A REVIEW ON SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT
Oral route is one of the most patient friendly routes for the most of the pharmacologically chronic disease treatment. Nearly 40% of new drug candidates exhibit low water solubility and hence high intra- and inter-subject variability and lack of dose proportionality. Much attention has been given to lipid-based formulation with particular emphasis on self-micro emulsifying drug delivery system to improve the oral bioavailability of lipophilic drugs. It requires small amount of dose and also drugs can be protected from hostile environment in gut. Self micro emulsifying drug delivery systems are specialized form of delivery system in which drug is encapsulated in a lipid base with or without pharmaceutical acceptable surfactant. Self micro emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant and drug with a unique ability to form fine oil in water micro emulsion upon mild agitation following dilution with aqueous phase. SMEDDS is evaluated by various methods like visual assessment, droplet polarity and droplet size, size of emulsion droplet, dissolution test, and charge of oil droplets, viscosity determination, and in-vitro diffusion study. With future development of this technology, SMEDDS will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

Keywords: lipid-based formulation, Self micro emulsifying drug delivery systems, lipophilic drugs, surfactant, oral bioavailability, poorly soluble drugs, droplet size.

INTRODUCTION
So many drugs with an Impressive Pharmacological effect often have low systemic bioavailability because of low water solubility and poor absorption capacity [1]. Oral route is one of the most patient friendly route for the most of the pharmacologically chronic treatment disease [2, 3]. Nearly 40% of new drug candidates exhibit low water solubility and hence high intra and inter subject variability and lack of dose proportionality [36, 13]. Many strategies to enhance oral bioavailability have been proposed, such as salt forming techniques, complexation (i.e. cyclodextrins), particle size reduction,
solubilization based on cosolvent or surfactant. Self microemulsifying drug delivery systems (SMEDDS) have received great attention recently for its potential in improving oral bioavailability for the delivery of poorly water soluble drugs\textsuperscript{[4, 5, 6]}. Self Micro Emulsifying Drug Delivery System (SMEDDS) or self-emulsifying oil formulations (SEOF) is defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and cosolvents/surfactants which forms oil-in-water (o/w) microemulsion on dispersion with aqueous phase under gentle agitation\textsuperscript{[7,8]}. Self-emulsification comes from the agitation required for the digestive motility provided by the movement of stomach and intestine in the gastrointestinal tract. Drug present in SMEDDS in small droplet size and well-proportioned distribution, will increase the dissolution and permeability.

When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable and clear formulations with high drug solubilization capacity, that are easy to manufacture. An additional advantage of SMEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water\textsuperscript{[9, 10]}.

RATIONAL FOR SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEM\textsuperscript{[11, 12, 13]}

BCS class II or class IV compounds, when given orally to the gastrointestinal tract are typically dissolution rate-limited.

There is currently no single or simple solution to the challenge. Different formulation approaches can be used for this. Indeed, in some selected cases, these approaches have been successful. However, these methods have their own limitations.

- Salt formation of neutral compounds is not feasible and the synthesis of weak acid and weak base salts may not always be practical. Moreover, the salts that are formed may convert back to their original acid or base forms and lead to aggregation in the gastrointestinal tract.
Particle size reduction may not be desirable in situations where handling difficulties and poor wettability are experienced for very fine powders.

Problem with micronization is chemical / thermal stability, many drug may degrade and lose bioactivity when they are micronized by conventional method.

For solid dispersion the amount of carriers used is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. Moreover, since the carriers used are usually expensive and freeze-drying or spray-drying method requires particular facilities and processes, leading to high production cost.

Complexation with cyclodextrin techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents.

Realization that the oral bioavailability of poor water soluble drugs may be enhanced when co-administered with meal rich in fat has led to increasing recent interest in the formulation of poorly water soluble drugs in lipids.

