INTERNATIONAL RESEARCH JOURNAL OF PHARMACY ISSN 2230 – 8407
Available online www.irjponline.com Review Article

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

Mittal Pooja*, Rana A.C, Bala Rajni, Seth Nimrata
Rayat Institute of Pharmacy, Department of Pharmaceutics, Ropar , S.B.S Nagar-144533 (Punjab) India

Article Received on: 18/10/11 Revised on: 25/11/11 Approved for publication: 20/12/11

*Email: poojamittal2009@gmail.com

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, Self 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, Lipophillic 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 proportionality[1]. 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) fluids [1]. 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 nm [3]. 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 [4,5,6]. After self dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets [7]. 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 ileum [8]. A cationic emulsion has greater bioavailability than an anionic emulsion [9,10].

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 [11-17]

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.

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[18]
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 predicative *in vitro* models for assessment of the Formulations [19].
Formulation Consideration [11]
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 [20,21,22]
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 [10]. The usual surfactant concentration in SMEDDS formulation and maintaining emulsion stage ranges from 30-60% w/w of the formulation [11,12].
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/mandatory 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.

4. 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;

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

5. 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.

6. Polymers [23]: 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.

Drug Properties Suitable For SMEDDS[25,26]

- 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

Formulation Methodology[7]

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 screw capped glass vials containing vehicle in water bath with constant stirring using a vortex mixture 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)[26,27]

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 Self-Emulsification [11,23]

Self emulsification occurs, when the entropy change for dispersion is greater than the energy required to increase the surface area of the dispersion [28]. The free energy of conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation.

$$G=\Sigma N \pi r^2 \sigma$$

Where

δG is the free energy associated with the process

N is the number of droplets of radius r,

σ is interfacial energy with time

With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area and subsequently, the free energy of the system. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets and hence, reduce the interfacial energy, as well as providing a barrier to coalescence. In case of self micro emulsifying system, the free energy required to form the micro emulsion is either very low or negative, the emulsion process occurs spontaneously [29]

Mechanism Of Bioavailability Enhancement Of Drugs From SMEDDS[30,31,32]

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 lysolecithin 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[33]

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 addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well.

- **Heating cooling cycle**: Six cycles between refrigerator temperature (4°C) and 45°C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.
- **Centrifugation:** Passed formulations are centrifuged at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.
- **Freeze thaw cycle:** Formulations are subjected to three freeze thaw cycles. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking [34].

Dispersibility test

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 ^{0}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**: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

Turbidimetric Evaluation [35,36,37]

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self microemulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification).

Viscosity 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 conform 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 [34].

Droplet size determination

It is a precise method for evaluation of stability. Size of droplet is measured by photon correlation spectroscopy (PSC) with Zetasizer. All measurements are carried out at scattering angle of 90° and 25°C temperatures. Prior to measurement, microemulsion is diluted in two-steps with pure water then it is filtered through a 0.22um filter just before it is added to cuvette. In first step it is diluted with equal amount of water. In second step the mixture is further diluted to appropriate concentration for the measurement. That depends on droplet size (Usually diluted 100-200 times).

Zeta potential measurement

Gershanik and Benita introduced a new parameter for the characterization of SMEDDS i.e charge of the oil droplets. Barry and Eggenton have shown that the intestinal cell interior is negatively charged relative to mucosal fluid. The positively charged 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 tranmittance 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 [38].

