LIPID BASED SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) FOR LIPOPHILIC DRUGS: AN ACQUAIANTED REVIEW

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ABSTRACT
The solubility issue presents serious challenges to the successful development and commercialization of new drugs in the Pharmaceutical industry. By many estimates, approximately 40% of newly discovered drug candidates have little or no water solubility and therefore have low and erratic bioavailability profile. This may lead to high inter and intra subject variability, lack of dose proportionality and therapeutic failure. Various strategies are reported in the literature including micronization, solid dispersions, cyclodextrin complex formation and self-dispersing delivery systems for enhancement of bioavailability of lipophilic therapeutic agents. Among the various approaches, Sefl micro emulsifying drug delivery system has gained more attention due to enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drugs towards specific absorption window in Gastro intestinal tract and protection from the hostile environment in gut. Self micro emulsifying drug delivery system is an isotropic (one phase system) mixture of oil or modified oils, surfactants, co-surfactants which form fine oil-in-water microemulsion when introduced into aqueous phase under conditions of gentle agitation. The digestive motility of the stomach and intestine provide the agitation necessary for self emulsification in vivo. This review describes about the formulation methodology, evaluation parameters and the future aspects of Self micro emulsifying drug delivery system.

Key words: Solubility, Self micro emulsifying drug delivery system, Bioavailability, Lipophilic therapeutic agents, Absorption

INTRODUCTION
In recent years, the formulation of poorly aqueous soluble drugs is a challenging job to the pharmaceutical scientists. Owing to poor aqueous solubility, these drugs lead to low absorption following oral administration. A portion of the administered dose is absorbed which shows therapeutic effect and the remaining causes untoward actions due to improper drug distribution. With the concept of novel drug delivery system, emphasis has been placed on reduced toxicity of the drugs, to broaden their mode of administration, targeting and modification of distribution profile of drugs and enhancing bioavailability of bioactives. Oral delivery of poorly aqueous soluble drugs is frequently associated with low bioavailability, high inter- and intra-subject variability and a lack of dose proportionality1. This class of compound can be defined as low solubility and high permeability BCS (Biopharmaceutical Classification System) class II drugs. Here, drug dissolution is the rate limiting step in the absorption process. To overcome these problems, different formulation approaches have been exploited including the use of surfactants, lipids, permeation enhancers, and the formation of salt, solid dispersions, inclusion complexes with cyclodextrins, and colloidal vesicles like liposomes. The most popular and commercially viable lipid-based formulation approach for solving these problems is self microemulsifying drug delivery system (SMEDDS)2.

SMEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, and hydrophilic 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 (gastrointestinal) fluids3. They spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification and form transparent micro emulsions with a droplet size between 1-100 nm4. 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 occurs5,6. After self dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets7. 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 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 ileum8. A cationic emulsion has greater bioavailability than an anionic emulsion9,10.

SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds classified as class II drugs by Biopharmaceutical classification system (BCS), drugs with poor aqueous solubility and high permeability that exhibit dissolution rate-limited absorption, SMEDDS may offer an improvement in the rate and extent of absorption. The SMEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SMEDDS formulation contains oils, surfactants and co-surfactants/co-solvents, and if required an antioxidant.

Advantages of SMEDDS

Improvement in oral bioavailability of poorly water soluble drugs: Bioavailability enhancing property has been associated with a number of in vivo properties of lipid formulation including:

• The formation of fine dispersions and micellar suspensions to prevent precipitation and re-crystallization of the drug compound.
• The ability of certain lipid compounds and their metabolites to initiate changes in the gastrointestinal fluid to flavor improved drug absorption.
• The inhibition of cellular efflux mechanisms, which keep drugs out of the circulation.
• Certain lipid excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism in the liver.

Ease of manufacture and scale-up
Reduction in inter-subject and intra-subject variability and food effects
Protection of drugs from enzymatic hydrolysis in GIT (gastro intestinal tract)

No influence of lipid digestion process: The performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation.

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Ease of manufacture and scale-up
Reduction in inter-subject and intra-subject variability and food effects
Protection of drugs from enzymatic hydrolysis in GIT (gastro intestinal tract)

No influence of lipid digestion process: The performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation.
Increased drug loading capacity
Selective targeting of drug(s) toward specific absorption window in GIT

Control of delivery profiles: It can be achieved by incorporating suitable polymers.

Potential benefits of SMEDDS over other Approaches
Different formulation approaches like micronization, solid dispersion, liposomes, nanoparticles, complexation with cyclodextrins etc. can be used to improve bioavailability of lipophilic drugs but they offer many other disadvantages.

