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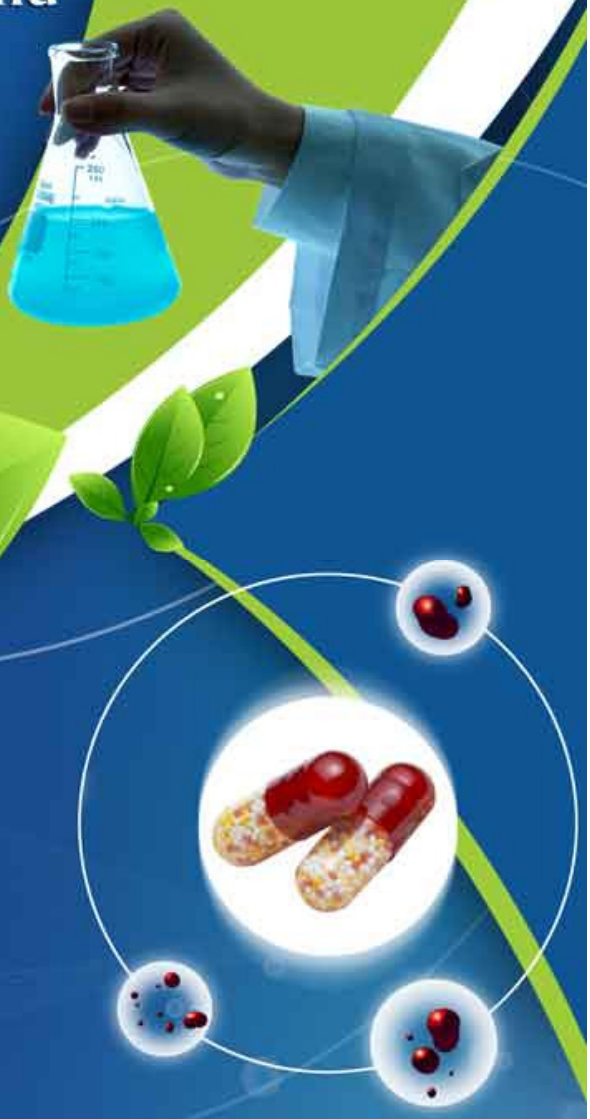

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Review Article

# SELF EMULSIFYING DRUG DELIVERY SYSTEM: AN APPROACH TO ENHANCE ORAL BIOAVAILABILITY

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## *ABSTRACT*

*Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are mixtures of oils, surfactants, and co surfactants, which are emulsified in aqueous media under conditions of gentle stirring and digestive motility that are encountered in the gastrointestinal (GI) tract. We found that SEDDSs could efficiently improve oral absorption of the sparingly soluble drugs by rapid self-emulsification and, subsequently, dispersion in the absorption sites. SEDDSs possess unparalleled potential in improving oral bioavailability of poorly water soluble drugs. Following their oral administration, these systems rapidly disperse in GI fluids, yielding micro-or nano emulsions containing the solubilized drug. Owing to its miniscule globule size, the micro/nanoemulsifed drug can easily be absorbed through lymphatic pathways, bypassing the hepatic first-pass effect.*

***KEYWORDS:****Co-solvents, Excipients, Poorly soluble, Self-emulsifying drug delivery systems, Self-micro emulsifying drug delivery system, Solid carriers.*

## INTRODUCTION

The oral route is the most preferred route of drug delivery for treatment of a number of diseases. Nearly 35 to 40% of newly launched drugs possess low aqueous solubility which leads to their poor dissolution and thereby low bioavailability, resulting in high intra & inter subject variability & lack of dose proportionality. For these drugs absorption rate from gastrointestinal tract is mainly governed by dissolution and improvement in solubility may lead to enhanced bioavailability. [1] These drugs are classified as class II drug by Biopharmaceutical classification system (BCS). [2]

There are number of techniques to overcome such problems arising out of low solubility and bioavailability, which may result into improved therapeutic efficacy of these drugs.

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The techniques like complex formation with cyclodextrins, solid dispersion, liposome formation, co precipitation, micronization, salt formation, use of micelles, co grinding and emulsification had been used for improving the dissolution profile of drugs with low solubility. [3-4]

Recently a new technique, Self Emulsifying Drug Delivery System (SEDDS) has been developed to enhance the solubility of drug. SEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents & co-solvents/co-surfactants. [5] (SEDDS) to improve the oral bioavailability of lipophilic drugs. There has been emergent attention in the use of lipid excipients in self-emulsifying lipid formulations (SELFs) for the reason that of their capability to solubilize poorly water-soluble 'lipophilic' drugs and prevail over the problem of poor drug absorption and bioavailability. [6]

In recent years, lipid micro emulsions incorporating medium-chain glycerides have attracted much interest as oral dosage forms to improve drug dissolution and/or intestinal absorption because (1) they are stable food grade products and generally recognized as safe by the US Food and Drug Administration; (2) micro emulsions incorporating these excipients can be formulated at ambient temperature over a wide range of compositions; and (3) early studies have shown that medium-chain glycerides and fatty acids improve intestinal absorption of many drug molecules. In the small intestine, they are hydrolyzed by intestinal lipases to generate monoglycerides and free fatty acids that can be directly absorbed through the portal route and detected in the plasma.