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 (*C*max) and the corresponding time (*T*max) 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

Relative BA *(%)* = $(AUC_{test} / AUC_{ref}) \times (Dose_{ref} / Dose_{test})$

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, SMEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

REFERENCES

1. Kyatanwar AU, Gajbhiye ND, Jadhav KR, Kadam VJ. Solid Self-Emulsifying Drug Delivery Systems: A Review. J Pharm Res 2010; 3(4): 877-882
2. Stegemanna S, Leveillerb F. When poor solubility becomes an issue: From early stage to proof of concept. Eur J Pharm Sci 2007; 31: 249-261
3. Wakerly MG, *et al*. Self-emulsification of veg: Oilnon-ionic surfactant mixtures. ACS symp 1986; 311: 242-255
4. Wakerly MG, Pouton CW, Maekin BJ. Evaluation of the Self Emulsifying performance of Non-ionic Surfactant-Vegetable-oil mixture. J Pharm Pharmacol 1987, 39
5. Pouton CW. Effects of the inclusion of a Model Drug on the Performance of Self-Emulsifying Formulations. J Pharm Pharmacol 1985, 37
6. Gupta RN, Gupta R, Singh RG. Enhancement of Oral Bioavailability of Lipophillic Drugs from Self-Microemulsifying Drug Delivery System (SMEDDS). Int J Drug Dev Res 2009; 1(1): 10-18
7. Corbo DC, Liu JC, Chein YW. Characterization of the Barrier Properties of Mucosal Membranes. J. Pharm. Sci 1990; 79: 202-206
8. Gershanik, T. et al. Charge Dependent Interaction of Self Emulsifying Oil Formulations with CaCo-2 Cell Monolayers: Binding Effects on Barrier Function and Cytotoxicity. Int J Pharm 2000; 211 (1-2): 29-36
9. Gershanik, T. Benzeno, S and Benita S, Interactions of the SELDDS with Mucosa of Everted Rat Intestine as a Function Charge and Particle Size. Pharm Res 1998; 15: 863-869
10. Shinde G, Kuchekar S , Kamble P, Kuchekar A, Kshirsagar R, Kuchekar B. Self Micro Emulsifying Drug Delivery System: A Novel Approach for Hydrophobic Drugs. Int J Pharm sci 2011; 3(1): 988-1005
11. Khoo SM, Humberstone AJ, Porter CJ, Edwards GA, Charman WN. Formulation Design and Bioavailability Assessment of Lipidic Self-Emulsifying Formulations of Halofantrine. Int J Pharm 1998; 167: 155-164
12. Kawakami K, Yoshikawa T, Moroto Y *et al*. Microemulsion Formulation for Enhanced Absorption of Poorly Soluble Drugs. Prescription design. J Control Res 2002; 81: 75-82.
13. Cortesi R, Espositi E, Maietti A, Menegatti E, Nastruzzi C. Formulation Study for the Antitumor Drug Camptothecin: Liposomes, Micellar Solutions and a Microemulsion. Int J Pharm 1997; 159: 95-103
14. Tolle S, Zuberi T, Lawrence MJ. Physiochemical and De-Solubilisation Properties of N, N-dimethyl-N-(3-dodecyloxy propyl) Amine Oxide: A Biodegradable Non-ionic Surfactant. J Pharm Sci 2000; 89:798-806
15. Sachan R, Khatri K, Kasture S.B. Self Emulsifying Drug Delivery System: A Novel Approach for Enhancement of Bioavailability. Int J Pharm Tech Res 2010; 2(3): 1738-1745
16. Patravale VB, Date AA, Kale AA. Oral Self Microemulsifying System: Potential in DDS. Pharm Tech, Express Pharma Pulse Special Feature 2003; 44-48.
17. Shukla BJ, Koli RA, Ranch MK *et al*. Self Micro Emulsifying Drug Delivery System. Pharma Science Monitor 2010; 1(2): 13-33
