SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS): A PROMISING DRUG DELIVERY SYSTEM FOR ENHANCEMENT OF BIOAVAILABILITY

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ABSTRACT
In modern drug discovery techniques, there has been a consistent increase in the number of new pharmacologically active lipophilic compounds that are poorly water-soluble. Approximately 40% of new drug candidates are lipophilic and exhibit poor water solubility. Various techniques are used to improve the bioavailability of such drugs, like salt formation, pH change, β-cyclodextrin complex, Micro emulsions etc. Self-micro emulsifying drug delivery system (SMEDDS) is the one of the method for improvement of oral bioavailability. Self-micro emulsifying drug delivery system (SMEDDS) is class of emulsion that has received particular attention as a means of enhancing oral bioavailability of poorly water soluble drugs. SMEDDS is ideally an isotropic mixture of oils and surfactants and sometimes co-solvents/surfactants. Upon mild agitation followed by dilution in aqueous media such as GI fluids; these systems can form fine oil-in-water (o/w) emulsion or Micro emulsions. Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. When compared with simple emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. The drugs such as, griseofulvin, cyclosporine, ibuprofen, ritonovir etc. which comes under lipophilic class were formulated in SMEDDS to improve its safety and efficacy.

KEY WORDS: SMEDDS, BCS Classification, Bioavailability.

INTRODUCTION
The oral route has been the major route of drug delivery for chronic treatment of many diseases. Oral drug delivery system is the most cost-effective and leads the world wide drug delivery market. However, in the present scenario, oral drug delivery is continuously looking into newer avenues as 40% of new drug candidates have poor water solubility and/or absorption, high intra-and inter-subject variability, rapid metabolism, high fluctuation in the drug plasma level, variability due to food effect, and lack of dose proportionality which are playing major role in disappointing in vivo results leading to failure of conventional drug delivery system. To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrin, solid dispersion (suspension), co-precipitation, micronization, salt formation, emulsion, use of micelles, and co grinding. Recently much attention has been focused on lipid solutions, emulsions and emulsion pre-concentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs. Emulsion systems are associated with their...
own set of complexities, including stability and manufacturing problems associated with their commercial production. Self-emulsification systems are one formulation technique that can be a fitting answer to such problems. The 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. SMEDDS formulation is in theory, comparatively simple. The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SMEDDS formulation contains oils, surfactants and if required an antioxidant. Often co-surfactants and co-solvents are added to improve the formulation characteristics.

Definition
Self-micro emulsifying drug delivery systems (SMEDDS) 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 that have a unique ability of forming fine oil-in-water (o/w) Micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. The basic difference between self-emulsifying drug delivery systems (SEDDS) also called as self-emulsifying oil formulation (SEOF) and SMEDDS is, SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent Micro emulsions with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS.

Rational for Self-Micro Emulsifying Drug Delivery System
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.

Table 1: Basic Difference and Similarities between SEDDS and SMEDDS

<table>
<thead>
<tr>
<th>SEDDS</th>
<th>SMEDDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIFFERENCE</strong></td>
<td></td>
</tr>
<tr>
<td>1. Can be a simple binary formulation with the drug and a lipidic surfactant &amp; oil able to Self-emulsify in Contact with GIF.</td>
<td>1. Are composed of the drug compound, surfactant, co-surfactant and oil for lipid Phase.</td>
</tr>
<tr>
<td>2. Lipid droplet size in the dispersion ranges from 200nm-5µm providing large surface Area absorption and has a turbid appearance.</td>
<td>2. Lipid droplet size in the dispersion range from less than 200nm and has an optically Clear to translucent appearance.</td>
</tr>
<tr>
<td>3. SEDDS are not thermodynamically stable in water or physiological fluid.</td>
<td>3. SMEDDS are thermodynamically stable in Water or physiological fluid.</td>
</tr>
<tr>
<td>4. Concentration of oil is 40-80%</td>
<td>4. Concentration of oil &lt;20%</td>
</tr>
<tr>
<td>5. Optimization of SEDDS require ternary Phase diagram.</td>
<td>5. Optimization of SMEDDS require Pseudo ternary phase diagram.</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>

