SELF-EMULSIFYING DRUG DELIVERY SYSTEM: A NOVEL APPROACH

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ABSTRACT

Nowadays, a large number of research followed in pharmaceuticals field but the mainly problem arises due to the 35-40% of drugs have poor aqueous solubility problem. This lead various of interlink problems like low bioavailability, inter or intra variability issues etc. There are several of techniques used by the scientist to resolve this problem. Eg. Formulation of solid dispersion, by forms Salt of the molecule etc. SEDDS is the newer approach widely used to improve the solubility of lipophilic drugs. SEDDS are the isotropic mixtures of oils, surfactants, solvents and co-solvents. The micro or nano-size provide the benefit to easily pass through the lymphatic side and bypass the hepatic circulation and also improve the absorption at the gastro intestinal site. We exhausted the updated outcomes of following articles and patents to represent the mechanism of work by self emulsification method, The advantages of SMEDDDS over conventional emulsions are listed, optimization technique discussion like making of pseudo-ternary phase digram, Characterization techniques and marketed patent preparations.

INTRODUCTION

Patients and manufacturers alike accept oral formulas for treating a range of pathological conditions. As a result, oral drug delivery systems account for the vast majority of drug delivery systems on the market today. Since more than half of new molecular entities (NMEs) are hydrophobic (BCS class 2), they have low and inconsistent bioavailability, designing such oral drug delivery products presents significant challenges to pharmaceutical
production scientists.\textsuperscript{[1]} Poor aqueous solubility, an extensive hepatic first-pass effect, acid liability in gastric fluid, restricted intestinal permeability, gut wall metabolism by the cytochrome P450 (CYP450) family of isozymes, and high P-glycoprotein (P-gp) efflux are all ostensible causes for these variable bioavailability issues.\textsuperscript{[2]}

SMEDDSs are isotropic and thermodynamically stable solutions made up of gasoline, surfactant, cosurfactant (CoS; or solubilizer), and drug mixtures that spontaneously form oil-in-water (o/w) micro-emulsions when combined with water. The agitation required for self-emulsification in vivo is provided by the stomach and intestine motility. SEDDS spreads easily in the GI tract, and the stomach and intestine's digestive motility provide the requisite agitation for self-emulsification. The drug is solubilized in this spontaneous emulsion formation in the gastrointestinal tract, and the small size of the shaped droplet provides a large interfacial surface area for drug absorption. Aside from solubilization, the presence of lipid in the formulation improves bioavailability by influencing drug absorption. By promoting lipoprotein formation and intestinal lymphatic liquid flux, the lipid composition of SEDDS may be linked to facilitating the degree of lymphatic drug transport.\textsuperscript{[3,4]}

The bioavailability of poorly water soluble and extremely permeable compounds has been enhanced by self-emulsifying lipid formulations by following of ways are:

- To avoid precipitation and recrystallization of the drug compound, fine dispersions and micellar suspensions are produced.
- Drug absorption was enhanced by the ability of some lipid compounds and their metabolites to induce changes in the gastrointestinal fluid.
- Inhibition of cellular efflux processes, which prevent drugs from entering the bloodstream.
- Lipid excipients have been related to selective drug uptake into the lymphatic transport system, reducing the influence of first-pass drug metabolism in the liver.\textsuperscript{[4,5]}

**SEED has the following benefits**

- It prevents cellular efflux processes, which keep drugs out of circulation.
- The association of such lipidic excipients with selective drug uptake into the lymphatic transport system decreases first-pass drug metabolism throughout the liver.
- Preparation of fine dispersions and micellar suspensions to keep the drug compound from precipitating and recrystallizing.
• Improvements in the GI fluid are introduced in favour of better drug absorption due to the capacity of some lipid compounds and their metabolites.
• Activity takes place rapidly.
• Medication dosage is reduced.
• Scalability and ease of manufacture.
• Improved oral bioavailability.

SEDDS appear in some kind of different forms.

