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SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS): A CONVENTIONAL AND ALTERNATIVE APPROACH TO IMPROVE ORAL BIOAVILABILITY

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ABSTRACT: The oral delivery of hydrophobic drugs presents a major challenge because of the low aqueous solubility of such compounds. Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. SEDDS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil-in-water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids. The efficiency of oral absorption of the drug compound from the SEDDS depends on many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-emulsifying systems. Although many studies have been carried out, there are few drug products on the pharmaceutical market formulated as SEDDS confirming the difficulty of formulating hydrophobic drug compounds into such formulations. At present, there are four drug products, sandimmune and sandimmunneoral (cyclosporin A), norvir (ritonavir), and fortovase (saquinavir) on the pharmaceutical market, the active compounds of which have been formulated into specific SEDDS. Significant improvement in the oral bioavailability of these drug compounds has been demonstrated for each case. The fact that almost 40 % of the new drug compounds are hydrophobic in nature implies that studies with SEDDS will continue, and more drug compounds formulated as SEDDS will reach the pharmaceutical market in the future.

INTRODUCTION: SEDDS are used to solve low bioavailability issues of poorly soluble and highly permeable compounds.

Hydrophobic drugs can be dissolved in these systems, enabling them to be administered as a unit dosage form for per-oral administration.

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When SEDDS formulation is released in the lumen of the gastrointestinal tract, they come in contact with GI fluid and form a fine emulsion (micro/nano) so called as in situ emulsification or self-emulsification which further leads to solubilization of drug that can subsequently be absorbed by lymphatic pathways, bypassing the

hepatic first-pass effect. This bioavailability enhancing property has been associated with a number of *in-vivo* properties of the lipid formulations including ¹:

- Formation of fine dispersions and micellar suspensions to prevent precipitation and re-crystallization of the drug compound.
- Ability of certain lipid compounds and their metabolites to initiate changes in the gastrointestinal fluid to favour improved drug absorption.
- Inhibition of cellular efflux mechanisms, which keep drugs out of circulation.

Certain lipid excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism. Fig. 1 shows how self-emulsification of drugs occurs after oral administration.

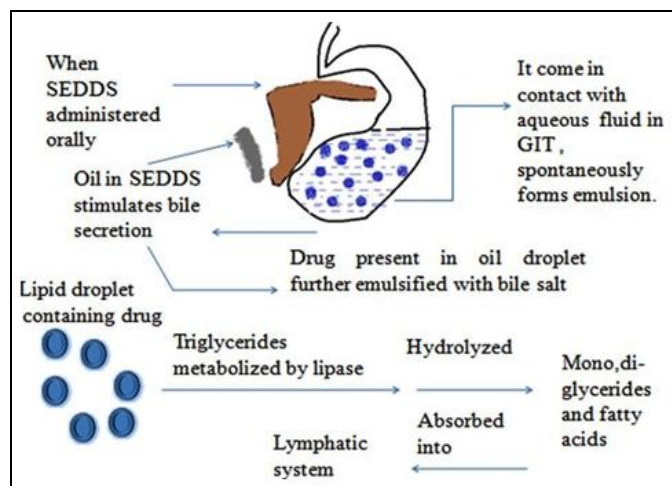


FIG. 1: PROCESS OF SELF EMULSIFICATION

1.1. Self-Nano Emulsifying Drug Delivery System (SNEDDS): SNEDDS are nano-emulsions formed by SEDDS. They are heterogeneous dispersions of two immiscible liquids (oil-in-water [O/W] or water-in-oil [W/O]) having a mean droplet size in the nanometric scale (typically 20-200 nm), regardless of method of preparation. This is particularly important for drugs for increasing the solubility such as simvastatin, atorvastatin ².

1.2. Self-Micro Emulsifying Drug Delivery System (SMEDDS): SMEDDS are micro-emulsions formed by the SEDDS. It is thermodynamically stable and forms optically transparent emulsion. The major difference

between micro-emulsions and common emulsions is mainly due to particle size of droplets. 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. Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of solid dosage form and it can easily penetrate the gastrointestinal tract and be absorbed. The bioavailability of drugs is therefore improved ³.

1.3. Properties of SEDDS: ⁴

1. They are able to self-emulsify rapidly in gastrointestinal fluids and under the influence of gentle agitation provided by peristaltic and other movements of gastro intestinal tract, they form a fine o/w emulsion.

2. They can effectively incorporate drug (hydrophobic or hydrophilic) within the oil surfactant mixture.

3. They can be used for liquid as well as solid dosage forms.

4. They require lower dose of drug with respect to conventional dosage forms.

1.4. Advantages of Self-emulsifying Drug Delivery System over Conventional Drug Delivery Systems: ³

1. Fine oil droplets of SMEDDS would pass rapidly facilitating wide distribution of the drug throughout the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.

2. Emulsions are sensitive and metastable dispersed forms while SMEDDS are physically stable formulations.

3. As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.

4. Potential advantages of these systems include enhanced oral bioavailability, more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile

environment in the gut. Thus, for 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.