**Biopharmaceutical Classification System**

There are number of formulation strategies that could be used to improve bioavailability of class II drugs, either by increasing the dissolution rate/ by presenting the drug in solution and maintaining the drug in solution in the intestinal lumen. As shown below in figure 2. Bioavailability of class IV drugs can be improved by attention to the formulation. Formulation may improve bioavailability of class IV drugs but they are likely to be compromised by their poor membrane permeability. If a class II drug can be maintained in a solubilise state in the lumen of the gut one can achieve an absorption profile more like that of a class I drug. Formulation strategies can do little to improve the absorption of class IV and III drugs which are limited by poor membrane Permeability₁.
Figure 2: A Typical Representation of Biopharmaceutical Classification System

Table 2: Summarizes Examples of Drugs Related to II, III and IV Classes

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>Artemether</td>
<td>Abacavir</td>
<td>Albendazole</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Dapsone</td>
<td>Allopurinol</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Captopril</td>
<td>Carbamazepine</td>
<td>Ethambutol</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Folic acid</td>
<td>Biperiden</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Greciofulvin</td>
<td>Captopril</td>
<td>Mesylate</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Ibuprofen</td>
<td>Metformin Hydrochloride</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Itraconazole</td>
<td>Cementidine</td>
<td></td>
</tr>
<tr>
<td>Levodopa</td>
<td></td>
<td>Atropine Sulphate</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: SMEDDS as a Solution to Various Problems to Different Classes of Drugs

<table>
<thead>
<tr>
<th>BCS class</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Enzymatic degradation, gut wall efflux</td>
</tr>
<tr>
<td>Class II</td>
<td>Solubilization and bioavailability</td>
</tr>
<tr>
<td>Class III</td>
<td>Enzymatic degradation, gut wall efflux and bioavailability</td>
</tr>
<tr>
<td>Class IV</td>
<td>Solubilization, Enzymatic degradation, gut wall efflux and bioavailability</td>
</tr>
</tbody>
</table>

Advantages

Potential advantages of these systems (SMEDDS) include-
- Enhanced oral bioavailability enabling reduction in dose. E.g. Halofantrine
- More consistent temporal profiles of drug absorption.
- Selective targeting of drug(s) toward specific absorption window in GIT.
- Protection of drug(s) from the hostile environment in gut.
- Control of delivery profiles.
- Reduced variability including food effects.
- Protection of sensitive drug substances.
- High drug payloads.
- Liquid or solid dosage forms.
- Ease of manufacture and scale up.

Disadvantages
- Lack of good predicative in-vitro models for assessment.
- High surfactant concentrations (=30-60%) irritates.
- Volatile co-solvents in the conventional formulations migrate into the shells of soft or hard gelatine capsules resulting in precipitation of lipophilic drugs.
- Lack of good IVIVC correlation and suitable animal model for in-vivo studies.

The Emulsification Process\textsuperscript{13-16}
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.

**Mechanism of Self Emulsification**

According to 'Reiss' self-emulsification occurs when the entropy change that favours 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 (1):

\[
\Delta G = S N P r^2 s
\]

Where, 
\(\Delta G\) 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).

**Dilution phases**

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

![Figure 4: Representation of the commonly encountered phases upon addition of water to an oil surfactant combination](image)

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 4).