Table 1: Forms of self-emulsifying formulations and their comparative characteristics.[5]

<table>
<thead>
<tr>
<th>Types of SEDDS</th>
<th>Comparative features</th>
<th>HLB value of surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>oil droplet size</td>
<td>Appearance</td>
</tr>
<tr>
<td>Self-emulsifying formulations (SEFs)</td>
<td>200 nm to 5 μm</td>
<td>Turbid</td>
</tr>
<tr>
<td>Self-micro emulsifying formulations(SMEFs)</td>
<td>Less than 200 nm</td>
<td>Optically clear to translucent</td>
</tr>
<tr>
<td>Self-nanoemulsifying formulations (SNEFs)</td>
<td>Less than 100 nm</td>
<td>Optically clear</td>
</tr>
</tbody>
</table>

Self-emulsification process

Equation defines the thermodynamic relationship for the net free energy change:

\[ \Delta G = \sum N a_i 4 \pi r_i^2 \]

where G is the process's free energy, ri is the droplet's radius, Ni is the number of droplets, and is the interfacial energy. When the energy involved in the dispersion is greater than the energy needed for the formation of droplets, self-emulsification occurs. Traditional emulsions have a high free energy since it takes a lot of energy to form a new surface between two immiscible phases like oil and water.

The emulsion may not be stable due to the high free energy, and the two phases may separate. However, since the free energy of the device is very low, and often negative due to the presence of a flexible interface, emulsion formation occurs instantly in the case of SMEDDS. An interface is formed between two phases when oil and surfactant/cosurfactant mixture are mixed with water with mild agitation. The aqueous phase then penetrates the interface and solubilizes within the oil phase until it exceeds the solubilization limit.[6]
Table 2: SEDDS commercial preparations.\(^7\)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Trade name (Company)</th>
<th>Drug molecule</th>
<th>Type of formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Vasanoid(^{®}) (Roche)</td>
<td>Tretinoin</td>
<td>Soft gelatin capsule (10 mg)</td>
</tr>
<tr>
<td>2.</td>
<td>Gengraf(^{®}) (Abbott)</td>
<td>Cyclosporin A</td>
<td>Hard gelatin capsule (25, 100 mg)</td>
</tr>
<tr>
<td>3.</td>
<td>Fortovase(^{®}) (Roche)</td>
<td>Saquinavir A</td>
<td>Soft gelatin capsule (200 mg)</td>
</tr>
<tr>
<td>4.</td>
<td>Agenerase(^{®}) (GSK)</td>
<td>Amprenavir</td>
<td>Soft gelatin capsule</td>
</tr>
<tr>
<td>5.</td>
<td>Aptivus(^{®}) (Borhringeringelheim)</td>
<td>Tipranavir</td>
<td>Soft gelatin capsule (200 mg)</td>
</tr>
</tbody>
</table>

**Composition of SEDDS**

1. **Oils**
2. **Surfactants/ Cosurfactants**
3. **Solvents/ cosolvents**

**1. Oils**

Oils are the essential factor regarding SMEDDS, as much solubilization then get entry to on the cure to the lymphatic convention over negative water soluble drugs rely over the type and awareness regarding lubricant back because formulation. The oily/lipid factor is generally a fat waterbrash ester and a medium/long band saturated, partially unsaturated hydrocarbon, among liquid, semisolid or consolidated form at wagon temperature. Examples encompass mettle oil, vegetable oil, siliconoil, mono-/di/triglycerides. Unmodified fit to be eaten oils supply the almost ‘natural’ foundation because lipid vehicles, but their bad capacity after evaporate substantial amounts on hydrophobic pills and theirs kin subject within efficient self-emulsification markedly decrease theirs makesuse of within SEDDS. Eg. Cotton seed oil, Soybean oil, Corn oil, Sunflower oil, Sesame oil, Peanut oil, Labrafil, Captex 200, Captex 300, Captex 500, Ethyl oleate, etc.\(^6,8\)

