactant. In all formulations the level of drug is constant. The amount of SEDDS should be such that it should solubilise the drug completely. The drug added in mixture then the components mixed by gentle stirring and mixing and heated at 37°C. The mixture stored at room temperature until used. The liquid SEDDS is optimized and further converted into solid self emulsifying drug delivery system formulation.<sup>10</sup>

## Composition of solid SEDDS:

The composition of S-SEDDS is given in table 1.

## Solidification techniques for transforming liquid or semisolid SEDDS to S-SEDDS:

### 1. Capsule filling with liquid and semisolid SEDDS formulations:

Capsule filling is the simplest and most common technology for encapsulation of liquid or semisolid SEDDS formulation for oral route. The steps are given below:

- I] Heating of semisolid excipients at least 20°C above its melting point;  
 II] Incorporation of active substances with stirring;  
 III] Capsule filling with the molten mixture and cooling to room temperature.

For liquid formulations, it involves a two step process: filling of formulation into capsule followed by sealing of body and cap of the capsule, either by banding or by microspray sealing. Advantages of this technique are simplicity of manufacturing; suitable for low dose highly active drug and high drug loading potential up to 50% W/W.

**Table1: Examples of components of solid SEDDS.**

<b>Oil</b>	<b>Surfactants</b>	<b>Co surfactants</b>	<b>Adsorbents</b>
Cotten seed oil	Polysorbate 20	Ethanol	Neusilin US2
Corn oil	D- alpha tocopheryl polyethylene glycol 1000 succinate	Polyethylene glycol	Silicates
Soyabean oil	Polyoxyetylated glycerides	Polypropylene glycol	Lactose
F palm seed oil	Polyoxy-40-hydrogenated castor oil	Glycerine <sup>9</sup>	Cellulose
Olive oil	Polyoxy-35-hydrogenated castor oil		Fujicalin
Oleic acid	Sorbitan mono oleate		Silicon dioxide <sup>5</sup>

## 2. Adsorption to solid carriers:

Free flowing powders may be obtained from liquid SEDDS by adsorption to solid carriers. The adsorption process is simple and just involves addition of 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. The significant benefit of the adsorption technique is good content uniformity. 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, examples- silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose. Cross-linked polymers create a favourable environment to sustain drug dissolution. Nanoparticle adsorbents comprise porous silicon dioxide, carbon nanotubes, and carbon nanohorns<sup>12</sup>.

## 3. Spray drying:

In this technique first the prepared SEDDS formulation containing oil, surfactant, drug, solid carrier etc, is sprayed into a drying chamber through a nozzle. The volatile vehicles firstly evaporate leaving behind small solid particles. These particles are then filled into capsules or compressed into tablets<sup>13</sup>.

### Advantages:

- Spray drying process is very rapid.
- Offers high precision control over particle size, bulk density, and degree of crystallinity, organic volatile impurities and residual solvents.
- Powder quality remains constant during the entire run of the dryer. Nearly spherical particles can be produced, uniform in size.

### Disadvantages:

- The equipment is very bulky and with the ancillary equipment is expensive.
- The overall thermal efficiency is low<sup>14</sup>.

## 4. Supercritical fluid based method:

Lipids may be used in supercritical fluid based methods either for coating of drug particles or for producing solid dispersions. The coating process is subsequently facilitated by a gradual reduction in pressure and temperature leading to reduced solubility of the coating material in the supercritical fluid allowing gradual deposition onto the

drug particles, to form coating layers. The supercritical fluid of choice is supercritical carbon dioxide. The process for obtaining solid particles the dissolving drug and lipid based excipients in an organic solvent such as methanol and then in supercritical fluid followed by lowering the temperature. The important considerations with this formulation technique

- The solubility of the formulation components in the supercritical fluids.
- The integrity or stability of the active substance under the process conditions<sup>15</sup>.

#### **5. 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. A wide range of solid and semisolid lipids can be applied as meltable binders. These are Gelucire, PEG, lecithin polysorbates<sup>7</sup>.

#### **6. Extrusion sponization:**

Extrusion is a solvent free process that allows high drug loading up to 60%, as well as content uniformity. Extrusion is a procedure in which a raw material with plastic properties is converted 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 determines the approximate size of the resulting spheroids. The extrusion-sponization process is commonly used in the Pharma industry to make uniformly sized pellets. Applying extrusion-sponization, SE pellets of diazepam and bi-layered cohesive SE pellets have been prepared<sup>16</sup>.

#### **Dosage forms of S-SEDD:**

##### **1. Self emulsifying sustained release / controlled release:**

Combination of lipids and surfactant has been presented great potential preparing SE tablets. Inclusion of indomethacin for example into SE tablets may increase its penetration efficacy through GI mucosal membrane, potentially reducing GI bleeding.