**MATERIALS AND METHODS**

A large number of oils and surfactants are available which can be used as components of Micro emulsions systems but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and non-aggressive Micro emulsions. Early studies revealed that the self-micro emulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-micro
emulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self-micro emulsifying systems\textsuperscript{18}. The materials used in SMEDDS formulation are as follows:

- Active pharmaceutical ingredient (API)
- Oil phase
- Surfactant
- Co-surfactant
- Co-Solvent
- Consistency builder
- Polymers

\textbf{API}

Active pharmaceutical agent should be soluble in oil phase as this influence the ability of SMEDDS to maintain the API in solubilised form. Drugs which have low solubility in water or lipids are difficult to deliver through SMEDDS. Drugs which are administered in very high dose are not suitable for formulation unless they have extremely good solubility in at least one of the components of SMEDDS, preferably oil phase. High melting point drugs with log P values of about 2 are poorly suitable for SMEDDS, while lipophilic drugs having log P values greater than 5, are good candidate for SMEDDS\textsuperscript{19, 20}

\textbf{Oils}

Oil is one of the most important excipients because oil can solubilise the lipophilic drug in a specific amount and it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, mainly the long chain and medium chain triglycerides are use. The concentration of oil present in SMEDDS is about the 40-80\% the modified and hydrolyzed vegetable oils widely because they show the more solubility and good self-emulsifying property. Solvent capacity for less hydrophobic drugs can be improved by bending triglycerides with mono and di-glycerides\textsuperscript{18, 20}

\textbf{Surfactants}

Surfactant molecules consist of two parts, polar head group region and non-polar tail region. Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows (Khoo, 1998)

- Anionic surfactants
- Cationic surfactants
- Ampholytic surfactants
- Non-ionic surfactants

- Anionic Surfactants: where the hydrophilic group carries a negative charge such as carboxyl (RCOO\textsuperscript{-}), sulphonate (RSO3\textsuperscript{-}) or sulphate (RO- SO3\textsuperscript{-}). Examples: Potassium laurate, sodium lauryl sulphate.
- Cationic surfactants: where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.
- Ampholytic surfactants (also called zwitterionic surfactants) contain both a negative and positive charge. Example: sulfobetaines.
- Non-ionic surfactants, where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH2CH2O). Examples: Sorbitan Ester (Spans), Polysorbates (Tweens).
Figure 5: Surfactant molecule containing hydrophilic head and hydrophobic tail.

Co-surfactant
For the production of an optimum SMEDDS, high concentration of surfactant is required in order to reduce interfacial tension, which can be harmful, so co-surfactants are used to reduce the concentration of surfactants. Co-surfactants together with the surfactants provide the sufficient flexibility to interfacial film to take up different curvatures required to form micro-emulsion over a wide range of composition. Selection of proper surfactant and co-surfactant is necessary for the efficient design of SMEDDS and for the solubilization of drug in the SMEDDS. Generally co-surfactant of HLB value 10-14 is used. Organic solvents like ethanol, propylene glycol, polyethylene glycol are able to dissolve large amount of either drug or hydrophilic surfactant in lipid base and are suitable for oral delivery, so they can be used as co-surfactant for SMEDDS. Alcohols and other volatile co-solvents show a disadvantage that by evaporation they get entered into soft/hard gelatin capsule shells results in precipitation of drug. On the other hand, formulations which are free from alcohols have limited lipophilic drug dissolution ability. Hence, proper choice of components has to be made for formulation of efficient SMEDDS\(^{18, 19}\).

<table>
<thead>
<tr>
<th>Oils</th>
<th>Surfactants</th>
<th>Co-surfactants/Co-solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotton seed oil</td>
<td>Polysorbate 20 (Tween 20)</td>
<td>Span 20</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>Polysorbate 80 (Tween 80)</td>
<td>Span 80</td>
</tr>
<tr>
<td>Corn oil</td>
<td>D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)</td>
<td>Capryol 90</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>Polyoxy-35-castor oil (Cremophor RH40)</td>
<td>Lauroglycol</td>
</tr>
<tr>
<td>Castor oil</td>
<td>Polyoxy-40-hydrogenated castor oil (Cremophor RH40)</td>
<td>Transcutol</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>Labrasol</td>
<td>Isopropyl alcohol, Ethanol, Polyethylene glycol</td>
</tr>
<tr>
<td>Peanut oil</td>
<td>Labrafac</td>
<td></td>
</tr>
<tr>
<td>Labrafac</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Co-solvents
High concentration of surfactant (generally more than 30%) is required for optimum production of SMEDDS. Organic solvents enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in oil phase. Examples include ethanol, butanol, and propylene glycol etc., esters such as ethyl propionate, tributyl citrate and amides as 2-pyrolidine, caprolactum and polyvinyl pyrollidine\(^{21}\).
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.\textsuperscript{18}