**2. Surfactants/Co-surfactants**

A surfactant is necessary for SMEDDS to follow self-emulsification property, which is the primary method for forming microemulsions. It also helps in the solubilization of hydrophobic drugs, which improves the dissolution rate. The intestinal cell membrane, which is made up of lipids, can be disrupted by surfactant partition, resulting in increased permeability. Surfactants’ inhibitory impact on p-glycoprotein assists in the improvement of overall bioavailability of many drugs that are p-glycoprotein transporter substrates.
The HLB value is used to decide which surfactant to use. The development of an O/W microemulsion is supported by surfactants with a high HLB. For drugs with a low octanol:water partition coefficient, hydrophilic surfactants with an HLB value greater than 12 are combined with water soluble cosolvents to improve the solvent potential of the formulation, and these systems generate very fine droplets with a surfactant concentration of less than 100 nm. The non-ionic surfactants are non-toxic in nature. E.g., Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), D-alpha T ocopherol polyethylene glycol 1000 succinate (TPGS)\[^{[8,9]}\]

3. Solvents/Co-solvents

Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the micro emulsion systems.

The alcohol-free formulation's ability to dissolve lipophilic drugs, on the other hand, may be reduced. When the amount of cosurfactant in the formulation increases, so does the amount of drug released. Some examples of oils, surfactants, cosurfactants, and csosolvents are listed below.\[^{[6,8,9]}\]

Design of a formula

The steps for making SMEDDS are as follows

1. Excipients are screened.
2. Pseudoternary step diagram construction
3. SMEDDS planning.
4. SMEDDS characterization.

1. Excipients are screened.

Solubility Studies. These are primarily useful for evaluating the most appropriate excipients for use in the preparation of SMEDDS and for predicting drug precipitation in vivo. The drug's solubility in different oils, surfactants, and cosurfactants should be studied. These experiments are typically carried out using the shake flask process, in which the medication is added in excess to the excipient and then shaken for 48 hours at room temperature in a water bath shaker or an air oscillator. After that, the samples should be centrifuged before being filtered through 0.45 \(\mu\)m filters and the drug content determined. These solubility tests are
usually carried out with the intention of selecting an oil with the highest solubility for the drug and a surfactant or co-surfactant with the highest capacity to solubilize the drug.\textsuperscript{[6,10]}

**Surfactants and co-surfactants are tested for their ability to self-emulsify.**  
The capacity of surfactants to emulsify can be determined by combining equal amounts of selected oil and surfactant, followed by homogenization. When this mixture is applied to double distilled water, the number of flask inversions needed to form a homogeneous emulsion is measured, providing an indication of emulsification difficulty. The transparency, turbidity, and percentage transmittance of the resulting microemulsion should then be calculated.

2. **Pseudoternary step diagram construction**  
This reflects the mechanism in SEDDS, which has three components: oil, water, and surfactant. However, in the case of SMEDDS, the addition of a cosurfactant/cosolvent portion is the most common. The three corners of a ternary diagram correspond to 100 percent of the part in question. When a fourth part is added, the ternary diagram is referred to as a pseudoternary step diagram.

The ratio of any two of the four components is kept constant in pseudoternary diagrams, and this ratio, along with the other two components, forms the three corners of the phase diagram. This is combined with the appropriate volume of the third step, such as oil or cosurfactant; then the other component, normally water, is added in gradual quantities, and the solution should be checked for clarity, flowability, self-emulsification time, and dispersibility after each addition of the fourth component. Each mixture's total percent concentration of all components should be 100 percent.