5. Ease of manufacture and scale-up is one of the most important advantages that make SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposome, nano particles, *etc.*, as they require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large - scale manufacturing. This explains the interest of pharmaceutical industry in the SMEDDS.

1. 5. Disadvantages of Self-Emulsifying Drug Delivery Systems:³

1. 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.

2. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.

3. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.

4. Volatile co-solvents in the conventional SMEDDS formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

5. Formulations containing several components become more challenging to validate.

6. High production costs.

7. Low drug incompatibility.

8. Drug leakage. So it may allow less drug loading.

1.6. Composition of Self Emulsifying Drug Delivery System:

1. Active Pharmaceutical Ingredient (API): As, SEDDS are used to increase the solubility of poor water-soluble drugs, BCS class II drugs are preferred *e.g.* itraconazole, nifedipine, vitamin E, simvastatin, danazol, ketoconazole, mefenamic acid, naproxen, carbamazepine^{5,6}.

2. Excipients used in SEDDS: Considering, pharmaceutical acceptability and the toxicity issues the selection of excipients is really critical. So there is a great restriction as to which excipients should be used. The self-emulsification process is specific to the concentration and nature of the oil/surfactant ratio, surfactant/co-surfactant ratio and the temperature at which self-emulsification occurs. So, this entire factor must be considered during selection of excipients in SEDDS.

a. Oils: Oils can solubilize the required dose of the lipophilic drug and facilitate self-emulsification and also they can increase the fraction of lipophilic drug transported *via* the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride⁷. Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Novel semi-synthetic MCT, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular MCT oils in the SMEDDS MCT are more soluble and have a higher mobility in the lipid/water interfaces than LCT associated with a more rapid hydrolysis of MCT.

In general, when using LCT, a higher concentration of cremophor RH40 is required to form microemulsions compared with MCT. Edible oils are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties⁸. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. **Table 1**, given below gives a list of different oils used to solubilize different drugs.

b. Surfactants: Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively

high hydrophilic- lipophilic balance (HLB) and less toxicity than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. Safety is a major determining factor in choosing a surfactant.

Hence emulsifiers of natural origin are preferred than the synthetic surfactant, but they have a limited self-emulsification capacity. There is a relationship between the droplet size and the concentration of the surfactants being used. In some cases, increasing the surfactant concentration could lead to decreasing mean droplet size (SMEDDS), this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface.

On the other hand, the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase. The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited p-glycoprotein drug efflux. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. A list of surfactant used in marketed SEDDS is given in **Table 2**.

TABLE 1: TYPE OF OILS USED IN MARKETED SEDDS

Type of oil	Drug	Marketed Product
Corn oil	Valproic acid	Depakene capsule
Sesame oil	Dronabinol	Marinol soft gelatin capsule
Soya bean oil	Isotretinoin	Accutane soft gelatin capsule
Peanut oil	Progesterone	Prometrium soft gelatin capsule
Hydrogenated soya bean oil	Isotretinoin	Accutane soft gelatin capsule

TABLE 2: TYPE OF SURFACTANTS USED IN MARKETED SEDDS

Surfactant	Drug	Marketed Product
Span 80, Tween 80	Cyclosporine	Gengraf soft gelatin capsule
Tween 20	Bexarotene	Targretin hard gelatin Capsule
Cremophor RH 40	Carmustine	BCNU self-emulsifying implant
D-alpha Tocopheryl Poly ethylene Glycol	Amprenavir	Agenerase Soft Gelatin capsule, Agenerase oral solution

c. Co-surfactants: The production of an optimum SMEDDS requires relatively high concentrations (generally more than 30 % w/w) of surfactants but it causes GI irritation. So co surfactant is used to reduce concentration of surfactant. Role of the co-surfactant together with the surfactant is to lower 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 and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again.

This process known as 'spontaneous emulsification' forms the micro emulsions. Organic solvents, suitable for oral administration {ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc} may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base

and can act as co-surfactant in the self- emulsifying drug delivery systems, although alcohol- free self-emulsifying micro emulsions have also been described in the literature ³.

Such systems may exhibit some advantages over the other formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug.

On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Hence, proper choice has to be made during selection of components. A list of surfactant used in marketed SEDDS is given in **Table 3**.

TABLE 3: TYPE OF CO SURFACTANTS USED IN MARKETED SEDDS

Co-surfactants	Marketed preparation
Glycerin	Sandimmune soft gelatin capsule.
Propylene glycol	Neoral soft gelatin, Neoral oral solution, Gengraf hard gelatin, Lamprene soft gelatin capsule.
Ethanol	Neoral Soft gelatin and Neoral oral, sandimmune soft gelatin and oral sol, gengraf hard gelatin capsule.

d. Viscosity Enhancers: The viscosity of the emulsions can be altered by the use of additional material such as acetyl alcohol, tragacanth, beeswax and stearic acids *etc.*

e. Polymers: Polymer matrix (inert) present in 5 to 40 % w/w, which is not ionisable at physiological pH are able to form matrix. Examples are hydroxyl propyl methyl cellulose, ethyl cellulose, *etc.*

f. Antioxidant Agents: Lipophilic antioxidants (*e.g.* α tocopherol, propyl gallate, ascorbic palmitate) stabilize the oily content of SEDDS formulations.