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.

General Preparation Method of SMEDDS:
The appropriate quantity of lipid and surfactant are melted together in a crucible at 40 °C to 60 °C. The drug is added and stirred thoroughly. The mixture is injected drop wise into a stirred solvent using a syringe fitted with an 18G needle at a stirring speed approximately of 1000 rpm. The SMEDDS is filtered out from the solvent with aid of a filter paper (Whatman no.1) and then dried for 72 h in desiccators\textsuperscript{9}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{The General Strategy of Formulating Self Micro-Emulsifying Systems and Their Subsequent Conversion to Micro/Nano Emulsions.}
\end{figure}

Construction of a Phase Diagram:
Micro emulsion is prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. Micro emulsion are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on the chemical composition and concentration of each component. The understanding of their phase equilibriums and demarcation of the phase boundaries are essential aspects of the study. As quaternary phase diagram (for component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to find the different zones including Micro emulsions zone, in which each corner of the diagram represents 100% of the particular component. 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. The number of different phases present for particular mixture can be visually assessed. A highly schematic (pseudo) ternary phase diagram illustrating in these figure.
It should be noted that not every combination of components produces Micro emulsions over the whole range of possible compositions, in some instances the extent of Micro emulsion formation may be very limited. A Titration method is employed to construct phase diagram. Mixture of oil with surfactant is prepared at different ratios (Ex - 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 min. and is incubated at 25 °c for 48 h with gentle shaking. The resulting mixture is evaluated by visual and microscopic observation. For phase diagram the Micro emulsion is the region of clear and isotropic solution. Coarse emulsion is the region of cloudy dispersion (Constantinides, 1995). 

Table 5: Examples of Marketed Self Emulsifying formulation

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Compound</th>
<th>Dosage form</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoral®</td>
<td>Cyclosporine A/I</td>
<td>Soft gelatin capsule</td>
<td>Novartis</td>
<td>Immune suppressant</td>
</tr>
<tr>
<td>Norvir®</td>
<td>Ritonovir</td>
<td>Soft gelatin capsule</td>
<td>Abbott Laboratories</td>
<td>HIV Antiviral</td>
</tr>
<tr>
<td>Fortovase®</td>
<td>Sequinavir</td>
<td>Soft gelatin capsule</td>
<td>Hoffmann-La Roche inc.</td>
<td>HIV Antiviral</td>
</tr>
<tr>
<td>Agenerase®</td>
<td>Amprenavir</td>
<td>Soft gelatin capsule</td>
<td>Glaxo Smithkine</td>
<td>HIV Antiviral</td>
</tr>
<tr>
<td>Convulex®</td>
<td>Valproic acid</td>
<td>Soft gelatin capsule</td>
<td>Pharmacia</td>
<td>Antiepileptic</td>
</tr>
<tr>
<td>Lipirex®</td>
<td>Fenofibrate</td>
<td>Hard gelatin capsules</td>
<td>Genus</td>
<td>Antihyperlipoprotein-eic</td>
</tr>
<tr>
<td>Sandimmune®</td>
<td>Cyclosporine A/II</td>
<td>Soft gelatin capsule</td>
<td>Novartis</td>
<td>Immune suppressant</td>
</tr>
<tr>
<td>Targetin®</td>
<td>Bexarotene</td>
<td>Soft gelatin capsule</td>
<td>Ligand</td>
<td>Antineoplastic</td>
</tr>
<tr>
<td>Rocaltrol®</td>
<td>Calcitriol</td>
<td>Soft gelatin capsule</td>
<td>Roche</td>
<td>Calcium regulator</td>
</tr>
<tr>
<td>Gengraf®</td>
<td>Cyclosporine A/III</td>
<td>Hard gelatin capsules</td>
<td>Abbott Laboratories</td>
<td>Immune suppressant</td>
</tr>
</tbody>
</table>
Mechanism of Bioavailability Enhancement from SMEDDS