***Properties of SEDDS***

- They are able to self emulsify rapidly in gastro-intestinal fluids & under the influence of gentle agitation provided by Peristaltic and other movements of gastro intestinal tract, they form a fine o/w emulsion. [1, 7]
- They can effectively incorporate drug (hydrophobic or hydrophilic) within the oil surfactant mixture.
- They can be used for liquid as well as solid dosage forms.
- They require lower dose of drug with respect to conventional dosage forms.

***Advantages associated with SEDDS***

- Protection of drug from GIT environment. [7]
- Selective targeting of drug toward specific absorption window in GIT. [7]
- Enhanced oral bioavailability. [8]
- Consistent drug absorption profile.
- Better control of drug delivery profiles.
- Versatility of dosage form as can be used with liquids or solids.
- Predictable therapy due to reduced variability including food effects. [9]
- Drug payloads are high.
- Protection of sensitive drug substances.

**MICHANISM OF SELF EMULSIFICATION**

Self emulsifying processes are related to the free energy, ΔG [10] given by:

$$\Delta G = \Sigma N \pi r2 \sigma$$

Where, N = Number of droplets with radius r
σ = Interfacial energy

It is apparent from the above equation that spontaneous formation of interface between oil & water phase is not favorable due to higher energy level. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in true thermodynamic sense.

*Groves & Mustafa* developed a method of quantitatively assessing the ease of emulsification by monitoring the turbidity of oil-surfactant system in aqueous system, using phosphate nonylphenoxylate (PNE) and phosphate fatty alcohol ethoxylate (PFE) in n hexane
and suggested that emulsification process may be associated with the ease with which water penetrates the oil-water interface, with formation of liquid crystalline phase resulting in swelling at interface, thereby resulting in greater ease of emulsification. [11]

*Pouton* has said that the emulsification capacities of surfactant may be related to phase inversion behavior of the system. If one increases the temperature of the oil in water system which is stabilized by using non-ionic surfactants, the cloud point of the surfactant will be reached followed by phase inversion. [12]

The surfactant is highly mobile at phase inversion temperature due to which o/w interfacial energy is minimized leading to a reduction in energy required for emulsification.

**TYPES OF SEDDS**

On the basis of the water solubility of components, SEDDS can be classified as shown in Figure 1. [13]

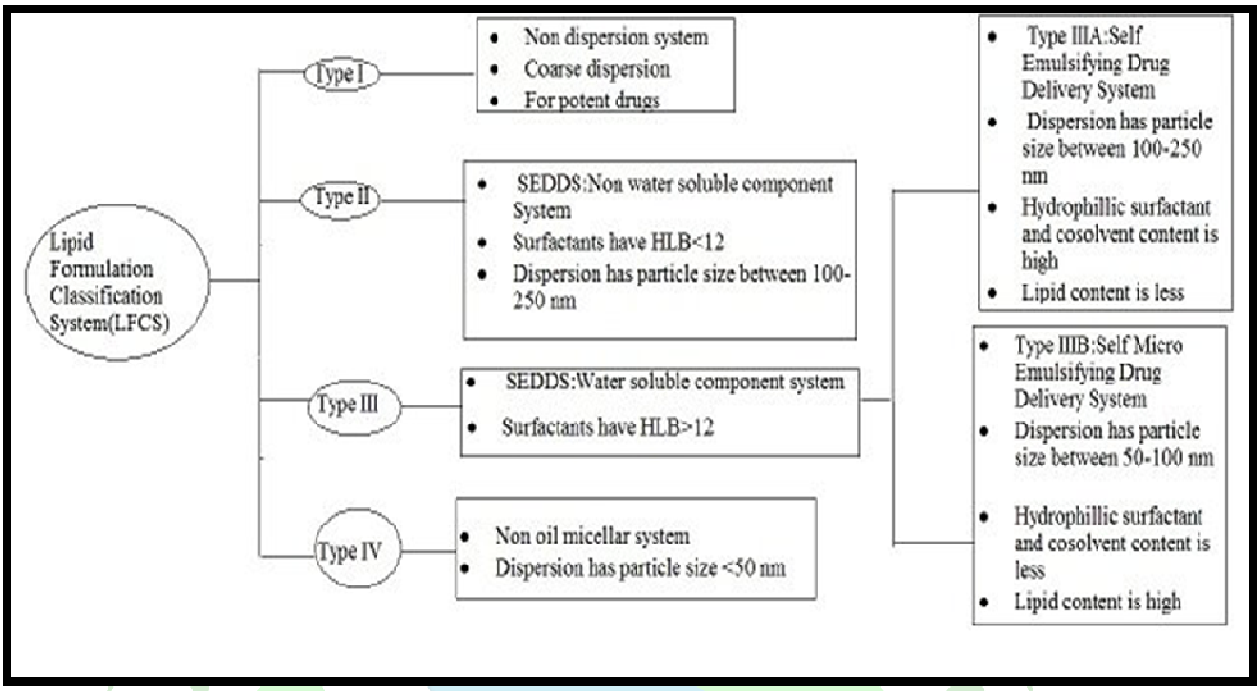


***Figure 1: It shows lipid formulation classification system (LFCS)***

***(A) Non-water soluble Component Systems***

These systems are isotropic mixtures of lipids & lipophillic surfactants having HLB value less than 12 that self emulsify to form fine oil in water emulsion in aqueous medium. Self emulsification is generally obtained at a surfactant level above 25% w/w. But at a surfactant level of 50-60% w/w the emulsification process may be compromised by formation of viscous liquid crystalline gels at the oil/water interface. This system is also known as Type-II SEDDS according to lipid formulation classification System (LFCS). [14]

Poorly water soluble drugs can be incorporated in SEDDS & encapsulated in capsules (hard or soft gelatin) to produce convenient single unit dosage forms.