- The main problem with micronization is chemical / thermal instability, 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 dosage form would be large in size 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 cyclodextrins techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents.
- Liposomes, nanoparticles etc. require specific equipments and manufacturing processes (extensive sonication) leading to high production cost.
- The size of the droplets of common emulsion ranges between 0.2 and 10 μm, and that of the droplets of micro emulsion formed by the SMEDDS generally ranges between 2 and 100 nm (such droplets are called droplets of nano particles).
- Emulsion cannot be autoclaved as they have phase inversion temperature, while SMEDDS can be autoclaved.

One of the obstacles for the development of SMEDDS and other lipid-based Formulations is the lack of good predictive in vitro models for assessment of the Formulations.

Formulation Consideration
Studies have revealed that the self-micro emulsification process is specific to the nature and concentration 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. The formulated Self-Micro Emulsifying Drug Delivery Systems is specific to that particular drug only. Various major components of SMEDDS are:

1. Oils
2. Surfactant
3. Co-surfactant
4. Co-solvent
5. Consistency Builder
6. Enzyme Inhibitors
7. Adsorbents/solidifying agents
8. Polymers

1. Oils: The majorities of hydrophobic therapeutic agents are lipophilic, and have greater solubility in triglycerides than in surfactants. As a result, triglycerides such as medium chain and long chain with different degree of saturation have been used for the solvation of hydrophobic therapeutic agent 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. Whereas modified or hydrolyzed vegetable oils have contributed widely to the success of SMEDDS owing to their biocompatibility. Because of higher fluidity, better solubilizing potential and self-micro emulsification ability these excipients form good emulsification systems. Almond oil, Canola oil, Coconut oil, Coconut oil, Corn oil, Cottonseed oil, Olive oil, Peanut oil, Safflower oil, Sesame oil, Shark liver oil, Soya bean oil, Wheat germ oil etc are the commercially available Triglycerides.

2. Primary surfactant: Combinations of surfactants are used in the formulation of SMEDDS one of which is hydrophilic surfactant with the remaining surfactant or surfactants being hydrophilic or hydrophobic. To function as a surfactant, a compound must necessarily include polar or charged hydrophilic moieties as well as non-polar hydrophobic (lipophilic) moieties i.e. a surfactant compound must be amphiphilic. Impirical parameters commonly used to characterize the relative hydrophobicity and hydrophilicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance (HLB value). Surfactants with lower lipophilic values are more hydrophobic and have greater solubility in oils, whereas surfactants with higher HLB values are more hydrophilic and have greater solubility in aqueous mediums. Using HLB value as rough guide, hydrophilic surfactants are generally considered to be those compounds having an HLB values greater than about 10, as well as anionic, cationic or zwitter ionic compound for which the HLB scale is not generally applicable. Similarly, hydrophobic surfactants are those compounds having HLB value less than about 10. The choice of specific surfactants should be made keeping in mind the particular triglycerides and optional therapeutic agents to be used in the composition of the SMEDDS, and the range of polarity appropriate for the chosen therapeutic agent. A very broad range of surfactants is suitable for use in the preparation of SMEDDS.

Commercially available surfactants are listed in Table 1.

Concentration of surfactant
Hydrophilic and hydrophobic surfactants present in the SMEDDS in amounts such that upon dilution with an aqueous solution, the carrier (oil) forms a clear, aqueous dispersion of the hydrophobic and hydrophilic surfactants containing hydrophobic therapeutic agent. The relative amounts of hydrophilic and hydrophobic surfactants are readily determined by observing the properties of the surfactant dispersion i.e. when the relative amounts of surfactant (hydrophilic and hydrophobic) are within a suitable range, the resulting aqueous dispersion is optically clear. When the relative amount of hydrophobic surfactant is too great, the resulting dispersion is visibly cloudy, resembling a conventional emulsion or multiple phase system. The usual surfactant concentration in SMEDDS formulation and maintaining emulsion stage ranges from 30-60% w/w of the formulation.

3. Secondary surfactant (co-surfactant): Generally co-surfactant of HLB value 10-14 is used with surfactant together to decrease the interfacial tension to a very small even transient negative value. At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant until their bulk condition is depleted enough to make interfacial tension positive again. The process named “spontaneous emulsification” forms the micro emulsion. However, for many non-ionic surfactants it is not compulsory/mandotory to use co-surfactant in micro emulsion. The selection of co-surfactant and surfactant is crucial not only to form the formation of microemulsion, but also to solubilization in microemulsions. Other variables such as the chemical nature of oil, salinity and temperature are also expected to influence the curvature of the interfacial film. Organic solvents like ethanol, propylene glycol, polyethylene glycol suitable for oral administration may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as cosurfactant in the microemulsion systems.
5. Co-Solvents: Organic solvents and additional compounds suitable for oral administration are used in SMEDDS to enhance the solubility of therapeutic agent or triglyceride in the composition. Examples include:

- Alcohols and Polyls: Such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol etc.
- Amides such as 2-pyrrolidone, 2-piperidone, caprolactam, N-alkylpyrrolidone and N hydroxyalkyepyrrolidone.
- Esters, such as ethyl propionate, tributyl citrate, acetyl triethyle citrate and acetyl tributyl citrate.