Most SMEDDS are based on triglycerides; it is helpful to consider the mechanisms by which SMEDDS are absorbed from the GI tract (Fig. 6).

The absorption of fats from the GIT: Constantinides (1995) demonstrated that 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. Some hydrolysis may occur in the stomach due to the presence of gastric lipase. On entering the upper section of the small intestine, two processes occur. The fat droplets are further emulsified by the bile salts, monoglycerides, cholesterol, lecithin and lysolecithin to produce droplets with a diameter of approximately 0.5-1 μm. The triglyceride droplets are then 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.

Figure 6: Diagrammatic representation mechanistic pathways for transportation of drugs across the GI lumen using SMEDDS

The fatty acids are distributed between the aqueous solution, the emulsion droplet and the micelles, while the monoglycerides are incorporated into the micelles and are believed to swell the structure, allowing incorporation of other water insoluble components. The micelles then diffuse through the gut contents to the intestinal mucosa. Once in the intestinal mucosa, the monoglycerides are resynthesized into triglycerides and covered with a layer of lipoprotein, cholesterol and phospholipids. The resulting particles are released into lymphatic system. Short chain fatty acids may diffuse directly into the portal supply.

Bioavailability of Drugs from Oily Vehicles: According to studies of (Benet and Cummins, 2001) compared the absorption of griseofulvin from commercial tablets, a corn oil emulsion (equivalent to 12 g oil) and an aqueous suspension in humans. The authors found that emulsion gave a much more
rapid excretion of griseofulvin metabolite, desmethyl griseofulvin. The authors suggested that factors such as the inhibition of gastric motility caused by the presence of the lipid might have allowed more time for dissolution and absorption of drug. Alternatively, the presence of the emulsified oil may have stimulated bile secretion, which may have improved bioavailability. Later hypothesis has included increased mucosal permeability via incorporation of lipids from mixed micelles and enhanced mesenteric lymph flow.

**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. The authors also suggested that the presence of the surfactant in the formulation might play a role in increasing the absorption of the drug (Charman et al., 1992).

![Figure 7: Mechanisms Proposed for Bioavailability Enhancement of Drug](image)

**Factors Influencing Formulation of SMEDDS:**

**Dose of Drug**

Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately 2) are most difficult to deliver by SMEDDS.

**Solubility of Drug**

The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. If surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut.

**Polarity of Lipid Phase**

The polarity of the lipid phase is another factor that influences the drug release from the Micro emulsion. The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. Polarity indicates the affinity of drug towards solvent, oil or water and type of
forces involved. The high polarity promotes rapid release of the drug into the aqueous phase. It was observed that the rate of release of idebenone from SMEDDS is dependent upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oil phase with highest polarity.

CHARACTERIZATION OF SMEDDS

Differential Scanning Calorimetry
Differential scanning calorimetry for SMEDDS can be determined using DSC 60. Liquid sample and solid sample should be placed in the aluminium pan and result can be recorded. Any type of chemical interaction should be determined using DSC. DSC allows study of the thermal behaviour of excipients melting, crystallization, solid to solid transition temperatures and determination of solid fat content of the excipient verses temperature.

Fourier Transform-Infrared Spectroscopy
Fourier transform-infrared for SMEDDS can be determined using FT-IR. Liquid sample should be placed in the liquid sample holder and result can be recorded. Any type of chemical interaction should be determined using FT-IR.