These systems offer advantages -

- They are able to generate large interfacial areas which cause efficient partitioning of drug between oil droplets and the aqueous phase.
- They can overcome the slow dissolution step typically observed with solid dosage forms.

***(B) Water soluble component system***

These systems are formulated by using hydrophilic surfactants with HLB more than 12 & co solvents such as Ethanol, Propylene Glycol & Polyethylene glycols.

Type III SEDDS are commonly known as self micro-emulsifying drug delivery systems (SMEDDS). [15]

Type III formulations can be further divided into type III A & Type III B formulations in order to identify more hydrophilic forms. In Type IIIB, the content of hydrophilic surfactants and co solvents is increased and lipid content is reduced. [16]

**DIFFERENCE BETWEEN SEDDS AND SMEEDS**:-

***There are two types of SELF systems will be Present:*** **[6]**

- Self-emulsifying drug delivery systems (**SEDDSs**).
- Self-micro-emulsifying drug delivery Systems (**SMEDDSs**).

Both **SEDDS**s and **SMEDDS**s have different characteristics associated with improved drug release properties.

- **SEDDS** formulations will be having the simple binary systems which include

lipophilic phase and drug, or lipophilic phase, surfactant and drug. And they are having the droplet size in the range of 200nm-300nm and the dispersion has a turbid appearance. And also the concentration of oil is 40-80% in **SEDDS**.

- The formulation of a **SMEDDS** requires the use of a co-surfactant to make a microemulsion. And they are characterized by having droplet size below 50nm, and the dispersion has an optically clear-to-translucent appearance. And the concentration of oil in SMEDDS is less than 20 %. [6]

**SEDDS** may be solid or liquid in nature and they may be formulated into tablets, capsules, pellets, solid dispersions, microspheres, nanoparticles or dry emulsions. [13]

**EXCIPIENTS USED IN SEDDS FORMULATION**

The self-emulsifying process depends on:

- The nature of the oil-surfactant pair
- The surfactant concentration
- The temperature at which self-emulsification occurs [9]

***Different excipients used are:***

- Oils /lipids
- Surfactants
- Co-surfactant/Polar oils/Co-solvents

***Oils:***

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract**.[17] [18]** Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride oils. [19]

***Surfactants***:

Surfactants will improve bioavailability by different mechanisms:

- Improved drug dissolution
- Increased intestinal epithelial permeability.
- Increased tight junction permeability

Non-ionic surfactants with high hydrophilic-lipophilic balance (HLB) values are used in formulation of SEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30 and 60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen**.** [20] Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as following**:** [21]

- ***Anionic surfactants***: where the hydrophilic groups carries a negative charges such as carboxyl (ROO-), Sulphonates ($RSO_3$), Or sulphates ($ROSO_3$). Examples: - Potassium laureates, Sodium lauryl sulphate.
- ***Cationic surfactants***: - where the hydrophilic group carries positive charges. Example: quaternary ammonium halide.
- ***Ampholytic surfactants*** (also called Zwitterionic surfactants) contain both a negative and positive charges. Example: Sulfobetaines
- ***Non ionic surfactants***, where the hydrophilic groups carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene ($OCH_2CH_2O$). Examples: Sorbiton ester (span).

***Co solvents/Co-surfactants***

They improve solvent capacity and emulsification.

Generally high surfactant concentrations (usually greater than 30% w/w) are required for formulation of **SEDDS**. Organic solvents such as ethanol, propylene glycol, glycerol, polyethylene glycol, aids in dissolving large amount of either the drug in hydrophilic surfactants or the lipid base. These solvents also act as co-surfactant in the micro emulsion systems. It has been observed that drug release from the formulation improves with increasing amount of co-surfactant. **[13]**

Hence, they are most widely used in pharmaceuticals.

***Other Components***

- pH adjusters
- Flavours
- Antioxidants: - Lipophilic antioxidants (Eg. alpha tocopherol,propyl gallate, scorbyl palmitate) are required to stabilize the oily content of **SEDDS** formulation.
- Consistency builder

**FACTORS USED FOR SELECTION OF EXCIPIENTS**

- Self- dispersible
- Digestibility
- Capsule compatibility
- Purity, chemical stability
- Costs of goods
- Morphology at room temperature
- Solvent capacity
- Irritancy, toxicity
- Solvent capacity
- Miscibility

**FORMULATION OF SEDDS**

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants to water soluble co-solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions**.[22]**The following should be considered in the formulation of **SEDDS**: the solubility of the drug in different oils, surfactants and co-solvents; the selection of oil, surfactant and co-solvent based on the solubility of the drug, and the preparation of the phase diagram**,[23]** and the preparation of an **SEDDS** formulation by dissolving the drug in a mix of oil, surfactant and co-solvent. The addition of a drug to an **SEDDS** is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil-surfactant ratio. So, the design of an optimal **SEDDS** requires preformulation solubility and phase diagram studies. In the case of prolonged **SEDDS**, formulation is made by adding the polymer or gelling agent[24].