1.7. Factors affecting SMEDDS:

1. Nature and Dose of the 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 SMEDDS³. The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase.

2. Concentration of Surfactant or Co- surfactant: If surfactant or co-surfactant is contributing to the greater extent in drug solubilization 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.

3. Polarity of the Lipophilic Phase: The polarity of the lipid phase is one of the factors that govern the drug release from the microemulsions. 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 micronized drug.

1.8. The Emulsification Process:

Mechanism of Self-emulsification: Self emulsification occurs, when the entropy (energy) change occurs. 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.

$$\Delta G = \Sigma N \pi r^2 \sigma \dots\dots\dots (i)$$

Where, ΔG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r , σ is interfacial energy 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 coalescence⁹. In case of self-emulsifying system, the free energy required to form the emulsion is either very low or positive or negative then, the emulsion process occurs spontaneously¹⁰.

Emulsification require very little input energy, involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing¹¹. Emulsification can be associated with the ease by which water penetrates into the various liquid crystals or phases get formed on the surface of the droplet. The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the interface formation between the oil and aqueous continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface, which occurs until the solubilization limit is reached close to the interface¹².

Further, aqueous penetration will result in the formation of the dispersed liquid crystalline phase. As the aqueous penetration proceeds, eventually all materials close to the interface will be liquid crystal, the actual amount depending on the surfactant concentration in the binary mixture once formed, rapid penetration of water into the aqueous

cores, aided by the gentle agitation of the self-emulsification process causes interface disruption and droplet formation. The high solubility of these self-emulsified systems to coalescence is considered to be due to liquid crystal interface surrounding the oil droplets.

1. Construction of Ternary Phase Diagrams:

This is the first step before starting the formulation. It is useful to identify best emulsification region of oil, surfactant and co-surfactant combinations. Ternary phase diagram of surfactant, co-surfactant and oil will plot; each of them, representing an apex of the triangle¹³. The methods are used to plot ternary phase diagrams are namely Dilution method and Water Titration method are shown in Fig. 2.

a. Dilution Method: Ternary mixtures with varying compositions of surfactant, co-surfactant and oil were prepared. The percentage of surfactant, co-surfactant and oil decided on the basis of the requirements. Compositions are evaluated for nanoemulsion formation by diluting appropriate amount of mixtures with appropriate double distilled water. Globule size of the resulting dispersions was determined by using spectroscopy. The area of nanoemulsion formation in Ternary phase diagram (as shown in Fig. 2a) was identified for the respective system in which nanoemulsions with desire globule size were obtain.

b. Water Titration Method: The pseudo- ternary phase diagrams were also constructed by titration of homogenous liquid mixtures of oil, surfactant and co-surfactant with water at room temperature (as shown in Fig. 2b). Oil phase, surfactant and the co-surfactant, at Km values 1.5 and 1 (surfactant: co-surfactant ratio), oily mixtures of oil, surfactant and co-surfactant were prepared varied from 9:1 to 1:9 and weighed in the same screw-cap glass tubes and were vortexed⁸. Each mixture was then slowly titrated with aliquots of distilled water and stirred at room temperature to attain equilibrium.

The mixture was visually examined for transparency. After equilibrium was reached, the mixtures were further titrated with aliquots of distilled water until they showed the turbidity. Clear and isotropic samples were deemed to be within the micro-emulsion region. No attempts were made to completely identify the other regions of the phase diagrams. Based on the results,

appropriate percentage of oil, surfactant and co-surfactant was selected, correlated in the phase diagram and were used for preparation of SMEDDS.