**BASIC DIFFERENCE AND SIMILARITIES BETWEEN SEDDS AND SMEDDS**

<table>
<thead>
<tr>
<th>SEDDS</th>
<th>SMEDDS</th>
</tr>
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<tbody>
<tr>
<td><strong>DIFFERENCE</strong></td>
<td></td>
</tr>
<tr>
<td>Can be a simple binary formulation with the drug and a lipoidic surfactant &amp; oil able to self-emulsify in Contact with GIF.</td>
<td>Are composed of the drug compound, surfactant, co-surfactant and oil for lipid phase.</td>
</tr>
<tr>
<td>Lipid droplet size in the dispersion ranges from 200nm-5 μm providing large surface area absorption and has a turbid appearance.</td>
<td>Lipid droplet size in the dispersion range from less than 200nm and has an optically clear to translucent appearance.</td>
</tr>
<tr>
<td>SEDDS are not thermodynamically stable in water or physiological fluid.</td>
<td>SMEDDS are thermodynamically stable in water or physiological fluid.</td>
</tr>
<tr>
<td>Concentration of oil is 40-80%.</td>
<td>Concentration of oil &lt;20%.</td>
</tr>
<tr>
<td>SMEDDS formed using surfactant HLB&lt;12</td>
<td>SMEDDS formed using surfactant HLB&gt;12</td>
</tr>
<tr>
<td><strong>SIMILARITIES</strong></td>
<td></td>
</tr>
<tr>
<td>Form fine oil-in-water dispersion in contact with GIF.</td>
<td></td>
</tr>
</tbody>
</table>
POTENTIAL ADVANTAGES OF SMEDDS \cite{14, 15, 16}

1. Novel approach to improve water solubility and ultimate bioavailability of lipophilic drugs.
2. Shows large inter and intra subject variations in absorption leading to fluctuation in plasma profile.
3. Minimizing irritation with contact of GIT and gut wall.
4. Ease of manufacture and scale up.
5. Deliver peptides that are prone to enzymatic hydrolysis in GIT.
6. It gives prolonged release of medicaments when polymer is incorporated in the composition of SMEDDS.
8. Selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut.
9. Longer shelf life and higher drug solubilization capacity.
10. Reduced variability including food effects.
11. Liquid or solid dosage forms.

Figure 1
Self-emulsifying formulations enhancing the bioavailability of drugs through oral absorption
BIOPHARMACEUTICAL ASPECTS\textsuperscript{[17, 18, 19]}

Biopharmaceutical drug classification is a fundamental guideline classifying drugs based on the solubility and permeability, as shown in Table 2.

Purpose

1. Highly important consideration in the formulation of solid SES is effective incorporation of the drug. In terms of both the solubilization within the oil

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>II</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>III</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>IV</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Surfactant mixes in order to allow a suitable solid dosage to form and once formed the effect that the drug may have on the emulsification properties.

Figure 2
A Typical Representation of the Biopharmaceutical Classification System
TABLE 3: SUMMARIZES EXAMPLES OF DRUGS RELATED TO II, III AND IV CLASSES

<table>
<thead>
<tr>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether</td>
<td>Abacavir,</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Acetylsalicylic Acid,</td>
<td>Mesylate</td>
</tr>
<tr>
<td>Dapsone,</td>
<td>Allopurinol,</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Danazol</td>
<td>Atropine Sulfate</td>
<td>Albendazole</td>
</tr>
<tr>
<td>Efavirenz,</td>
<td>Biperiden,</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>Hydrochloride</td>
<td>Azathioprinei,</td>
</tr>
<tr>
<td>Glibenclamide,</td>
<td>Captopril.</td>
<td>Cefpodoxime proxetil</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Chloramphenicol</td>
<td>Didancosine</td>
</tr>
<tr>
<td>Haloperidol,</td>
<td>Cimetidine,</td>
<td>Indinavir etc.</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Colchicines</td>
<td></td>
</tr>
<tr>
<td>Phenytin Sodium</td>
<td>Ergometrine,</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Ethambulol</td>
<td></td>
</tr>
<tr>
<td>Vitamin E,</td>
<td>Hydrochloride,</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Hydralazine</td>
<td></td>
</tr>
<tr>
<td>Tocotrienols</td>
<td>Hydrochlorothiazide</td>
<td></td>
</tr>
<tr>
<td>Ontazolast etc.</td>
<td>Lamivudine etc.</td>
<td></td>
</tr>
</tbody>
</table>

2. The advantage of solid SES is in its dose reduction, if an improvement in oral bioavailability is established.

3. SES are usually formulated in a liquid form, which has some disadvantages, especially during the manufacturing processes, leading to high production costs, tedious process control, and low stability.