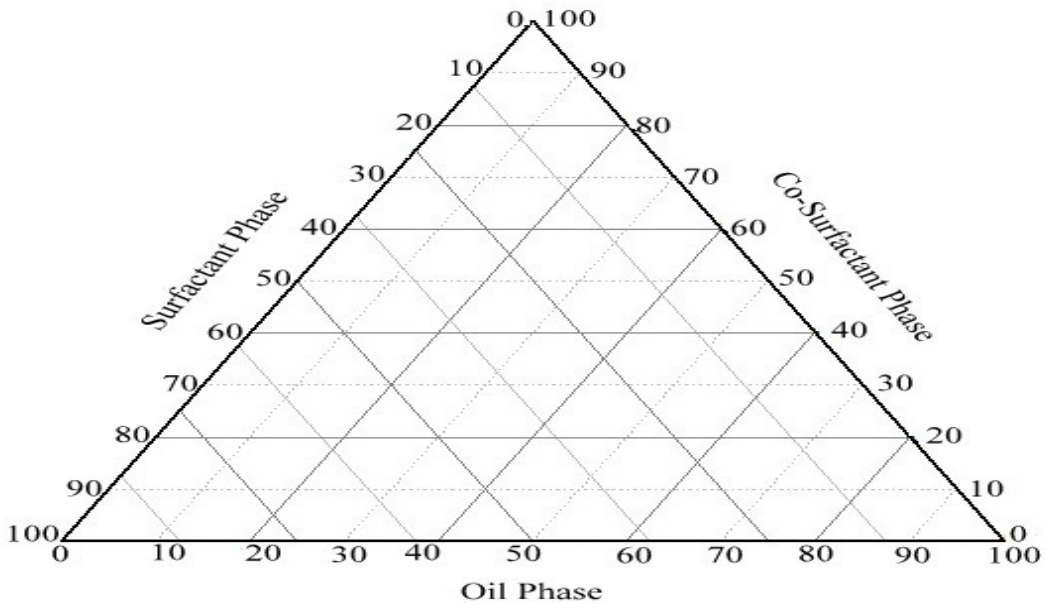


***Figure No. 1*** Ternary-***Phase Diagram***

**FACTORS AFFECTING SEDDS [2]**

- ***CONCENTRATION OF DRUGS*:**

Drugs at very high dose are not suitable for **SEDDS** unless they exhibit extremely good solubility in at least one of the components of SEDDS, preferably liphophilic phase.

- ***SOLUBILITY OF DRUG***:

The ability of SEDDS to maintain a drug in solubilized form is greatly influenced by the solubility of the drug in oily phase. If the surfactant and co-surfactant contribute to a greater extent for solubilization then there is risk of precipitation.

- ***POLARITY OF LIPID PHASE***:

The polarity of lipid phase is one of the factors that govern the release of the drug from the micro-emulsion. HLB, chain length, degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets.

**METHODS OF SOLIDIFICATION**

There are number of techniques for transformation of liquid & semi-solid SE formulations into solid **SEDDS**.

***Spray Drying***

In this technique, first of all formulation having oil, surfactant, drug and solid carrier are sprayed into a drying chamber through a nozzle. The volatile vehicles evaporate leaving behind small solid particles which may be compressed into tablets or filled into capsules. The technique is shown in figure 3. This technique has been used to prepare dry emulsions by removing water from an ordinary emulsion. 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 dexibuprofen.