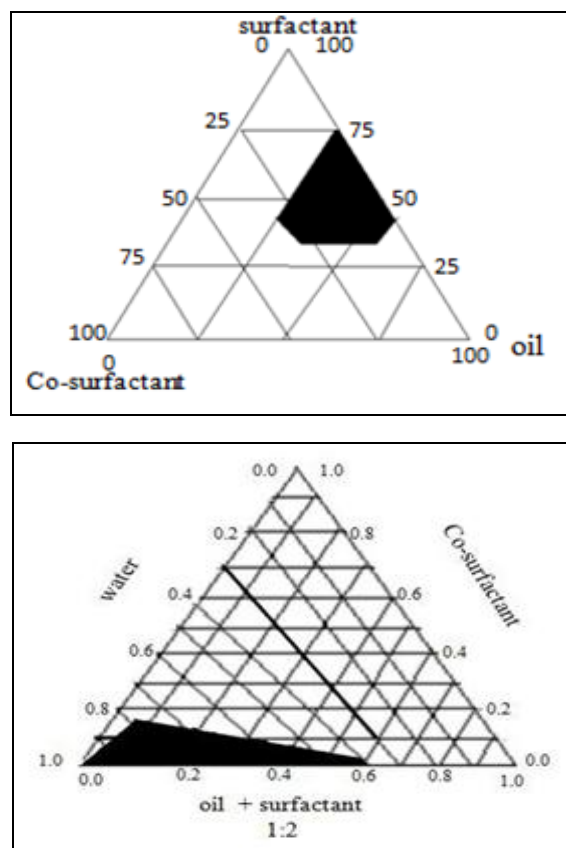


FIG. 2 (a): DILUTION METHOD (b): TITRATION METHOD TERNARY PHASE DIAGRAM

1.9. Evaluation of SEDDS: A number of tests are carried out for characterization and evaluation of SEDDS.

1. Drug Content: Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is analyzed by suitable analytical method¹⁴.

2. Dispersibility Test: The dispersibility test of SEDDS is carried out to assess its capability to disperse into emulsion and categorize the size of resulting globules. It is carried by using a standard USP dissolution apparatus 2 (paddle type). One ml of each formulation is added to 500 ml of water at 37 ± 0.5 °C and the paddle is rotated at 50 rpm. On titration with water the SEDDS formulation forms a mixture or gel which is of different type depending upon which the *in-vitro* performance of formulation can be assessed using the following grading system¹⁵.

Grade A: Rapidly forming (within 1 min) nano emulsion, 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. The stability of the formulation decreases from micro emulsion to emulgel given in **Table 4**.

TABLE 4: TYPE OF FORMULATION DEPENDING UPON VISUAL OBSERVATION

Type of formulation	Mixture/Gel
Micro emulsion	Transparent mixture
Micro emulsion gel	Transparent Gel
Emulsion	Milky or cloudy mixture
Emulgel	Milky Gel

3. Rheological Properties Determination: The SEDDS system can also be administered in soft gelatin capsules, where, it should have appreciable flow properties for processing. The rheological properties (viscosity, flow, thixotropy, static yield, creep value) of formulation (diluted to 5 % v/v water) are determined by rotational viscometers, digital instruments coupled with either cup and bob or coaxial measuring device.

A type of rotational viscometer has also been used for determination of viscosity of fresh as well as other SEDDS formulations which has been stored for longer duration of time ¹⁶.

Viscosity determination of liquid SEDDS also indicates whether the system is o/w or w/o, as low viscosity systems are o/w and high viscosity systems are usually w/o in nature. Viscosity of formulation is inversely proportional to dilution.

4. Thermodynamic Stability Studies: The physical stability of a formulation is very important

for its performance as it can be adversely affected by precipitation of the drug in excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficacy. Also the incompatibilities between formulation and gelatin shell of capsule (if formulation filled in capsule) may cause brittleness, softness and delayed disintegration or incomplete release of drug. The following cycles are carried out for these studies).

a. Heating Cooling Cycle: ¹⁷ Six cycles of cooling and heating between refrigerator temperature (4 °C) and elevated temperature (45 °C) with exposure at each temperature for not less than 48 hours are carried. Those formulations, which are stable, are then subjected to centrifugation test.

b. Centrifugation: Formulations which pass the heating cooling cycle are centrifuged at 3500 rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze thaw stress test.

c. Freeze Thaw Stress Cycle: Three freeze thaw cycles b/w -21 °C and 25 °C with storage at each temperature for not less than those formulations which pass this test show good stability with no phase separation, cracking or creaming. The formulations that pass this test are then further taken for dispersibility test for assessment of self-emulsification efficiency.

5. Robustness to Dilution: Emulsions upon dilution with various dissolution media should not show any phase separations or precipitation of drug even after 12 hrs of storage, such formulation is considered as robust to dilution ¹⁸.

6. Turbid Metric Evaluation: Turbidity is a parameter for determination of droplet size and self-emulsification time ¹⁹ Fixed quantity of SEDDS is added to fixed quantity of suitable medium (0.1 N HCl or Phosphate Buffer) under continuous stirring at 50 rpm on magnetic stirrer at optimum temperature and the turbidity is measured using a turbidimeter. Since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity *i.e.* rate of emulsification. Turbidimetric evaluation

is carried out to monitor the growth of droplet after emulsification.

7. Droplet Size Analysis and Particle Size Measurements: 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 nm⁴.

8. Self-Emulsification Time: The self emulsification time is determined by using USP dissolution apparatus 2 at 50 rpm, where 0.5 g of SEDDS formulations is introduced into 250 ml of 0.1N HCl or 0.5% SLS (Sodium Lauryl Sulphate) solution. The time for emulsification at room temperature is indicated as self- emulsification time for the formulation⁴.