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed. Although incompletely understood; the
currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including:

- Alterations (reduction) in gastric transit: Thereby slowing delivery to the absorption site and increasing the time available for dissolution.

- Stimulation of intestinal lymphatic transport: For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism ([22]).

- Changes in the biochemical barrier function of the GI tract: It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism ([23]).

- Changes in the physical barrier function of the GI tract: Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties.

**THE EMULSIFICATION PROCESS** ([23, 24, 25, 26])

Self-emulsification is a phenomenon which has been widely exploited commercially in formulations of emulsifiable concentrates of herbicides and pesticides. Concentrates of crop-sprays are to be diluted by the user, such as farmers or house-hold gardeners, allowing very hydrophobic compounds to be transported efficiently. In contrast, SMEDDS, using excipients acceptable for oral administration to humans, have not been widely exploited and knowledge about their physicochemical principles is therefore limited.

(a) Mechanism of Self Emulsification

According to ‘Reiss’ self emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the
energy required to create a new surface between the oil and water phases and can be described by the equation:

$$\Delta G = S N r^2$$

Where,

$G$ is the free energy associated with the process (ignoring the free energy of mixing), $N$ is the number of droplets of radius $r$ and $S$ represents the interfacial energy. The emulsion is stabilized by emulsifying agents who form a monolayer on emulsion droplets and hence reduce the interfacial energy. In the case of self emulsifying systems the free energy required to form the emulsion is either very low or positive or negative (then the emulsification process occurs spontaneously).

b) Dilution phases

Upon dilution of a SMEDDS formulation, the spontaneous curvature of the surfactant layer changes via a number of possible liquid crystalline phases.

The droplet structure can pass from a reversed spherical droplet to a reversed rod-shaped droplet, hexagonal phase, lamellar phase, cubic phase and various other structures until, after appropriate dilution, a spherical droplet will be formed again (figure 3).

Figure 3

Representation of the commonly encountered phases upon addition of water to an oil surfactant combination [14].
Formulation of SMEDDS

The following should be considered in the formulation.

- The solubility of the drug in different oil, surfactants and co solvents.
- The selection of oil, surfactant and co solvent based on the solubility of the drug.
- Preparation of the phase diagram.
- The preparation of SMEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co solvent.
- The concentration of surfactant.
- The temperature at which self emulsification occurs.

SMEDDS formulation containing following components

Oils

Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SMEDDS. Unmodified edible oils provide the most natural basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-micro emulsification markedly reduces their use in SMEDDS. Recently medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound such as GELUCIRE, other suitable oil phases are digestible or non-digestible oils and fats such as olive oil, corn oil, and soya bean oil, palm oil and animal fats. etc

Surfactant

Nonionic surfactants with high Hydrophilic Lipophilic Balance (HLB) values are used in formulation of SEDDS (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.
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 hexanole, pentanol, and octanol which are known to reduce the oil water interface and allow the spontaneous formation of microemulsion.

Co-solvent
Organic solvents are suitable for oral administration. Examples are ethanol, propylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid base. Addition of aqueous solvents such as Triacetin, for example glycercyl triacetate or other suitable solvents act as co-solvents.

Consistency builder
Additional material can be added to alter the consistency of the emulsion; such materials include tragacanth, cetyl alcohol, stearic acid and/or beeswax etc.

Polymers
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.

Physicochemical properties for the selection of drug
Poorly water soluble drugs are a broad class of drugs that differ significantly in physicochemical properties, so it would be useful if there were practical guidelines to help identify the most appropriate formulation for specific drugs. High melting point drugs with log P values of about 2 are poorly suited to SMEDDS. At the other end of the spectrum, lipophilic drugs, such as cinnarizine with log P values greater than 5, are good candidate for SMEDDS.

General Preparation Method of SMEDDS
Figure 4
The general strategy of formulating self micro-emulsifying systems and their subsequent conversion to micro/nano emulsions.

