SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEED) O/W MICROEMULSION FOR BCS CLASS II DRUGS: AN APPROACH TO ENHANCE AN ORAL BIOAVAILABILITY

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ABSTRACT
Most of the drugs are being discovered are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Due to their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophilic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs one of them is Self-Micro Emulsifying Drug Delivery Systems (SMEDDS).

Keywords: Novel SEDDS, SMEDDS, Lipid/oil based system, Self emulsifying system

INTRODUCTION
Recently synthesized drug that are being discovered are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Because of their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophilic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs.

The Self-Dispersing Lipid Formulations (SDLFs) is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/organic drugs and to improve the oral bioavailability of poorly absorbed drugs. The SDLFs contain oil and a surfactant mixture into which the drug is incorporated. They emulsify when mixed with aqueous environment. The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs [1, 2, 3]. After self-dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. Bioavailability enhancement results from the finely dispersed state of the drug containing lipid globules. The large surface area enhances the dissolution. The emulsion globules are further solubilized in the gastrointestinal tract by bile fluids. The presence of surfactant causes enhanced absorption due to membrane induced permeation changes. The droplets formed are either positively charged or negatively charged. As the mucosal lining is negatively charged it was observed that positively charged particles penetrated deeper into the enter [4]. A cationic emulsion has greater bioavailability than an anionic emulsion [29, 30]. The SDLFs are of two kinds namely, Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion. Therefore, they are not dependent on bile secretion for absorption. The emulsified form itself is readily absorbable. This ensures a rapid transport of poorly soluble drugs into the blood. Many researchers have reported applications of SEDDS for delivering and targeting lipophilic drugs eg, coenzyme Q10, vitamin E, halofantrine and cyclosporin A.

Potential advantages
Includes
1. Enhanced oral bioavailability (enabling dose reduction)
2. More consistent temporal profiles of drug absorption
3. Selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut.

Drawbacks of SEDDS
Includes
1. Chemical instabilities of drugs and high surfactant concentrations.
2. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered.
3. Moreover, volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

Various major components of SMEDDS
Drugs
Mainly drugs from BCS II class are used in formulation of the SEDDS includes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
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<tbody>
<tr>
<td>Ontazolast</td>
<td>24</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>22</td>
</tr>
<tr>
<td>Danazol</td>
<td>22</td>
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Vitamin E 27    | Tocotrienols 28 |
| Itraconazole 24  |

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, 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, Gremophore, 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 amphipathic 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 [22].

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 formulation of micro emulsion [12, 14].

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 hydrophobic surfactant or drug in liquid base [13]. Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl tricetate or other suitable solvents act as co-solvents.

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 [15] 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 hydroxypropyl methylcellulose, ethyl cellulose, [16] etc

Recent advancements in SEDDS
Includes
1. Self-emulsifying sustained/controlled-release tablets
2. Self-emulsifying capsules
3. Self-emulsifying suppositories
4. Micro emulsion Drug Delivery
5. Self-emulsifying Nanoparticles
6. Self-emulsifying sustained/controlled-release pellets

Mechanism of SMEDDS
No single theory explains all aspects of micro emulsion formation. Schulman et al. [16] considered that the spontaneous formation of micro emulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant. Thermodynamic theory of formation of micro emulsion explains that emulsification occurs, when the entropy change that favours dispersion is greater than the energy required to increase the interfacial area, and subsequently, the free energy of the system decreases. Therefore, the emulsion resulting from aqueous dilution are stabilized by conventional emulsifying agents, which forms a monolayer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to prevent coalescence.

Evaluation of SMEDDS
1. Visual assessment may provide important information about the self-emulsifying property of the SMEDDS and about the resulting dispersion [10, 18, and 19]. Estimation of the increased drug dissolution and absorption from large surface area afforded by the emulsion. Inhibit gastric motility by oil / lipid phase of emulsion allows more time for dissolution and absorption of drug from lipid phase. Fatty acids are distributed between other aqueous solution emulsion droplets and the micelles (formed by bile salt) Monoglycerides along with water insoluble components such as vitamins, lipophilic drugs are moved into the micelles, which diffuse through gut content to intestinal mucosa. Short chain fatty acids along with hydrophilic drug are diffused directly to portal supply, while longer fatty acids are utilized in chylomicron formation. Once monoglycerides along with lipophilic drugs are transported into intestinal mucosa, chylomicron synthesis takes place and are released into lymphatic’s efficiency of the self-emulsification can be done by evaluating the rate of emulsification and particle size distribution [20] Turbidity measurement to identify efficient self-emulsifying can be done to establish whether the dispersion has reached equilibrium rapidly and in reproducible time [20].

2. Droplet polarity and droplet size are important emulsion characteristics. Polarity of oil droplets is governed by the HLB value of oil, chain length and degree of unsaturation of the fatty acids, the molecular weight of the hydrophilic portion and concentration of the emulsifier. A combination of small droplets and their appropriate polarity (lower partition coefficient o/w of the drug) permit acceptable rate of release of the drug. Polarity of the oil droplets is also estimated by the oil/water partition coefficient of the lipophilic drug [10, 11].

3. Size of the emulsion droplet is very important factor in self-emulsification / dispersion performance, since it determine the rate and extent of drug release and absorption [10, 19] The Coulter nano-sizer, which automatically performs photon correlation analysis on scattered light, can be used to provide comparative measure of mean particle size for such system. This instrument detects dynamic changes in laser light scattering intensity, which occurs when particle oscillates due to Brownian movement. This technique is used when particle size range is less than 3μm; a size range for a SEDDS is 10 to 200 nm [19].

4. For sustained release characteristic, dissolution study is carried out for SEDDS. Drugs known to be insoluble at acidic pH can be made fully available when it is incorporated in SEDDS [10].

CONCLUSION
Self-Micro Emulsifying Drug Delivery Systems appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs. As there is increase in oral drug absorption of BCS II class drugs, so we can say it is one of the method for enhancing oral bioavailability of drug

REFERENCES