9. In-vitro Diffusion Study: This study is done to determine release behaviour of formulation using dialysis technique where phosphate buffer (pH 6.8) is generally used as dialyzing medium²⁰. One end of the dialysis membrane is tied with a thread and 1 ml of the SEDDS formulation along with 0.5 ml of dialyzing medium are filled in the membrane. The other end of membrane is also tied with thread and then allowed to rotate in dialyzing medium at 100 rpm using magnetic stirrer or dissolution apparatus. Samples are withdrawn at different time intervals and then after suitable dilution are analyzed. Volume of samples withdrawn is replaced with fresh dialyzing medium.

10. In-vitro Dissolution Technique: The quantitative in vitro dissolution studies are carried out to assess drug release from oil phase into aqueous phase by USP type 2 dissolution apparatus using 500 ml of simulated gastric fluid containing 0.5 % w/v of SLS at 50 rpm and maintaining the temperature at 37 ± 0.5 °C. Aliquots of samples are withdrawn at regular intervals of time and volume withdrawn is replaced with fresh medium. Samples taken are then analyzed by using UV spectrophotometer or any other suitable technique³¹.

11. Liquefaction Time: This test is done to determine the time required by solid SEDDS formulation to melt *in-vivo* in the absence of

agitation in simulated gastric fluid²¹. The formulation is packed in a transparent polyethylene film and tied to the bulb of thermometer. The thermometer is then placed in round bottom flask in which simulated gastric fluid without pepsin is filled. The temperature is maintained at 37 ± 0.5 °C by using heating mantle²¹.

12. Refractive Index (R.I.) and Percent Transmittance: Refractive Index and percent transmittance are determined to check the transparency of formulation. Refractive Index of the formulation is measured by refractometer by placing drop of solution on slide and then comparing with water (R.I = 1.333). The percent transmittance of the formulation is measured at a particular wavelength using UV spectrophotometer by using distilled water as blank²².

If R.I. of formulation is similar to that of water and formulation having percent transmittance is greater than 99%, then the formulation are transparent in nature.

1.10. Dosage Forms of SEDDS: Table 5 shows, Studies carried out on different dosage forms.

1. Self-Emulsifying Capsules: Capsule having conventional liquid self-emulsifying formulation, upon administration form droplets of micro emulsion spontaneously and then disperse in gastro intestinal tract and yield improved absorption. They however have certain limitations as if irreversible phase separation of microemulsion takes place, then drug absorption decreases. In such cases, to improve the absorption, sodium dodecyl sulphate is added to SE formulations and super-saturable SEDDS is formulated by using a small quantity of polymer in the formulation to prevent drug precipitation by generating and maintaining supersaturated state *in-vivo*. These formulations contain a reduced amount of surfactant and minimize any gastrointestinal side effects³⁰.

2. Dry Emulsion: It is mainly o/w emulsion, converted into solid by spray drying, using solid carrier adsorption or freeze drying technique. Dry emulsion may were dispersed in water before use. These are actually powders in which emulsification spontaneously occurs *in-vivo* or after exposure to an aqueous solution. Dry emulsion technology not only avoids the use of harmful or toxic organics

solvents but effectively removes the stability problems (such as phase separation, creaming & contamination by micro-organism during storage) associated with classic emulsion. MCT (Medium Chain Triglycerides) are generally used as oil phase for these formulations. Dry emulsions can be used for further preparation of tablets and capsules³⁰.

3. Self-Emulsifying Solid Dispersion: Solid dispersions had widely being used to increase the dissolution rate and bioavailability of poorly water soluble drugs although stability is a major concern during their manufacturing. Hot-melt granulation is a widely used technique for the preparation of solid dispersion.

4. Self-Emulsifying Tablets: Preparation of Self Emulsifying Tablets involved adsorption of nanoemulsion on granular materials and then compressed to form tablets. The dissolution profile of optimized self-emulsifying tablet showed 80-90 % drug release in 45 minutes.

5. Self-Emulsifying Beads: In SE systems, solid dosage forms can be developed by using less amount of excipient *i.e.* by formation of Beads. Paradkar and Patil used solvent evaporation technique for deposition of SE system into micro porous polystyrene beads. Porous polystyrene beads are having complex internal void structures. These beads are produced by copolymerization of monomers styrene and divinyl benzene. It is chemically inert, biocompatible and stable over a wide range of pH, temperature and humidity. Geometrical features of porous materials like bead size and pore architecture governs the loading efficiency and *in-vitro* drug release from SES loaded porous poly styrene beads.

6. Self-Emulsifying Nanoparticles: It can be prepared by solvent injection method, sonication emulsion-diffusion-evaporation method. In solvent injection method molten lipid mass containing lipid, surfactant and drug is injected drop wise into a non-solvent system. Larger particles are removed by filtration and then filtrate is dried to get nanoparticles³⁰.

1.11. Solidification Techniques for Transforming Liquid/Semisolid: Various solidification techniques are as listed below in **Table 6**.