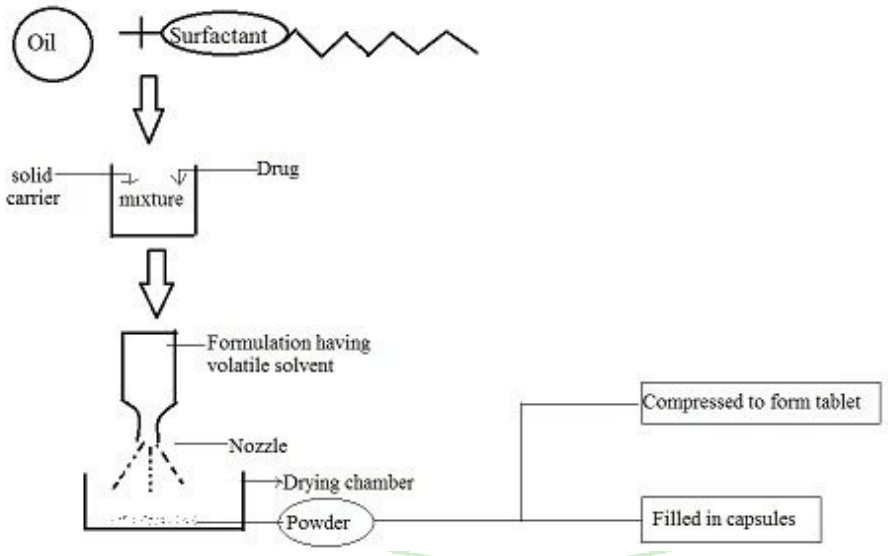


***Figure 2 – It shows spray drying technique***

***Spray cooling***

The technique spray cooling is also known as spray congealing, where, the molten formulation is sprayed into a cooling chamber. When this molten mixture comes in contact with cooling air, the molten droplets congeal & recrystallize into spherical solid particles which collect into the bottom of the chamber as fine powder. The fine powder may then be used for development of solid dosage from such as capsules, tablets etc. To atomize the liquid mixture & to generate droplets, different atomizers can be used but ultrasonic atomizer is most preferred. The excipients used with this technique are polyoxyl glycerides specially steroyl polyoxyl glycerides, gelucire. Praziquantel & diclofenac **SEDDS** have been

prepared by using spray cooling technique. [13]

***Melt Extrusion/Extrusion Spheronization***

Extrusion Spheronization technique is based on the property of materials which can be easily extruded and spheronized. These techniques do not require liquid excipients although constant temperature and pressure has to be maintained to achieve high drug loading. Melt extrusion ensures content uniformity & is widely used method for preparing pellets and granules. In extrusion, raw materials with plastic properties are converted into uniform pellets of varying size which depend on size of extruder aperture.

The bioavailability of propranolol has also been improved by using this technique. Self emulsifying pellets & bilayered cohesive self emulsifying pellets of diazepam have also been prepared by extrusion spheronization technique. [13]

***Melt Granulation***

Melt granulation is a one step process, where, powder agglomerates are obtained by adding binder that melts or softens at low temperature. Melt granulation is also known as "thermoplastic pelletization." It is used for those excipients that exhibit thermoplastic properties. A large range of solid & semi-solid lipid can be used as a binder for solid dispersions prepared by melt granulation whereas, lipids with a low HLB & high melting point are suitable for sustained release formulations. Semi-solids with high HLB are used for immediate release and bioavailability enhancement. Gelucire, a lipid based excipient, is able to further increase the dissolution rate as compared to poly ethylene glycol because of its self emulsifying ability. [25] Gelucire has high HLB value of 14 and possesses good self emulsifier property. [26]

***Super Critical Fluid Technology***

The most commonly used super critical fluid is super critical carbon dioxide. The lipid materials may be used in super critical fluid technology either for preparing solid dispersion or for coating of drug particles. In this technique drug & lipid excipients are dissolved in an organic solvent such as methanol & then in a supercritical fluid. Generally, the coating process involves dispersing the drug particles in the super critical fluid containing coating material. Initially, the solubility of coating material is sustained by elevated temperature & pressure and then coating is facilitated by a gradual decrease in pressure & temperature which decreases the solubility of the coating material in the supercritical fluid leading to its gradual deposition onto drug particles.

Lipid based excipients used for preparation of controlled release formulation are glyceryl trimyristate (dynasan) and stearoyl poly oxylglycerides (gelucire).

In pharmaceutical industry, this technique has been successfully applied for bioavailability improvement of carbamazepine using vitamin E, TPGS & Gelucire however, following points must be considered while using this technique –

- The integrity/stability of the active substance under the process conditions.
- The solubility of the formulation components in the supercritical fluid.
- The energy requirement or environmental conditions relating to evaporation of solvents.
- Economic considerations as this method have lower drug loading capacity and should be used for highly potent & low dose drugs.

***Solid-Lipid Nanoparticles (SLN) and Nano Structured Lipid Carriers (NLC)***

SLN and NLC have size in the range 50-1000 nm and differ in state of core as SLN have a solid core while NLC have a liquid core. In the preparation of SLN, drug is dissolved in aqueous solution of the surfactants & then high pressure homogenization of the solid matrix & drug solution is carried out.NLC are reservoir system derived from SLN to increase the drug loading capacity of system. In addition to the classic SLN components, NLC also contain liquid lipid excipients such as MCT (medium chain triglycerides). They have been mainly used for controlled release formulations via the oral, [I.V.] or topical Route.

The advantages of SLN are that they can be prepared without use of organic solvents & with a wide range of lipid excipients.

Coenzyme 10 has been formulated as an NLC using caprylic/capric triacyl glycerols as liquid lipid as carriers. [13]

**Recent advancements in SEDDS**

Includes [13]

