SELF EMULSIFYING DRUG DELIVERY SYSTEM: AN APPROACH TO IMPROVE THE SOLUBILITY OF POORLY WATER SOLUBLE DRUG

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ABSTRACT:

There are number of new drug candidates developing which has poor water solubility and the oral delivery of such drugs is frequently associated with implications of low bioavailability, high intra and inter-subject variability, and lack of dose proportionality. The solubility of such drug is increased by formulating self emulsifying drug delivery system. Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly water soluble drugs. SEDDS are mixtures of oils and surfactants, ideally isotropic, and sometimes containing cosolvents, which emulsify to produce fine oil-in-water emulsions upon gentle agitation. SEDDSs typically produce emulsions with a droplet size between 100–300 nm. 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. Purpose of this review article is to provide brief outline of self emulsifying drug delivery system & its potential to increase the bioavailability of poorly soluble drugs.

KEYWORDS: Self emulsifying drug delivery system, SEDDS, bioavailability, lipophilic, SMEDDS, SNEDDS.
INTRODUCTION

In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Upto 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which leads to poor oral bioavailability, high intra- and inter-subject variability, and lack of dose proportionality\(^1\). Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. There are several strategies to improve the bioavailability of poorly water soluble drug include the solubilization and surfactants, the use of different polymorphic/ amorphic drug forms, the reduction of drug particle size, the complexation (e.g., cyclodextrins) and the formation of solid drug solutions/dispersions\(^2,3\). For the therapeutic delivery of lipophilic active moieties (Class II drugs), lipid based formulations are inviting increasing attention\(^4\).

There are several techniques that increase the rate & extent of drug absorption.

1. By increasing the rate or extent of dissolution.
2. By facilitating the absorption process.

So to formulate a self emulsifying formulation these approaches are generally used\(^4\).

Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs\(^5\). Their solubilising and absorption promoting effect is thought to lay in the reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract. This bioavailability enhancing property has been associated with a number of in vivo properties of lipidic formulation including: the formation of fine dispersions and micellar suspensions, the ability of certain lipid compounds to initiate changes in the gastrointestinal fluid to favour improved drug absorption. Certain lipidic excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism in the liver\(^6\). SEDDS or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/ surfactants\(^6-10\). Fine oil droplets would pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substances and the gut wall\(^10\). The self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self-emulsification occurs. The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet\(^8\). When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture\(^10\). These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the
drug absorption. These characteristics result in faster drug release from emulsion in a reproducible manner, which can be designed further to make the release characteristics independent of the gastrointestinal physiology and the fed/fasted state of the patient. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm–5 mm and the dispersion has a turbid appearance.

Potential advantages of these systems include enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, and protection of drug(s) from the hostile environment in gut. Thus, for lipophilic drugs with dissolution-limited oral absorption, these systems may offer an improvement in the rate and extent of absorption and more reproducible plasma concentration profiles.

MERITS OF SEDDS

- **Improvement in oral bioavailability:** SEDDS is a novel approach to improve the water solubility and ultimately bioavailability of lipophilic drugs. The ability of SEDDS to present the drug to GIT in globule size between 1-100 nm and subsequent increase in specific area enables more efficient drug transport through the intestinal aqueous boundary layer leading to improvement in bioavailability.

- **Ease of manufacture and scale-up:** SEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing.

- **Reduction in inter-subject and intra-subject variability and food effects:** SEDDS offer reproducibility of plasma profile.

- **Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT:** One unique property that makes SEDDS superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis.

- **Fine oil droplets empty rapidly from the stomach and promote wide distribution of the drug throughout the intestinal tract and thereby minimizing irritation frequently associated with extended contact of drugs and gut wall.**

- **It provides prolonged release of medicaments after incorporation of polymer in the composition.**

COMPOSITION OF SEDDS

The self-emulsifying process depends on

- The nature of the oil–surfactant pair
- The surfactant concentration
- The temperature at which self-emulsification occurs.

**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 SEDDSs owing to their formulation and physiological advantages\textsuperscript{15}. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride\textsuperscript{20}.

**Surfactant:**

The choice of surfactants is limited as very few surfactants are orally acceptable. Nonionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules\textsuperscript{6}. The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited p-glycoprotein drug efflux\textsuperscript{15}.

**Co-solvents:**

Relatively high surfactant concentration (usually more than 30%w/w) is needed to produce an effective SEDDS. Cosolvents like diethylene glycol monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the microemulsification systems\textsuperscript{21}.

**MECHANISM OF SELF EMULSIFICATION**

The self emulsification takes place when the entropy change that favors dispersion is greater than energy required to increase the surface area of the dispersion\textsuperscript{14}. In self emulsifying system the interfacial tension is made sufficiently low that interfacial energy become comparable and lowers their entropy of dispersion and free energy of formation become zero or negative. Thus the main driving force of SSEF is ultra low interfacial tension, which is achieved by using two or more emulsifier in combination, but sometime single nonionic surfactant may work.