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 process⁴:

A) Heating of the semisolid excipient to at least 20°C above its melting point.

B) Incorporation of the active substances (with stirring).

C) Capsule filling with the melt cooling to room temperature. For liquid formulations, it involves a two-step process.

D) 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.

1. Spray Drying: 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; the volatile vehicles evaporate leaving behind small solid particles which may be compressed into tablets or filled into capsules *e.g.* Nimodipine self-micro emulsifying formulation has been prepared by spray drying technique using dextran as a solid carrier. This technique has also been applied for development of self-emulsifying curcumin and dexibuprofen²⁴.

2. Spray Cooling: This technique is also known as spray congealing. It involves the preparation of molten formulation by mixing lipids, surfactants, and drug. Then it is sprayed into a cooling chamber. The molten droplets congeal and recrystallize into spherical solid particles which collect in the bottom of the chamber as fine powder. The fine powder may then be used for development of solid dosage form such as capsules, tablets etc. To atomize the liquid mixture and to generate droplets, different atomizers can be used but ultrasonic atomizer is most preferred²⁵. The excipients used with this technique are polyoxyl glycerides specially steroyl polyoxyl glycerides, gelucire 50/13 *e.g.* Praziquantel and diclofenac

SEDDS have been prepared by using spray cooling technique.

3. Adsorption to Solid Carriers: Adsorption to solid carriers is done by simply adding liquid SEDDS onto the solid carriers by mixing in a blender. Solid carriers can be micro porous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked

polymers or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, cross povidone and then the resulting free 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.

TABLE 5: STUDIES CARRIED OUT ON DIFFERENT DOSAGE FORMS

Dosage forms	Studies carried out
Dry Emulsion:	<ul style="list-style-type: none"> Poorly water soluble drug- amlodipine ²². Entericcoateddryemulsionformulationswhicharemoreappropriateforpeptide&protein drugs oral delivery. These formulations are prepared by using surfactant, vegetable oil & pH responsive polymer followed by lyophilization ²³.
Self-Emulsifying Solid Dispersion:	SE solid dispersion granules of seven drugs are prepared which includes using four carboxylic acid containing drugs, an amide containing drug (Phenacetin), a hydroxyl containing drug and a drug having no proton donating groups (Progesterone) in which Neusilin US2 was used as surface adsorbent and gelucire 50/13 was used as dispersion carrier ²⁴ .
Self-Emulsifying Tablets	<ul style="list-style-type: none"> For studying effect of formulation ingredients on the release rate of drug and to evaluate an optimized self nano emulsifying tablet ²⁵ formulation-ubiquinone Self-emulsifying tablet using goat fat and Tween ²⁶ - diclofenac
Self-Emulsifying Nanoparticles	<ul style="list-style-type: none"> Biodegradable homolipid with particle size of approximately 100nm are obtained with loading efficiency of 70-75% ²⁷ - Solvent injection method. 5 Flourouracil (5-FU) and antisense Epidermal Growth Factor Receptor (EGFR) plasmid in biodegradable PLGA/o-CMC nanoparticles. This combination <i>i.e.</i> PLGA and o- carboxymethyl chitosan shows self-emulsifying effect without any surfactant stabilizer ²⁸ It was found that the release rate of 5-FU from self-emulsifying nanoparticles was sustained for as long as three weeks-sonication emulsion-diffusion-evaporation Trickler <i>et al.</i>, (2008) used multiple emulsion (o/w/o) for preparation of self-emulsifying nanoparticle system with chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel. These nanoparticles possessed bioadhesive properties and increased cellular association of the drug ²⁹ - solvent evaporation method

TABLE 6: VARIOUS SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID OR SEMISOLID

Technique	Benefits	Description
Capsule filling	Simple manufacturing and suitable for low-dose drugs	Liquids and semisolid self-emulsifying system are filled into the capsules
Spray drying	Simple	Spray drying of mixture containing lipids, solid carriers, surfactants and drug.
Spray cooling	Simple	The molten formulation is sprayed into a cooling chamber.
Direct adsorption on Carrier	Provide good drug content uniformity and simpler approach	L-SEDDS adsorb on solid carrier

1.12. Specific Applications of SEDDS: ³²

1. Oral bioavailability Enhancement Poorly Water Soluble Drugs: In case of poorly water soluble drugs dissolution rate dependent absorption is a major factor that limits the bioavailability. The ability of SEDDS to release in the drug to GIT and disperses to micro emulsified form (globule size between 1- 100 nm). As the globular size is so small subsequent increase in specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the

absorptive brush border membrane leading to improved bioavailability ³. A chart of all the drugs whose bioavailability was increased by using SEDDS is given in **Table 7**.

2. In delivery of Peptides: SEDDS have ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors by protecting them from enzymatic hydrolysis. These systems are formed spontaneously without aid of energy or heating thus suitable for thermo labile drugs such

as peptides 22 e.g. the intestinal hydrolysis of pro-drug by cholinesterase can be protected if Polysorbate 20 Emulsifier in micro emulsions formulation.