6. 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.

7. Solvents: Inert surfactant / Co surfactant and solvent. Mix thoroughly the oil phase, if necessary, by heating or other means, with the solubilized drug formulation. The samples are then centrifuged and supernatant is discarded.

8. Drug Properties Suitable For SMEDDS: Dose should not be so high. Drug should be oil soluble. High melting point drug is poorly suited to SMEDDS. Log P value should be high.

9. Formulation Methodology: The method of making self- micro emulsion drug delivery system includes various steps as described below:

- Solubility determination of drug in various components- The saturation solubility of drug is determined in various oils, surfactants and co- surfactants. The excess amount of drug is added to a capped glass vials containing vehicle in water bath with constant stirring using a vortex mixer to facilitate drug Solubilization. The mixture is kept at ambient temperature for 72 hours to attain equilibrium. The samples are then centrifuged and supernatant is taken and drug assay is performed.

- Preparation of phase diagram (pseudo ternary phase diagram): The phase behavior of simple micro emulsion 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. 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 a particular mixture can be visually assessed. It should be noted that not every combination of components produce micro emulsions over the whole range of possible compositions, in some instances the extent of micro emulsion formation may be very limited. Heat and sonication are often used, particularly with systems containing nonionic surfactants, to speed up the process. Care must be taken to ensure not only that the temperature is precisely and accurately controlled, but also that observations are not made on metastable system. Clearly, however, time constraints impose a physical limit on the length of time system can be left to equilibrate and consequently the elimination of metastable states can be difficult to ensure in practice, although centrifugation can be useful to speed up any separation. Within this region, and indeed other multi phase regions of the ternary phase diagram, micro emulsions can exist in equilibrium with excess water or oil phases.

- Solubilizing a poorly water-soluble drug and/or pharmaceutical ingredient, in a mixture of surfactant, co surfactant and solvent. Mix thoroughly the oil phase, if necessary, by heating or other preparatory means, with the solubilized drug formulation. The emulsion can then be added or filled to a suitable dosage form such as soft or hard-filled gelatin capsules and allowed to cool.

Mechanism Of Bioavailability Enhancement Of Drugs From SMEDDS: It is important to have some understanding of what happens to SMEDDS on ingestion. As triglyceride is the one of the component of SMEDDS, it is helpful to consider the mechanisms by which these materials are absorbed from the GI tract.

- The triglyceride molecule contains saturated or unsaturated alkyl groups. The ester groups of the triglycerides are prone to hydrolysis and this represents the major initial route of metabolism within the GIT.

- Digestion of triglycerides may occur in the stomach due to the presence of gastric lipase, the digestion of fats is believed to be due to emulsification of fats via mechanical agitation.

- On entering to the upper section of small intestine, two processes occur
  1. The fat droplets are further emulsified by the bile salts, monoglycerides, cholesterol, lecithin and lyssolecithin to produce droplets with a 0.5-1 µm diameter.
  2. The fatty acids are distributed in the aqueous solution, the emulsion droplet and micelles, while the monoglycerides are incorporated into the micelles and are believed to swell the structure, allowing incorporation of other water insoluble components such as certain vitamins.

- The micelles then diffuse through the gut contents to the intestinal mucosa, adjacent to which is unstirred water layer. Incorporation into micelles facilitates this diffusion process compared to the much larger oil droplets.

- Short chain fatty acids may diffuse directly into the portal supply, while longer chain acids are (<12 carbon atoms) re synthesized into triglycerides in the intestinal mucosa.

Evaluation of SMEDDS: Thermodynamic stability studies: The physical stability of a lipid based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In the event of poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well.
The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 mL of water at 37 ± 0.5 °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

- **Grade A:** Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
- **Grade B:** Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
- **Grade C:** Fine milky emulsion that formed within 2 min.
- **Grade D:** Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).
- **Grade E:** Formation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Droplet size determination

The SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. so, it should be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination confirm whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosities then it is w/o type of the system.