Construction of phase-diagram

The relationship between the phase behavior of a mixture and its composition can be captured with the aid of a phase diagram. Compositional variables can also be studied as a function of temperature and, pressure, although with the exception of microemulsion prepared using supercritical or near critical solvents, or with HFA propellants. The phase behavior of simple microemulsion systems comprising oil, water and surfactant can be studied with the aid of ternary phase diagram in which each corner of the diagram represents 100% of that particular component.
A Titration method is employed to construct phase diagram. Mixture of oil with surfactant is prepared at different ratios (e.g. 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10) into different vials. A small amount of water in 5 % (w/w) increments is added into the vials. Following each water addition the mixture in vials is centrifuged for 2 to 3 minute and is incubated at 25°C for 48 hrs with gentle shaking. The resulting mixture is evaluated by visual and microscopy observation. For phase diagram the micro emulsion is the region of clear and isotropic solution.

In the case where four or more components are investigated, pseudo-ternary phase diagrams are used where a corner will typically represent a binary mixture of two components such as surfactant / Co-surfactant, water /drug or oil / drug.
MECHANISM OF BIOAVAILABILITY ENHANCEMENT FROM SMEDDS

The absorption of fats from the GIT: Triglyceride molecules are fatty acid esters of glycerol. The ester groups of the triglycerides are prone to hydrolysis and this represents the major initial route of metabolism within the GI tract. On ingestion of the triglycerides, the lipids enter the stomach. On entering the upper section of the small intestine the triglyceride droplets are metabolized by pancreatic lipase, to free fatty acids and 2-monoglycerides, the last two contributing to the digestion process as they themselves are emulsifying agents.

Bioavailability of drugs from oily vehicles: According to studies the absorption of Griseofulvin from commercial tablets, a corn oil emulsion (equivalent to 12 g oil) and an aqueous suspension in humans. The emulsion gave a much more rapid excretion of Griseofulvin metabolite, Desmethyl - Griseofulvin. The inhibition of gastric motility caused by the presence of the lipid might have allowed more time for dissolution, absorption and of drug.

Drug absorption from SMEDDS: The authors suggested that as the oil phase was a medium chain triglyceride, lymphatic uptake was unlikely to be enhanced; hence, the drug absorption may be a function of the increased surface area for dissolution provided by the emulsion.

FACTOR AFFECTING SMEDDS

Drug Dose: Usually drugs having high dose are not preferred for developing SMEDDS. However, such drug if extremely soluble in any components of SMEDDS particularly in lipid phase. The drug which are not well soluble both in water and oil, and also posses low Log P value (around 2) are not suitable candidates for SMEDDS.

Drug solubility in oil phase: Solubility of the drug in oil phase greatly influenced the ability of SMEDDS in maintaining the drug in solution state. When the drug is solubilized by the use of surfactant and co surfactant the dilution of
SMEDDS can lead to lowering the solvent capacity of surfactant or co surfactant, their by resulting precipitation.

v Equilibrium solubility: For assessment of possibilities of precipitation in the gut equilibrium solubility measurement can be employed. Such formulation can take up to 5 days to reach equilibrium and that the drug can remain in a super saturated state up to 24 h after the initial emulsification event.

EVALUATION OF SMEDDS  
[29, 30, 31, 32]

The efficiency of self micro emulsification could be estimated by determining the evaluation parameter.

1. Droplet size and particle size measurement: The particle size of the micro emulsion is determined by photon correlation spectroscopy or SEM (Scanning Electron Microscopy) which can measure sizes between 10 and 5000 nm. The nanometric size range of the particle is retained even after 100 or 1000 times diluted with distill water, which proves the system’s compatible with excess water.

2. Refractive index and percent transmission: Refractive index and percent transmittance proves the clearness of formulation. The refractive index of the SMEDDS is measured by refractometer and compared with that of water. The percent transmittance of the system is measured at particular wavelength using UV-vis spectrophotometer keeping distilled water as blank. If refractive index of system should be similar to that of water. Formulation showing transmittance >99 percent is transparent in nature.