Macroscopic Evaluation
Macroscopic analysis was carried out in order to observe the homogeneity of Micro emulsion formulations. Any change in colour and transparency or phase separation occurred during normal storage condition (37±2 °C) was observed in optimized Micro emulsions formulation.

Visual Assessment
To assess the self-emulsification properties, formulation (60 mg) was introduced into 100 ml of water in a glass Erlenmeyer flask at 25 °C and the contents were gently stirred manually. The tendency to spontaneously form a transparent emulsion was judged as good and it was judged bad when there was poor or no emulsion formation. Phase diagram was constructed identifying the good self-emulsifying region.

Determination of Self Emulsification Time
The emulsification time of SMEDDS was determined according to USP 22, dissolution apparatus 2. 300 mg of each formulation added drop wise to 500 ml purified water at 37 °C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time was assessed visually.

Solubility Studies
Unknown amount of selected vehicles was added to each cap vial containing an excess of drug. After sealing, the mixture was heated at 40 °C in a water bath to facilitate the solubilization. Mixing of the systems was performed using a vortex mixer. Formed suspensions were then shaken with a shaker at 25 °C for 48 h. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min, and excess insoluble LOV was discarded by filtration using a membrane filter (0.45 μm, 13 mm, Whatman, India). The concentration of drug was then quantified by U.V. Spectrophotometer.

Transmittance Test
Stability of optimized Micro emulsions formulation with respect to dilution was checked by measuring Transmittance through U.V. Spectrophotometer (UV-1700 SHIMADZU). Transmittance of samples was measured at 650 nm and for each sample three replicate assays were performed.

Droplet Size Determination
Photon correlation Spectroscopy (PCS) or dynamic light scattering (DLS) or Laser Diffraction Techniques are used to determine droplet size of emulsion. A number of equipments are available for measurement of particle size viz. Particle Size Analyzer, Mastersizer, Zetasizer etc. which are able to measure sizes between 10 and 5000 nm. In many instances nanometric size range of particle is
retained even after 100 times dilution with water which indicates the system’s compatibility with excess water.  

**Zeta Potential Measurement**

Zeta potential for Micro emulsion was determined using Zetasizer HSA 3000 (Malvern Instrument Ltd., UK). Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment.  

**Temperature Stability**

Shelf life as a function of time and storage temperature was evaluated by visual inspection of the SMEDDS system at different time period. SMEDDS was diluted with purified distilled water and to check the temperature stability of samples, they were kept at three different temperature range (2-8 °C (refrigerator), Room temperature) and observed for any evidences of phase separation, flocculation or precipitation.  

**Centrifugation**

In order to estimate metastable systems, the optimized SMEDDS formulation was diluted with purified distilled water. Then Micro emulsions was centrifuged at 1000 rpm for 15 min. at 0 °C and observed for any change in homogeneity of Micro emulsion.  

**In Vitro Release**

The quantitative *in vitro* release test was performed in 900 ml purified distilled water, which was based on USP 24 method. SMEDDS was placed in dialysis bag during the release period to compare the release profile with conventional tablet. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 μ membrane filter, dilute suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals was calculated using the Beer Lambert’s equation.  

**Dosage Form Development**

**Self-Emulsifying Sustained/Controlled-Release Tablets**

Numerous potent drugs exhibit low oral bioavailability due to their poor aqueous solubility or pre-systemic metabolism. Carvedilol one of those drug having low bioavailability, low solubility and having pre-systemic metabolism. The novel self-emulsifying osmotic pump tablet (SEOPT) containing Carvedilol has many advantages. It improves the bioavailability of Carvedilol, controls the release rate and makes the plasma concentrations more stable. The results of dissolution experiment showed that the release of Carvedilol from self-made SEOPT was controlled and complete and its profile was close to zero order release. Self-emulsifying capsule it is a capsules containing liquid or semisolid form of self-emulsifying system. In the GIT, the capsules get dispersed to SES uniformly in the fluid to micron size, enhancing bioavailability. Second type of self-emulsifying capsule is solid SES filled into capsule.  