![Figure 1: Pseudoternary phase diagram.](image-url)
3. Preparation of SMEDDS
The preparation starts with the addition of the drug to a mixture of liquid, surfactant, and cosurfactant, accompanied by vortexing. In certain situations, the drug is dissolved in one of the excipients before adding the remaining excipients to the drug solution. The solution should then be thoroughly blended and tested for turbidity. If necessary, the solution should be heated after 48 hours of equilibration at room temperature to form a transparent solution. The formulation should be stored in capsules of acceptable size depending on the final volume.[10]

4. Characterization of SMEDDS

Visual evaluation
Visual assessment may be used to test self-emulsification. The formation of macroemulsion is indicated by the opaque and milky white appearance of SMEDDS after dilution with water, while the formation of microemulsion is indicated by the clear, isotropic, translucent solution. Visual assessment can also be used to determine medication precipitation in diluted SMEDDS.[12]

Thermodynamic stability studies
Physical stability is also essential for a lipid-based formulation's efficiency, which can be harmed by drug precipitation in the excipient matrix.
1. Heating cooling cycle
The researchers looked at six cycles ranging from 4°C to 45°C, with storage periods of at least 48 hours at each temperature.
2. The centrifugation process
Centrifuged thaw cycles between 21°C and +25°C are conducted, with storage at each temperature for at least 48 hours at 3500rpm for 30 minutes.
3. Freeze thaw cycle
The formulations that passed this test demonstrated strong stability, with no phase separation, creaming, or cracking.[13,14]

Dispersibility test
A typical USP XXII dissolution apparatus 2, applied to 500 mL of water at 37 ± 0.5°C and 50 rpm, is used to determine the efficiency of self-emulsification of oral nano or micro emulsions. It is visually assessed by grades:
Grade A: nanoemulsion that forms rapidly (within 1 minute) and has a clear or bluish appearance.

Grade B: Rapidly forming emulsion with a bluish white appearance.

Grade C: Fines milky emulsion formed in less than 2 minutes.

Grade D: Dull is a greyish white emulsion that is sluggish to emulsify and has a slightly oily look (longer than 2 min).

Grade E: Formulation, with large oil globules on the surface and either low or partial emulsification.\textsuperscript{[13,15]}

Time for emulsification
The time required for self-emulsification for various formulations can be calculated using a dissolution apparatus USP type II, in which the formulation is dropped into a basket containing water and the formation of a clear solution is observed under agitation provided by a paddle rotating at 50rpm. Because of the rapid ejection of oil droplets caused by water penetration into the interface, higher surfactant concentrations result in a faster rate of emulsification.

Viscosity determination
The Brookfield viscometer is used to test the micro emulsion's rheological properties. This determination of viscosities is dependent on whether the device is w/o or o/w. If the system has a low viscosity, it is an o/w system, and if it has a high viscosity, it is a w/o system.

Droplet size analysis particle size measurement
Photon correlation spectroscopy (which analyses variations in light scattering due to Brownian motion of the particles) and a Zetasizer capable of measuring sizes between 10 and 5000 nm are used to determine the droplet size of the emulsions.\textsuperscript{[13,14]}

Refractive Index And Percent transmittance
Using a UV spectrophotometer and distilled water as a blank, the percent transmittance of the device is determined at a specific wavelength. If the refractive index of the device is equivalent to that of water (1.333) and the percent transmittance of the formulation is greater than 99 percent, the formulation is transparent.\textsuperscript{[14,15]}
Electro conductivity study
Ionic or non-ionic surfactant, oil, and water make up the SEDD system. As a consequence, this test is used to assess the system's electroconductive existence by using electroconductometer.

In vitro diffusion study
Using the dialysis procedure, an in vitro diffusion analysis is carried out to investigate the release behaviour of formulation from the liquid crystalline phase around the droplet.

Drug content
The drug content in the solvent extract was compared to a typical drug solvent solution using a suitable analytical process.

Stability assessment
The formulation, which is filled in gelatin capsules, is subjected to stability checks in compliance with ICH guidelines. If all of the properties of the formulation do not change during storage, the formulation is said to be stable.

CONCLUSION
We may infer from the preceding analysis that self-emulsifying drug delivery systems are a viable alternative for the formulation of drug compounds with low aqueous solubility. SEDDSs, which have been shown to greatly boost oral bioavailability, can be used to deliver hydrophobic drugs orally. SEDDSs will continue to allow innovative applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs as this technology advances.

REFERENCES