18. Mistry RB, Sheth N. A Review: Self Emulsifying Drug Delivery System. Int J Pharm pharmaceutical sci 2011; 3(2): 23-28
19. Patel PA, Chaulang GM, Akolkotkar A, Mutha SS, Handicap SR and Bhosale AV. Self Emulsifying Drug Delivery System- A Review. Res J Pharm and Tech 2008; 1(4): 313-323
20. V. Mahesh. Patel, Feng-Jing Chen. Compositions and Methods for Improved Delivery of Hydrophobic Agents. United States Patent 6451339. 2002.
21. Methods and formulation for increasing the bioavailability of poorly water-soluble drugs. J Pharm. Edu 2002; 36(4):184-190
22. Reiss H. Entropy Induced Dispersion of Bulk Liquids. J. Colloids Interface Science 1975; 53: 61-70
23. Patel PA, Chaulang GM, Akolkotkar SR, Mutha SS, Hardikar SR, Bhosale AV. Self Emulsifying Drug Delivery System: A Review. Res J Pharm and Tech. 2008; 1(4): 315
24. Poutan CW, Self Emulsifying Drug Delivery System: Assessment of the Efficacy of Emulsification. Int J Pharm 1985; 27: 335-348
25. Ho-JK, Kyung AY, Mikyoung H, Eunseok P, Sang-Cheol C. Preparation and In-vitro Evaluation of Self Micro Emulsifying Drug Delivery Systems containing Idebenone. Drug Dev Ind Pharm 2000; 26(5): 523-529
26. Patel MJ, Patel SS, Patel NM, Patel MM. A Self Emulsifying Drug Delivery System (SMEDDS). Int J Pharm Sci Rev Res 2010; 4(3): 29-35
27. Pouton CW. SEDDS: Assessment of the Efficiency of Emulsion, Int J Pharm 1985; 27:335-348
28. Craig DQM, Lievens HSR, Pitt KG, Storey DE. An Investigation into the Physico-Chemical Properties of Self-Emulsifying Systems using low frequency Dielectric Spectroscopy, Surface Tension measurements and Particle Size Analysis. Int J Pharm 1993; 96:147-155
29. Wakerly MG, Pouton CW, Meakin B, Morton F. Self Emulsification of Veg: Oil-Nonionic-Surfactant mixtures. ACS symp Ser 1986; 311: 242-255
30. Groves MJ, Mustafa RMA, Carless JE. Measurement of the Spontaneity of Self Emulsifiable Oils. J Pharm Pharmcol 1974; 26: 671-688
31. Bates TR, Sequeri JA. Bioavailability of Micronized Griseofulvin from Corn Oil in Water Emulsion, Aqueous Suspension and Commercial Tablet form in Humans. J Pharm Sci 1975; 64: 793-797
32. Bleodow DC. (P.h.D. Thesis), Washington University State. 1974
33. Shafiq S, Faiyaz S, Sushma T *et al*. Development and Bioavailability Assessment of Remipril Nanoemulsion Formulation. Eur J Pharm Biopharm 2007; 66: 227-243
34. Patil P, Vandana P, Paradkar P. Formulation of Self Emulsifying Drug Delivery System for Oral of Simvastatin: In Vitro and In Vivo Evaluation. Acta Pharma 2007; 57:111-122
35. Patel PA, Chaulang GM, Akolkotkar A *et al*. Self Emulsifying Drug Delivery System: A Review Research. J Pharm and Tech 2008; 1(8):313-323
36. Gershanik T, Benita S. Positively Charged Self Emulsifying Oil Formulation for Improving Oral Bioavailability of Progesterone. Pharm Dev Technol 1996; 1:147-157
37. Kang B, Lee J, Chon S *et al*. Development of Self Microemulsifying Drug Delivery Systems (SMEDDS) for Oral Bioavailability Enhancement of Simvastatin in Beagle Dogs. Int J Pharm 2004; 274: 65-73
38. Julianto T, Yuen K, Noor A. Improved Bioavailability of Vitamin E with a Self-Emulsifying Formulation. Int J Pharm 2000; 200: 53–57