**Self-Emulsifying Suppositories**

Some investigators proved that Solid-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption. Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester.  

**Self-Nanoemulsifying Drug Delivery System (SNEDDS) /Self-Emulsifying Nanoparticles**

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and
injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were there after filtered out and dried.\textsuperscript{30}

**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, reduction of inrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it seems very appealing to combine the advantages of pellets with those of SEDDS by SE pellets. Spherical pellets with low friability and self-emulsifying properties can be produced by the standard extrusion/spheronization technique. E.g. Lipid mixtures composed of Solutol\textsuperscript{®} HS 15 and medium chain glycerides were optimized with respect to their self-emulsifying properties. The liquid SE lipid was mixed with microcrystalline cellulose and transformed into pellets by extrusion/spheronization. The pellets were characterized for size, shape, surface characteristics and friability. The combinations of coating and SES could control in vitro drug release by providing a range of release rates and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution.\textsuperscript{21,30}

**Self-Emulsifying Solid Dispersions**

Gupta et al. prepared SE solid dispersion granules using the hot-melt granulation method for seven drugs, including four carboxylic acid containing drugs, a hydroxyl-containing drug, an amide containing drug (phenacetin) and a drug with no proton donating groups (progesterone) in which Gelucire 50/13 was used as the dispersion carrier, while Neusilin US2 was used as the surface adsorbent.\textsuperscript{29,30}

**Self-Emulsifying Beads**

Solidification of liquid systems has been a challenge that has attracted wide attention due to handling difficulties and machinability and stability problems that are often encountered with liquids. One of the solidification is to transform into SES beds form with minimum amounts of solidifying excipients, investigated SES as microchannels of porous polystyrene beads (PPB) using the solvent evaporation method. PPB with complex internal void structure is typically produced by co-polymerizing styrene and divinely benzene. Porous polymer structures such as macroporous high internal phase emulsion (HIPE) polymers were used as high capacity reservoirs for included liquids and as carriers for active pharmaceuticals for sustained delivery.\textsuperscript{18, 21}

**Self-Emulsifying Sustained-Release Microspheres**

Zedoary turmeric oil (ZTO) exhibits potent pharmacological actions including tumour suppression, and antibacterial, and antithrombotic activity. With ZTO as an oil phase, the solid SE sustained-release microspheres were prepared by the quasi-emulsion-solvent-diffusion method involving spherical crystallization. The ZTO release behaviour was controlled by the ratio of hydroxyl propyl methyl cellulose acetate succinate to Aerosil 200 in the formulation, and the plasma concentration time-profiles after oral administration to rabbits showed a bioavailability of 135.6% compared with the conventional liquid SEDDS.\textsuperscript{20}

**Positively Charged Self-Emulsifying Drug Delivery System**

One of the most persistent problems faced by the formulation scientists has been to find methods of improving the oral bioavailability of poorly water-soluble drugs. This positively charged SEDDS gives several fold increase in the bioavailability than the negatively charge done. Cationic lipids are use in this type of system. E.g. positively charged Meloxicam SEDDS were prepared using oil components (ethyl oleate, sunflower oil and arachis oil), cationic lipid (oleylamine) and surfactants (combination of Tween 80 and Span 80).\textsuperscript{20, 29}

**Self-Double-Emulsifying Drug Delivery System (SDEDDS)**
Can spontaneously emulsify to water-in-oil in-water (w/o/w) double emulsions in the mixed aqueous gastrointestinal environment, with drugs encapsulated in the internal water phase of the double emulsions. We employed SDEDDS to improve the oral absorption of pidotimod, a peptide-like drug with high solubility and low permeability.\textsuperscript{21, 29}