The ease of emulsification is suggested to be related to the ease of water penetration into various liquid crystal (LC) or gel phase formed on the surface of the droplet\textsuperscript{22-24}. The addition of binary mixture (nonionic surfactant/oil) water interface is formed between oil and continuous aqueous phase. This is followed by solubilization of water within oil phase as a result of aqueous penetration through interface. This will occur until the solubilization limit is reached close interphase which lead to dispersed LC phase so in the end all globule in close
proximity will be LC which mainly depend on surfactant concentration in binary mixture\textsuperscript{21}.

The presence of the drug may alter the emulsion characteristics, possibly by interacting with the liquid crystalline phase\textsuperscript{25}.

**FORMATION OF SEDDS**

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\textsuperscript{26}. The following should be considered in the formulation of a SEDDS.

- The solubility of the drug in different oil, surfactants and co-solvents (e.g. surfactants: Capmul\textsuperscript{®} GMO-50, Caprol, Poloxamer, Carbitol, Tween 80, & Oils: Castor oil, Lauroglycol, Miglyol 812, Myvacet, Labrafac)

- The selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram\textsuperscript{27}.

- The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and co-solvent.

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\textsuperscript{28}.

**APPLICATION**

SEDDS have potential uses as vehicles for the administration of lipophilic drugs. Some of them are mentioned in Table 1.

**CONCLUSION**

Self-emulsifying drug delivery system is a novel approach for the formulation of drug compounds with poor aqueous solubility. SEDDS represent a good alternative for the formulation of poorly water soluble drugs. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. By this approach it is possible to prolong the release of drug via incorporation of polymer in composition. SEDDS appears to be unique & industrially feasible approach. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.
Table 1: Application of SEDDS for delivery of various drugs

<table>
<thead>
<tr>
<th>Delivery system</th>
<th>Drug</th>
<th>Lipid used</th>
<th>Surfactant used</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEDDS</td>
<td>Griseofulvin</td>
<td>Myvacet</td>
<td>Capmul GMO-50</td>
<td>Increases in solubility due to the presence of hydrochloric acid&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
<tr>
<td>SEDDS</td>
<td>Puerarin</td>
<td>Oleic acid</td>
<td>Tween 80</td>
<td>Significant increase in bioavailability&lt;sup&gt;30&lt;/sup&gt;</td>
</tr>
<tr>
<td>SEDDS</td>
<td>Simvastatin</td>
<td>Lauroglycol: Captex (1:1)</td>
<td>Cremophor EL: Capmul MCM</td>
<td>Hypolipidemic activity is increased&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td>SMEDDS</td>
<td>Silymarin</td>
<td>Glyceryl monooleate</td>
<td>Polysorbate 20: HCO- 50 (1:1)</td>
<td>Bioavailability was 3-6 times higher than the reference capsule&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>SMEDDS</td>
<td>Fenofibrate</td>
<td>Labrafac CM10</td>
<td>Tween 80</td>
<td>Improvement in drug release&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td>SEDDS (gelled)</td>
<td>Ketoprofen</td>
<td>Captex 200</td>
<td>Tween 80</td>
<td>Silicon dioxide was used for the gelling agent. As the concentration of silicon dioxide increases, the droplet size of the emulsion increases and slows the drug diffusion&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>SMEDDS</td>
<td>Vinpocetin</td>
<td>Labrafac: oleic acid (40:10)</td>
<td>Cremophor EL</td>
<td>Improved bioavailability&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td>SNEDDS</td>
<td>Biphenyl dimethyl dicarboxylate</td>
<td>Miglyol 812</td>
<td>Tween 80</td>
<td>Significant improve in oral bioavailability as compared to commercial product&lt;sup&gt;36&lt;/sup&gt;</td>
</tr>
<tr>
<td>SMEDDS</td>
<td>Tacrolimus</td>
<td>Capmul MCM C8</td>
<td>Cremophor EL</td>
<td>Enhancement in pharmacological activity&lt;sup&gt;37&lt;/sup&gt;</td>
</tr>
<tr>
<td>SEDDS</td>
<td>Celecoxib</td>
<td>Capmul PG8</td>
<td>Tween 20</td>
<td>Improvement in bioavailability&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
<tr>
<td>SEDDS</td>
<td>Danazol</td>
<td>Soyabean oil: maisine</td>
<td>Cremophor EL</td>
<td>Decrease in lipid content reduces danazol bioavailability&lt;sup&gt;39&lt;/sup&gt;</td>
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<tr>
<td>SMEDDS</td>
<td>Exemestane</td>
<td>Capryol 90</td>
<td>Cremophor ELP, Transcutol HP</td>
<td>Dissolution is significantly increased&lt;sup&gt;40&lt;/sup&gt;</td>
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<tr>
<td>SMEDDS</td>
<td>Nimodipine</td>
<td>Gelucire 44/14</td>
<td>Labrasol</td>
<td>Improve the in vitro and in vivo performance of nimodipine&lt;sup&gt;41&lt;/sup&gt;</td>
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<tr>
<td>SMEDDS</td>
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<td>Vitamin E</td>
<td>DOC-Na, TPGS, Cremophor RH 40</td>
<td>Higher bioavailability&lt;sup&gt;42&lt;/sup&gt;</td>
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