Table 1: Example of Surfactants, Co-surfactant, Oils and Co-solvent used in Commercial Formulations[24]

Sr. No.	Excipient name (commercial name)	Examples of commercial products in which it has been used
1.	**Surfactants/co-surfactants**	
	Polysorbate 20 (Tween 20)	Targretin soft gelatin capsule
	(Cremophor RH40)	Ritonavir soft gelatin capsule, Ritonavir oral solution, Nerol soft gelatin capsule
	(Labrafil M 2125 Cs)	Sandimmune soft gelatin capsules
	(Labrafil M1944 Cs)	Sandimmune oral solution
	D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)	Agenerage Soft gelatin capsule, Agenerage oral solution
2	**Co-solvents**	
	Ethanol, Glycerin, Polypylene glycol	Nerol soft gelatin Capsule,
	Polypylene glycol, Ethanol	Nerol Oral Solution
	Polypylene glycol, Ethanol, polyethylene glycol	Gengraf hard gelatin capsule
	Ethanol, Glycerin	Sandimmune soft gelatin Capsule
	Ethanol	Sandimmune oral solution
	Polypylene glycol	Lamprene soft gelatin capsule
	Polypylene glycol, polyethylene glycol	Agenerase oral solution,
	Polyethylene glycol	Targretin soft gelatin capsule, Agenerase soft capsule

3	Lipid ingredients	
	Corn oil mono, di, tri-glycerides	Nerol soft gelatin Capsule
	DL-alpha-Tocopherol, Corn oil mono, di, tri-glycerides	Nerol Oral solution
	DL-alpha-Tocopherol, Medium chain mono-and di-glycerides	Fortavase soft gelatin capsule
	Fractionated triglyceride of coconut oil (medium-chain triglyceride)	Rocaltrol soft gelatin capsule, Hectrol soft gelatin capsule
	Fractionated triglyceride of palm seed oil (medium-chain triglyceride)	Rocatrol oral solution
	Mixture of mono-and di-glycerides of caprylic/capric acid	Avodat soft gelatin capsule
	Oleic oil	Norvir soft gelatin capsule, Ritonavir soft gelatin capsule
	Corn oil	Sandimmune soft gelatin capsule, Depakene capsule
	Olive oil	Sandimmune oral solution
	Sesame oil	Marinol soft gelatin capsule
	Hydrogenated soya bean oil, Peanut oil	Accutane soft gelatin capsule
	Soya bean oil	Vesanoid soft gelatin capsule

Table 2: Examples of Marketed SEDDS & SMEDDS Formulations[18]

Compound	Drug name	Dosage form	Company	Indication
Neoral®	Cyclosporine A/I	Soft gelatin capsule	Novartis	Immunosuppressant
Norvir®	Ritonavir	Soft gelatin capsule	Abbott Laboratories	HIV antiviral
Fortovase®	Saquinavir	Soft gelatin Capsule	Hoffmann La Roche inc.	HIV antiviral
Agenerase®	Amprenavir	Soft gelatin capsule	Glaxo Smithkline	HIV antiviral
Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Lipirex®	Fenofibrate	Hard gelatin Capsule	Genus	Antihyperlipoproteinemic
Sandimmune®	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immunosuppressant
Targretin®	Bexarotene	Soft gelatin capsule	Ligand	Antineoplastic
Rocaltrol®	Calcitriol	Soft gelatin capsule	Roche	Calcium regulator
Gengraf®	Cyclosporine A/III	Hard gelatin Capsule	Abbott	Immunosuppressant

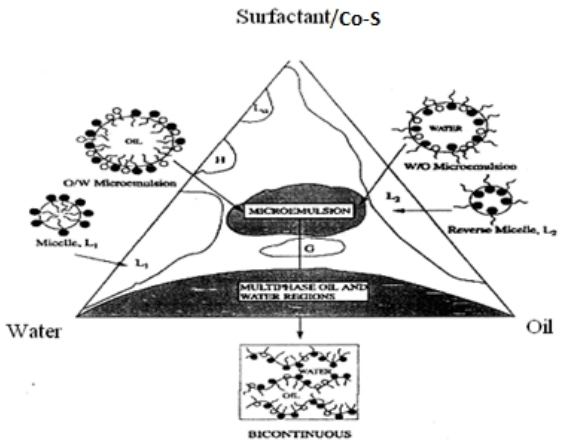

Figure 1: Pseudo-Ternary Phase Diagram Illustrating Region of Microemulsion Formation