![Types of Solid SMEDDS](image)

**Fig. 10: Types of Solid SMEDDS** \textsuperscript{28}

**Solidification Techniques for Transforming Liquid/Semisolid SMEDDS TO S-SMEDDS**

Various solidification techniques are as listed below;

**Capsule Filling with Liquid and Semisolid Self-Emulsifying Formulations**

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process: (i) Heating of the semisolid excipient to at least 20 °C above its melting point; (ii) Incorporation of the active substances (with stirring); (iii) Capsule filling with the molten mixture and (iv) Cooling to room temperature. For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing.\textsuperscript{29} The advantages of capsule filling are simplicity of manufacturing; suitability for low-dose highly potent drugs and high drug loading potential (up to 50% (w/w).

**Spray Drying**

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.\textsuperscript{29}

**Adsorption to Solid Carriers**

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the 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. A significant benefit of the adsorption
technique is good content uniformity. SEDDS/SMEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers.\textsuperscript{31, 32}

**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. Moreover, it is also a good alternative to the use of solvent.\textsuperscript{29}

**Melt Extrusion/Extrusion Spheronization**

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions.\textsuperscript{33}

**APPLICATIONS OF SMEDDS:**

**Super Saturable SMEDDS (SS-SMEDDS) (Rajesh 2010)**

The high surfactant level typically present in SMEDDS formulation can lead to GI side effects and a new class of supersaturatable formulation including supersaturatable SMEDDS. (S-SMEDDS) formulations have been designed and developed to reduce the surfactant side effects and achieve rapid absorption of poorly soluble drugs.

**Solid SMEDDS (Rajesh 2010)**

SMEDDS are normally prepared as liquid dosage form that can be administered in soft gelatine capsules, which has more disadvantages especially in manufacturing process. An alternative method is incorporation of liquid self-emulsifying ingredient into a powder in order to create solid dosage form (Tablet, capsules). A pellet formulation of progesterone in SMEDDS has been prepared by extrusion/spheronization (Jannin,2008) to provide a good in-vitro drug release (100% within 15 min. T50% in 13 min.) The same dose of progesterone (16 mg) in pellet.

**Solubilization in SMEDDS**

Owing to their frequently high content oil, as well as of surfactant, SMEDDS are usually efficient solubilizers of substances of a wide range of lipoplicity. Thus, the solubilising capacity of a w/o Micro emulsions for water soluble drugs is typically higher than that of o/w Micro emulsions, while the reverse is true for oil soluble drugs. Furthermore, the solubilisation depends on the SMEDDS composition.

**Sustain Release from SMEDDS (Porter, 2001)**

Due to wide range of structures occurring in them, SMEDDS display a rich behaviour regarding the release of solubilized material. Thus in case of O/W Micro emulsions, hydrophobic drugs solubilized mainly in the oil droplets, experience hindered diffusion and are therefore released further slowly (depending on the O/W partitioning of the substance). Water soluble drugs, on other hand, diffuse essentially without obstruction (depending on the volume fraction of dispersed phase) and are release fast. For balanced Micro emulsions, relatively fast diffusion and release occur for both water soluble and oil soluble drugs due to the bicontinuous nature of Micro emulsion “structure”. Apart from the Micro emulsions structure, the Micro emulsions composition is important for the drug release rate (Gursov, 2004).\textsuperscript{8}

**CONCLUSION**
Some bioactive molecules have poor aqueous solubility, high molecular weight, pre-systemic first pass effect, enzymatic degradation, gastric irritation, limited dissolution rate and low bioavailability creating different problems during formulation. Self-emulsifying drug delivery system is the most promising approach for formulation in case of such drugs. SMEDDS is suitable for all BCS class drugs where resulting emulsification gives faster dissolution rate and absorption. 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. Also this study explores the possibilities of loading a wide variety of hydrophobic drugs and as well as economical too.34

REFERENCES