TABLE 7: LITERATUREREPORTS ON BIOAVAILABILITY ENHANCEMENT USING SEDDS ³²

Drug	Bioavailability enhancement
Simvastatin	1.5 folds
Ketoprofen	1.13 folds
Vinpocetine	17.3 folds
Vitamin A	2 folds
Exemestane	2.9Folds

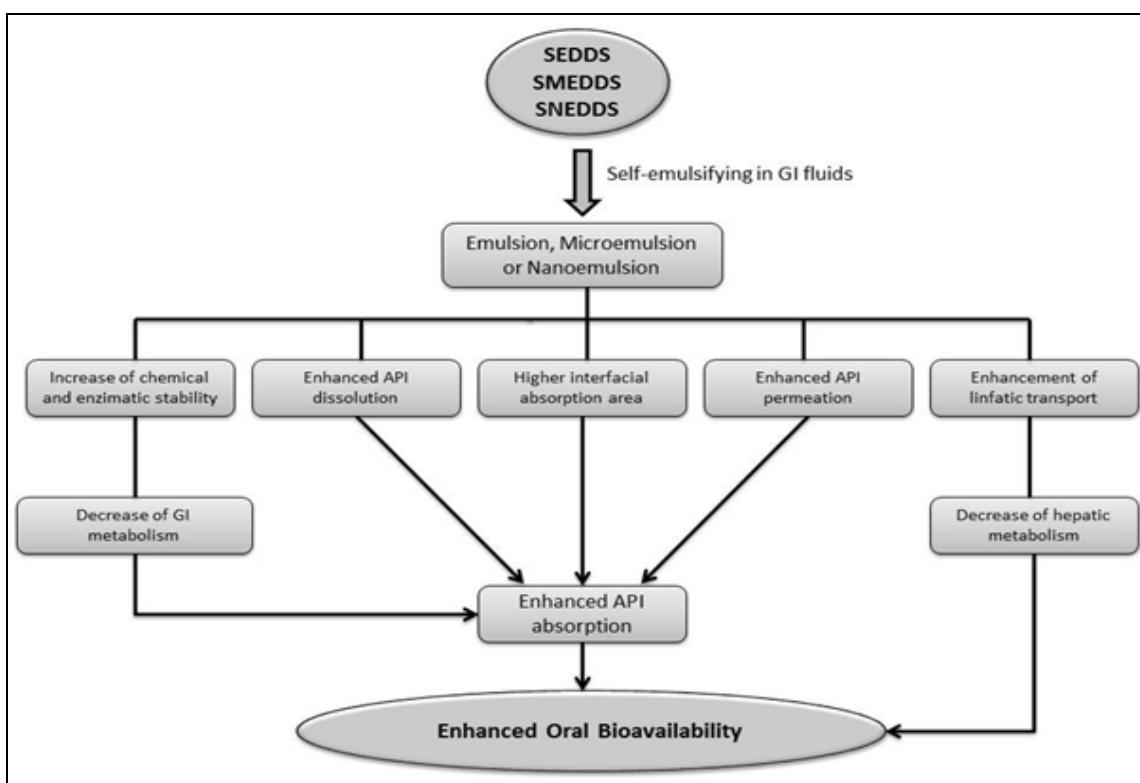


FIG. 3: ORAL BIOAVAILABILITY ENHANCEMENT POORLY WATER SOLUBLE DRUGS BY USING SEDDS

TABLE 8: COMMERCIALY AVAILABLE PHARMACEUTICAL PRODUCTS FORMULATED AS SEDDS FOR ORAL ADMINISTRATION ³²

Trade name	Year of Approval	Molecule	Composition	Therapeutic use	Company
Accutane	1982	Isotretinoin (10, 20 e 40 mg)	beeswax, butylatedhydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, soybean oil, glycerine, parabens (methyl and propyl), iron oxide (red), titanium dioxide, FD and C Red No. 3, FD and C Blue No. 1, FD and C Yellow No. 6, and D and C Yellow No. 10, and	Retinoid (acne)	Hoffmann La Roche
Sandimmune	1990	Cyclosporine A (25 e 100 mg)	corn oil, gelatin, iron oxide red, linoleoylmacrogolglycerides, sorbitol, titanium dioxide, and iron oxide yellow	Immunosuppressive Agent	Novartis
Vesanoid	1995	Tretinoin (10 mg)	beeswax, butylatedhydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils, soybean oil, glycerin, yellow iron oxide, red iron oxide, titanium dioxide, methylparaben, and propylparaben	Retinoid (leukemia)	Hoffmann La Roche
Neoral	1995	Cyclosporine A (25 e 100 mg)	orn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil NF, DL-α-tocopherol USP, gelatin NF, glycerol, iron oxide black, propylene glycol USP, titanium dioxide USP, carmine	Immunosuppressive Agent	Novartis
Norvir	1996	Ritonavir (100 mg)	butylatedhydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil, and titanium dioxide	Antiretroviral Agent	Abbott
Fortovase	1997	Saquinavir	medium chain mono- and diglycerides, povidone, dl-alpha	Antiretroviral	Hoffmann La