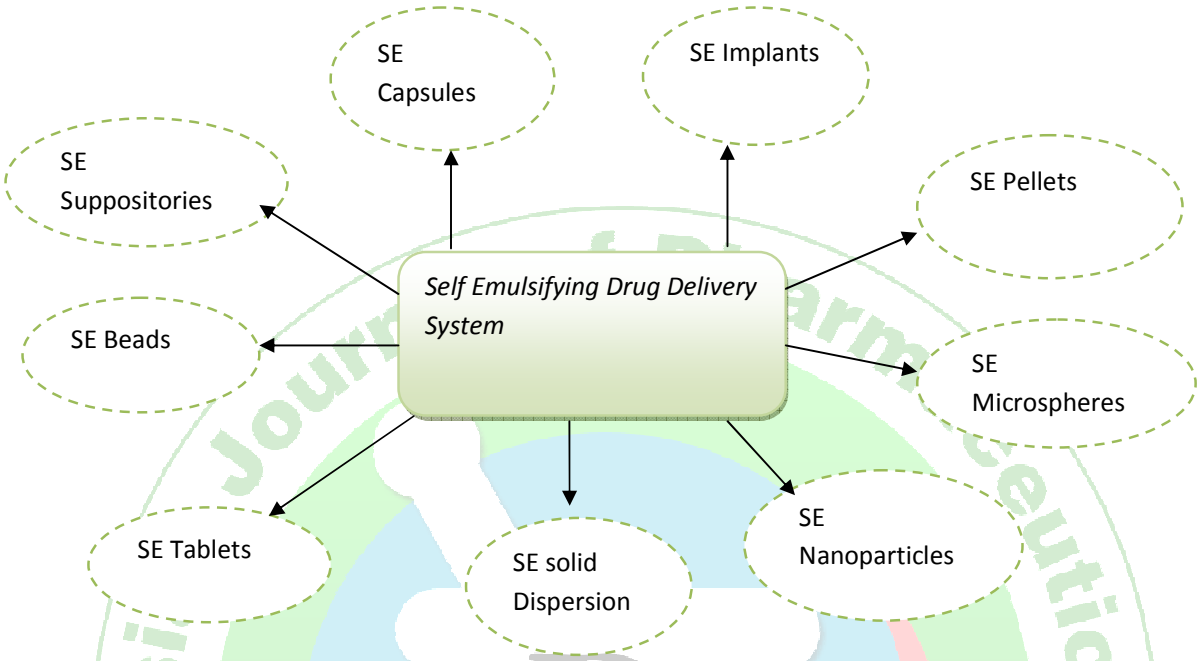


**Figure 3: Types of SEDDS**

***Self-emulsifying capsule:***

It is a capsule containing liquid or semisolid form of SES. In the GIT, the capsules get dispersed to SES uniformly in the fluid to micron size, enhancing the bioavailability. Second type of self-emulsifying capsule is solid SES filled into capsule.

***Self-emulsifying tablets***:

The preparation of self emulsifying tablets depends on combination of lipids and surfactants. [29] First self emulsifying (SE) tablet of ubiquinone was prepared by *S.Nazzal, et al*, for studying effect of formulation ingredients on therelease rate of drug & to evaluate an optimized self nano emulsifying tablet formulation. Prepared nano emulsion was adsorbed 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. [27]

***Self-emulsifying pellets***.

Pellets are the multiple unit dosage forms which possess a number of advantages over conventional solid dosage forms like ease of manufacturing, reduce the intra & inter subject variability of plasma profiles and also reduce GI irritation without lowering drug bioavailability. [28]

***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 & 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 &humidity. Geometrical features of porous materials like bead size & pore architecture governs the loading efficiency and *in vitro*

drug release from SES loaded porous poly styrene beads.[13]

***Self-emulsifying microsphere:-***

You et al. prepared solid SE sustained release microspheres using the quasiemulsion-Solvent diffusion method of the spherical crystallization technique, in this technique ZTO used as oil phase.[29]

***Self-emulsifying nanoparticle***:-

Nanoparticle technology can be applied to the formulation of self-emulsifying nanoparticle. One of the solvents is an injection. In this method, the prepared molten lipid mass contains lipid, surfactant and drug. This lipid molten mass is injected dropwise into a non-solvent system. This is filtered and dried to get nanoparticles. By this method, 100 nm size particles with 70-75% drug loading efficiency are obtained. The second technique is sonication emulsion diffusion evaporation. By this method are coloaded 5-flurouracil and antisense epidermal growth factor receptor (EGFR) plasmids into biodegradable polylactidecoglycolide (PLGA)/carboxmethylchitosan (CMC) nanoparticles. The mixture of PLGA and CMC had an SE effect, with no additional surfactant required. Trickler *et al.* developed a novel nanoparticle drug delivery system consisting of chitosan and glycerylmonooleate (GMO) for the delivery of PTX. These chitosan/GMO nanoparticles with bioadhesive properties increased cellular association and were prepared by multiple emulsion (o/w/o) solvent evaporation method.

***Self emulsifying Suppositories:-***

Some investigators proved that solid-SEDDs could not only increase the GI absorption but also increase the rectal/vaginal adsorption. Glycyrrhizin, hardly achieves therapeutic plasma concentrations by oral route, but can achieve acceptable therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories.**eg.** glycyrrizine suppositories

***Self emulsifying Implants:***

SE implants have very much improved efficacy under application of SSEDDS, since they have short half-life. e.g. - Wafer implants of Carmustine using cremophore RH 40 sand labrafil.