**Dispersibility test**

Nepheloturbidimetric evaluation is done to monitor the growth of turbidity (rate of emulsification) of oil droplets formed by self microemulsifying oily formulation could produce strong interaction with the mucosal surface, improve the adhesion of the positively charged droplets to the intestinal mucosa, and increase drug uptake from the mucosa, further improving the oral bioavailability.

Zeta potential for microemulsion is determined using Zetasizer HSA 3000 (Malvern Instrument Ltd., UK). Samples are 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.

**Refractive Index and Percent Transmittance**

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333). The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature.

**In vitro release**

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

**Drug content**

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

**Stability**

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

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

**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. The plasma profiles of the drug in experimental animals following oral administration of the conventional tablet and SMEDDS form are compared. Pharmacokinetic parameters of the maximum plasma concentration (Cmax) and the corresponding time (Tmax) for the drug following oral administration are calculated. The area under the concentration–time curve (AUC0→24h) is estimated according to the linear trapezoidal rule. The relative bioavailability (BA) of SMEDDS form to the conventional table is calculated using the following Equation

\[
\text{Relative BA (％)} = \left( \frac{AUC_{\text{test}}}{AUC_{\text{ref}}} \right) \times \left( \frac{\text{Dose}_{\text{test}}}{\text{Dose}_{\text{ref}}} \right)
\]
CONCLUSION

Self-microemulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SMEDDSs, which have been shown to substantially improve oral bioavailability and thus the dose of the drug can be reduced. 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.

REFERENCES


Table 1: Example of Surfactants, Co-surfactant, Oils and Co-solvent used in Commercial Formulations

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Excipient name (commercial name)</th>
<th>Examples of commercial products in which it has been used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Surfactants/co-surfactants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polysorbate 20 (Tween 20)</td>
<td>Targetin soft gelatin capsule</td>
</tr>
<tr>
<td></td>
<td>(Cremophor RH40)</td>
<td>Ritonavir soft gelatin capsule, Ritonavir oral solution,</td>
</tr>
<tr>
<td></td>
<td>(Labrafil M 2125 Cs)</td>
<td>Nerol soft gelatin capsule</td>
</tr>
<tr>
<td></td>
<td>D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)</td>
<td>Agenerase Soft gelatin capsule, Agerenase oral solution</td>
</tr>
<tr>
<td>2.</td>
<td>Co-solvents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethanol, Glycerin, Polypylene glycol</td>
<td>Nerol soft gelatin Capsule,</td>
</tr>
<tr>
<td></td>
<td>Polypylene glycol, Ethanol</td>
<td>Nerol Oral Solution</td>
</tr>
<tr>
<td></td>
<td>Polypylene glycol, Ethanol, polyethylene glycol</td>
<td>Gengraf hard gelatin capsule</td>
</tr>
<tr>
<td></td>
<td>Ethanol, Glycerin</td>
<td>Sandimmune soft gelatin capsule</td>
</tr>
<tr>
<td></td>
<td>Polypylene glycol</td>
<td>Sandimmune soft gelatin capsule</td>
</tr>
<tr>
<td></td>
<td>Polypylene glycol, polyethylene glycol</td>
<td>Sandimmune oral solution</td>
</tr>
<tr>
<td></td>
<td>Polypylene glycol</td>
<td>Lamprone soft gelatin capsule</td>
</tr>
<tr>
<td></td>
<td>Polyethylene glycol, polyethylene glycol</td>
<td>Agenerase oral solution</td>
</tr>
<tr>
<td></td>
<td>Polyethylene glycol</td>
<td>Targetin soft gelatin capsule, Agenerase soft capsule</td>
</tr>
</tbody>
</table>

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### Table 2: Examples of Marketed SEDDS & SMEDDS Formulations

<table>
<thead>
<tr>
<th>Compound</th>
<th>Drug name</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>Immunosuppressant</td>
</tr>
<tr>
<td>Norvir®</td>
<td>Ritonavir</td>
<td>Soft gelatin capsule</td>
<td>Abbott Laboratories</td>
<td>HIV antiviral</td>
</tr>
<tr>
<td>Fortovase®</td>
<td>Saquinavir</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 Smithkline</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 Capsule</td>
<td>Genus</td>
<td>Antihyperlipoproteinemic</td>
</tr>
<tr>
<td>Sandimmune®</td>
<td>Cyclosporine A/II</td>
<td>Soft gelatin capsule</td>
<td>Novartis</td>
<td>Immunosuppressant</td>
</tr>
<tr>
<td>Targretin®</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 Capsule</td>
<td>Abbott</td>
<td>Immunosuppressant</td>
</tr>
</tbody>
</table>

**Figure 1: Pseudo-Ternary Phase Diagram Illustrating Region of Microemulsion Formation**