		(200 mg)	tocopherol, gelatin, glycerol, red iron oxide, yellow iron oxide, and titanium dioxide	Agent	Roche
Gengraf	2000	Cyclosporine A (25 e 100 mg)	alcohol USP absolute, FD&C Blue No. 2, gelatin NF, polyethylene glycol NF, polyoxyl 35 castor oil NF, polysorbate 80 NF, propylene glycol USP, sorbitanmonooleate NF and titanium dioxide.	Immunosuppressive Agent	Abbott
Kaletra	2000	Lopinavir + Ritonavir (400+100 e 800+200)	FD and C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, water	Antiretroviral Agent	Abbott
Aptivus	2005	Tipranavir (250 mg)	polyethylene glycol 400, vitamin E polyethylene glycol succinate, purified water, and propylene glycol	Antiretroviral Agent	Boehringer

TABLE 9: APPLICATION OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS ³²

Type of delivery system	Drug	Oil: Surfactant: Co solvent	Improvement
SEDDS (gelled)	Ketoprofen	Captex 200: Tween 80: Capmul MCM	Silicon dioxide was used for gelling agent. As the Conc. of Silicon dioxide increases it causes an increase in the droplet size of emulsion and slows the drug diffusion.
SEDDS	Carvedilol	Labrasol: Labrafil M: Transcutol P	It improves the oral bioavailability of Carvedilol upto 43% when compared to conventional tablet.
SMEDDS	Simvastatin	Caproyl:Cremophor EL: Carbitol	The release rate was higher and oral bioavailability is about 1.5 fold higher than convectional tablet ²⁰ .
Self-emulsifying tablet	Diclofenac sodium	Goat fat: Tween 65	SEDDS tablet were formulated by pour molding using plastic mould the tablet containing higher tween 65: goat fat ratio gives better release rate ²⁶ .
Self-emulsifying pellet	Methyl and propyl parabens	Mono and diglycerides of capric and caprylic acids: Tween 80	The self-emulsifying formulation improve the rate of drug release from the pellets by applying a water insoluble polymer containing a water soluble plasticizer, it reduces the rate of drug Release ²⁷ .

2. Perspectives and Future Trends in SEDDS

Development: Lipid formulations such as self-emulsifying/ microemulsifying/ nanoemulsifying drug delivery systems have been attempted in many researches to improve the bioavailability and dissolution rate for their better dispersion properties. The performance and ongoing advances in manufacturing technologies has rapidly introduced lipid-based drug formulations as commercial products into the marketplace with several others in clinical development. Some medicines are already commercially available and many research works were published using SEDDS as an alternative to improve lipophilic drugs solubility and therefore bioavailability. **Table 8** shows a list of commercially available SEDDS products.

The fact that almost 50 % or more than of the new drugs are hydrophobic by nature implies that SEDDS studies should continue, where more

SEDDS formulations should be released at the pharmaceutical market. Formulating these compounds using lipid based systems is one of the growing interest and suitable drug delivery strategies are applied to this class of molecules. Recent advances in these formulation technologies have led to the successful commercialization of lipid-based formulations. Still there is low uptake of lipid-based formulations due to the large empirical development strategies, which include only few commercially successful drug products in the market. There are a number of issues in relation to lipid-based systems which require further investigation including; an understanding of physicochemical properties of lipids and how lipids reduce the variability in plasma profile, lipid drug interactions and formulation classification systems, a better understanding of the versatility of lipid systems and standard methodologies by which the best formulation can be selected for each drug.

CONCLUSION: Self-emulsifying drug delivery systems are actually mixtures of drug, lipid phase, emulsifier and/or co-solvent. SEDDS are a promising approach for drugs with poor aqueous solubility and hence can be more useful for BCS Class II and IV drugs as upon administration. When the dosage form reaches G.I.T, the SEDDS system take water from its surrounding environment and spontaneously forms oil in water emulsion which disperse into fine droplets. The finer droplets provide higher surface area for the drug to dissolve or permeate in surrounding medium. SEDDS are prepared generally in liquid dosage forms but solid SEDDS (tablets, capsules, beads, microspheres etc.) are preferred due to ease in handling, transportation and better stability. Also it avoids GI irritation and controlled and sustained release of drug release is achievable. Absence of suitable *in vitro* models explaining the state (whether dissolved or not) in G.I.T (*in-vivo*) for evaluation of SEDDS are major hurdles. Further, with solid SEDDS, compatibility and interaction studies between the excipients such as adsorbent, capsule shell and formulation components can be carried out in order to effectively harness its potential for the benefit of mankind. The SEDDS should be suitably exploited to develop platform technologies for improving bioavailability of BCS class II and IV drugs.

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