***Self emulsifying dispersions:***

Solid dispersions could increase the dissolution rate and bioavailability of poorly water soluble drugs. But some manufacturing difficulties and stability problems are arise to overcome these problems self emulsifying excipients like Gelucire1 44/14, Gelucire1 50/02, Labrasol1, Transcutol and TPGS (tocopheryl polyethylene glycol 1000 succi nate) have been widely used. [27]

***Dry emulsion*:**

It is mainly o/w emulsion, which is then converted into solid form by spray drying/solid carrier/freeze drying. [13]

***EVALUATION***

A number of tests are carried out for characterization and evaluation of **SEDDS.**

***Dispersibility Test:***

The dispersibility test of **SEDDS** is carried out to assess its capability to disperse into emulsion and the size of resulting globules to categorize them as SNEDDS. It is carried by using a standard USP dissolution apparatus 2 (Paddle Type). [12][31]1 ml of each formulation is added to 500 ml of water at 37 + 0.5 °C and the paddle is rotated at 50 r/ min. 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. [31]

The in vitro performance of the formulations is visually assessed using the following grading system:

- **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 2min
- **Grade D**: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2min).
- **Grade E**: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.[21]

***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. 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. [13]

***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 & 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

- ***Heating cooling cycle***:
  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

- ***Centrifugation***:
  Formulations which pass the heating cooling cycle are centrifuged at 3500 r/ min for 30 min. Those formulations that doesn't show any phase separation are taken for the freeze thaw stress test.

- ***Freeze thaw stress cycle***:
  Three freeze thaw cycles b/w -21° C & 25° C with storage at each temperature for not less than 48 hours. 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.[21]

***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, that formulation is considered as robust to dilution. [31]

***Turbid metric Evaluation:***

Turbidity is a parameter for determination of droplet size and self emulsification time. Fixed quantity of SEDDS is added to fixed quantity of suitable medium (0.1 N HCL or Phosphate Buffer) under continuous stirring at 50 r/ min on magnetic stirrer at optimum temperature and the turbidity is measured using a turbid meter. 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. Turbid metric evaluation is carried out to monitor the growth of droplet after emulsification. [32][33]

***Droplet size Analysis & 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 nm. In many instances nanometric size range of particle is retained even after 100 times dilution with water which indicates the system's compatibility with excess water.[33][34]

***Self Emulsification Time:***

The self emulsification time is determined by using USP dissolution apparatus II at 50 r/ min, where 0.5 g of SEDDS formulations is introduced into 250 ml of 0.1N HCL or 0.5% SLS solution. The time for emulsification at room temperature is indicated as self emulsification time for the formulation. [31]

***Zeta Potential Determination:***

The stability of emulsion is directly related to the charge present on mobile surface, which is termed as zeta potential. Zetasizer, Mastersizer etc are often used to determine zeta potential. The Zetasizer uses light scattering techniques to determine globule size, zeta potential and molecular weight of nanoparticulate systems. The instrument determines size and zeta potential for optimization of stability and shelf life and speeding up the formulation development The SEDDS formulation is generally diluted in a ratio of 1: 2500 (v/v) with distilled water with constant stirring for determination of zeta potential. Zeta potential is calculated according to

Helmholtz-Smoluchowski equation-
$U=\varepsilon\xi Ex/\mu$
U =Electrophoretic velocity ε = permittivity ξ = Zeta potential
μ = Viscosity Ex = Axial electric field [35]

***In vitro Diffusion Study:***

This study is done to determine release behavior of formulation using dialysis technique where phosphate buffer (pH 6.8) is generally used as dialyzing medium. 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 *r/ min* 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.

***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 II dissolution apparatus using 500 ml of simulated gastric fluid containing 0.5% w/v of SLS (Sodium Laurel Sulphate) at 50 r/ min and maintaining the temperature at 37 + 0.5 $^{o}$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 technique.

***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 fluid. 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 $^{o}$C by using heating mantle.

***Refractive Index (R.I.) & Percent transmittance:***

Refractive Index & 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 & then compare it 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 blank.[6] If R.I. of formulation is similar to that of water & formulation having percent transmittance is greater than 99%, then the formulation are transparent in nature.[13]

***Permeation studies***:

For information about oral bioavailability enhancement of a formulation, one must have to perform *in vitro* or *ex vivo* studies. For these studies, isolated and per fused organ systems have been developed. [36] These organ systems have the advantage that research scientist works with an intact organ, where physiological cells remain in contacts intracellular matrices are preserved. A number of techniques are available for such *in vitro* studies First is In Situ Single Pass Perfusion Technique (SPIP) in which perfusion solution is passed through the jejunum(a part of intestine) and the experimental conditions provided are closer to the *in vivo* conditions. This technique is also able to determine exact absorption mechanism that is passive or active or carrier mediated absorption.[37] Permeability parameters are determined by calculating the amount of drug which is not absorbed from intestine. [38]

Second technique is Everted sac technique in which a small part of intestine (2-4 cm) is tied at one end and everted using a glass rod or thread. The technique is used to determine kinetic parameters. [39] In the presence of sensitive detection methods (such as radiolabel led compounds), drug transport across the intestine and through the epithelial cells can be studied. [40]The method is suitable for calculating absorption at different sites in small intestine and estimating the first pass metabolism of xenobiotics in intestinal epithelial cells. The limitation of this technique is that muscular is mucosa is present which is usually not removed. From everted sac preparations. That is why this method is not preferred for accurate determinations. Third technique is Diffusion cell technique in which diffusion across a small part of intestine or any other tissue (such as buccal, rectal, skin, lung, gastric) is studied using the media with specific pH and temperature conditions. On both sides of diffusion membrane, buffer solution is continuously gassed with carbogen.