3. Zeta potential measurement: Zeta potential for microemulsion can be determined using a suitable Zetasizer, in triplicate samples.

4. Stability: SMEDDS was diluted with distilled water and to check the temperature stability of samples, they were kept at two different temperature range (2-8°C (refrigerator), room temperature) and observed for any evidences of phase
separation, flocculation or drug precipitation. In order to estimate metastable systems, the optimized SMEDDS formulation was diluted with distilled water. Then microemulsion was centrifuged at 1000 r min$^{-1}$ for 15 min at 37°C and observed for any alteration in homogeneity of microemulsions.

5. **Centrifugation**: Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 48 h 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.

6. **In vitro release study**: In vitro drug release study of SMEDDs formulation was performed by dialysis method, dissolution apparatus 2 and diffusion cell. Study of drug release was done by modified diffusion cell in 200 ml buffer solution 6.8 pH. 1 gm SMEDDS formulation was placed in boiling tube, both side of boiling tube was opened and one side of tube was tied with cellophane membrane and dipped in buffer solution kept in a beaker below. Upper side of the cylinder was clamped to hold. The beaker was continuously stirred by magnetic stirrer and sample was withdrawn after different time intervals it in straight position and analyzed by UV-Spectrophotometer % drug dissolved at different time intervals was calculated using the beer Lambert’s equation.

7. **Bioavailability study**: Based on the self emulsification properties, particle size data and stability of micro emulsion the formulation is selected for bioavailability studies. The in vivo study is performed to quantify the drug after administration of the formulation. Pharmacokinetic parameters of the maximum plasma concentration ($C_{max}$) and the corresponding time ($T_{max}$) for the drug following oral administration are calculated. The relative Bioavailability (BA) of SMEDDS form to the conventional table is calculated using the following Equation Relative BA ($\%$) = (AUC test/AUC reference) X (Dose reference/Dose test).
APPLICATION

Various dosage forms of SMEDDS are as listed below \[^{[33, 34]}\]

- Dry emulsions
- Self-emulsifying Capsules
- Self-emulsifying Sustained/Controlled-Release Tablets
- Self-emulsifying Sustained/Controlled-Release Pellets
- Self-emulsifying Solid Dispersions
- Self-emulsifying Beads
- Self-emulsifying Sustained-Release Microspheres
- Self-emulsifying Nanoparticles
- Self-emulsifying Suppositories
- Self-emulsifying Implant

DRAWBACK OF SEDDS \[^{[33, 34, 35]}\]

1. Lack of good predicative in vitro models for assessment of the formulations as Traditional dissolution methods do not work due to dependence on digestion prior to release of the drug.
2. To mimic this, an in vitro model simulating the digestive processes of the duodenum has been developed.
3. Need of different prototype lipid based formulations to be developed and tested in vivo in a suitable animal model.
4. The large quantity of surfactant in self emulsifying formulations (30-60%) irritates.
5. Chemical instabilities of drugs.

FUTURE PROSPECTS

The major limitation of lipophilic drugs regarding its solubility in GIT could be overcome by delivering these drugs through self-emulsifying systems. Proper selection of oil, surfactant, co-surfactant in proper ratio, the solubility of the drug can be enhanced by determining the self-emulsifying zone from pseudo ternary diagram. Thus, this novel
delivery system has made easy the delivery of lipophilic drugs orally which increases its bioavailability due to its small particle droplets.

There is still a long way to go, however, before more SMEDDS formulations appear on the market. Because there exist some fields of SMEDDS to be further exploited, such as studies about human bioavailability and establishment of an in vitro/in vivo correlation[36].

CONCLUSION

Some of the concealed features of Self micro emulsifying drug delivery systems (SMEDDS) have been revealed by the literature review. SMEDDS is a promising drug delivery system for the enhancement and improvement of bioavailability for a hydrophobic drug. This review article will definitely drag the attention of the young researchers to understand the role of individual lipids and surfactants used for the formulation of SMEDDS as lipid based formulations are still not very widespread as commercial formulations. Also this study explores the possibilities of loading a wide variety of hydrophobic drugs and as well as economical too[37].

REFERENCES


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