##### **2. 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. Thus, it is very appealing to combine the advantages of pellet with those of SEDDS by SE pellets. Serratori et al. Prepared SE controlled release pellets by incorporating drugs into SES that enhanced their rate of release.<sup>17</sup>.

##### **3. Self emulsifying solid dispersions:**

Solid dispersions could increase the dissolution rate and bioavailability of poorly water soluble drugs but still some manufacturing difficulties and stability problems existed. Serajuddin pointed out that these difficulties.

##### **4. Topical delivery:**

Topical administration of drugs by SEDDS can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drugs and related toxicity effects.

##### **5. Oculars and pulmonary delivery:**

For the treatment of eye disease, drugs are essentially delivered topically o/w microemulsion have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile by SEDDS formulation.

##### **6. Parenteral delivery:**

Parenteral administration of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered as target site can be delivered by SEDDS<sup>18</sup>.

#### **EVALUATION OF S-SEDDS:**

##### **1. Turbidity measurement:**

This identifies the efficient self emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.

## 2. 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 are mainly used for the determination of the emulsion droplet size.

## 3. Visual assessment:

This may offer vital information regarding the self emulsification and micro emulsifying property of the mixture and the resulting dispersion.

## 4. Zeta potential measurement:

This is used to identify the charge of the droplets. In conventional SEDDS the charge on an oil droplet is negative due to the presence of free fatty acid.

## 5. Determination of emulsification time:

Self emulsification time, dispersibility appearance and flow ability determined and scored according to techniques described in H. Shen et al.<sup>19</sup>.

## 6. 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 test:

The passed formulations in above test 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 does not show any phase separation are taken for the freeze thaw stress test.

## 7. Dispersibility test:

The efficiency of self emulsification of oral Nano or microemulsion is assessed using a standard USP dissolution apparatus 2. One ml of each formulation is added to 500 ml of water at  $37 \pm 0.5^\circ\text{C}$ . A standard stainless steel dissolution paddle rotating at 50 rpm provides gentle agitation. The in vitro performance of formulations assessed by following system:

**Grade A:** Rapidly forming Emulsion having clear and bluish appearance.

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

**Grade C:** a fine milky emulsion formed.

**Grade D:** dull, greyish white emulsion having slightly oily appearance that is slow to emulsify.

**Grade E:** formulation that exhibits poor 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 Grade C could be recommended for SEDDS formulation<sup>20</sup>.

## 8. Refractive index and percentage transmittance:

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water. The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to water and formulation have percent transmittance > 99 percent, then formulation have transparent nature.

## 9. Electro conductivity study:

The SEDDS system contains ionic or non ionic surfactant, oil, and water. So, this test is used to measure the electro conductivity by electro conductometer<sup>21</sup>.

## 10. Solid state characterization of solid SEDDS:

Outer macroscopic structure of solid SEDDS can be investigated by scanning electron microscope. Physical state of drug in solid SEDDS must be investigated as it may affect drug release as well as bioavailability of drug. Differential scanning calorimetric method as well as X-Ray diffraction can be used for this purpose<sup>22</sup>.

### 11. Flow properties of liquisolid system:

The flow properties can be determined by angle of repose, Carrs index and hausners ratio. Angle of repose is defined as the maximum angle possible between the heaps of powder to its horizontal plane.

$$\tan \theta = h/r.$$

### 12. Bulk density:

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by filling the weighed powder into a measuring cylinder and the volume noted. It can be expressed in g/cm<sup>3</sup>:

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Volume of powder}}$$

### 13. Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume, the equation is represented with the unit g/cm<sup>3</sup>.

$$\text{Tapped density} = \frac{\text{Total mass of powder}}{\text{Tapped volume of powder}}$$

### 14. Angle of repose:

The angle of repose of solid SEDDS determined by funnel method. Accurately weighed sample taken in a funnel. Height of funnel adjusted in such a way that the tip of the funnel just touches the apex of the heap of S-SEDDS powder. The diameter of the powder cone measured by:

$$\tan \theta = h/r \quad \text{or} \quad \theta = \tan^{-1} h/r.$$

### 15. Carrs compressibility index:

Carr's compressibility index is a measure of powder flow properties and was calculated using the following equation:

$$\text{Carrs index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

### 16. Hausner ratio:

Hausners ratio is the ratio of tapped density to bulk density and can be calculated by <sup>23</sup>:

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

### 17. In vitro drug release from solid SEDDS:

Usually in vitro dissolution is used for determination of drug release from solid SEDDS formulation. USP-II type dissolution apparatus containing appropriate dissolution media should be used for conducting drug release study<sup>22</sup>.

### CONCLUSION:

From the above review conclude that SEDDS are one of the promising approaches for formulation of poorly soluble drugs. But these formulations have some problems to avoid these problems solid SEDDS are developed. Solid SEDDS improve solubility, stability, absorption, dissolution and bioavailability of poorly soluble drugs.

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