**APPLICATIONS OF SEDDS**

- ***Improvement in solubility & Bioavailability***

In SEDDS, the lipid interacts readily with water leading to formation of fine o/w emulsion. The droplets of emulsion deliver the drug to G.I tract in the dissolved state which can be easily absorbed. There are number of examples (shown below) of drugs for which improved bioavailability have been reported by their SEDDS formulations

**Literature reports on bioavailability enhancement using SEDDS.**

| Drug | Bioavailability enhancement [13] |
|---|---|
| Simvastatin | 1.5 folds |
| Carvedilol | 3-4 folds |
| Phenytoin | 2.3 folds |
| Acyclovir | 3.5 folds |
| Halofantrine | 6-8 folds |
| Gentamycin | 5 folds |
| Ketoprofen | 1.13 folds |
| Vinpocetine | 17.3 folds |
| Vitamin A | 2 folds |
| Exemestane | 2.9 folds |

***Supersaturable SEDDS (S-SEDDS)***

S-SEDDS formulations have a reduced level of surfactant along with a polymeric precipitation inhibitor which stabilizes the drug in a super saturated state. HPMC & other cellulose polymers are used to inhibit crystallization and maintain supersaturated state of drug for longer duration. S-SEDDS are developed to reduce the side effects of surfactants & to achieve rapid absorption of poorly soluble drug because high surfactant level may cause GI irritation. [41] It has been noticed that the significantly reduced amount of surfactant used in the S-SEDDS formulation provides a better toxicity/safety profile than the conventional **SEDDS** formulation. The mechanism of inhibited crystal growth and stabilization of super saturation by means of polymers needs further

explanation. [41- 43]In salicylic acid and docetaxel SEDDS formulation, HPMC is used as precipitation inhibitor. A fivefold increase in bioavailability has been observed with PNU-91325 when HPMC in place of propylene glycol, is used as precipitation inhibitor. [44]

***Protection against Biodegradation***

Many drugs are degraded in physiological system due to acidic pH in stomach, enzymatic or hydrolytic degradation. In GI tract, acetylsalicylic acid undergo hydrolysis to generate salicylic acid in an acidic environment, but the drug is protected from such degradation when formulated in a galacticles oral lipid matrix system (self emulsifying system), showing good plasma profile as compared to the commercial formulation.[45]

Liquid Crystalline Nanoparticles (LCNPs) are very good solubilizers for sparingly soluble drugs & show high drug carrying capacity. Proteins and peptides can be protected from biodegradation by formulating LCNPs. For water soluble peptides, bioavailability enhancement may vary from 20 to 100 times. [6] LCNPs can be used for controlled release as well as drug targeting.

LCNP carriers can also be manipulated for targeted release at different absorption sites e.g. in lower or upper intestine.

***SEDDS for Herbal Drugs and Traditional Medicine***

A number of herbal drugs and traditional medicines are being exploited for development of **SEDDS** as many of them are either extracts or contain volatile and fixed oils. Silybin obtained from *Carduus marianus* is found to be effective in protecting liver cells from harmful effects caused by drinking, smoking, overworking, stress, environmental pollutants or drugs that cause liver damage.

Silybin has low oral bioavailability becausesss of its low aqueous solubility**. SEDDS** formulation of Silybin has increased its oral bioavailability by at least 4 folds. [46]

The extracts of *Ginkgo biloba* have antioxidant, antiischaemic, and neuroprotectant, cardiovascular and cerebrovascular activities & have beneficial effects on cognitive deficits including Alzheimer's disease & multi infarct dementia. The solubility of active components of *Ginkgo biloba* is less. [47]

**Examples of some marketed products in which it has been used [28]**

| | |
|---|---|
| Targretin soft gelatin capsule | Sandimmune oral solution |
| Gengraf hard gelatin capsule | Agenerage Soft gelatin capsule |
| Ritonavir soft gelatin capsule | Agenarage oral solution |
| Ritonavir oral solution | Nerol soft gelatin Capsule |
| Sandimmune soft gelatin capsules | Nerol Oral Solution |
| Lamprene soft gelatin capsule | Depakene capsule |
| Fortavase soft gelatin capsule | Norvir soft gelatin capsule |
| Rocaltrol soft gelatin capsule, | Marinol soft gelatin capsule |
| Hectrol soft gelatin capsule | Accutane soft gelatin capsule |
| Rocatrol oral solution | Vesanoid soft gelatin capsule |
| Avodat soft gelatin capsule | Accutane soft gelatin capsule |

**Drawbacks of SEDDS**

***Includes***

- Chemical instabilities of drugs and high surfactant concentrations.
- The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety

aspect of the surfactant vehicle had to be considered.

- Moreover, volatile co solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- It may allow less drug loading.
- Sometimes co-solvent remains into formulation and causes degradation of drugs.

## FUTURE PROSPECTS

More than 40% of new drugs exhibit poor aqueous solubility and **SEDDS** are a promising approach for the formulation of these drugs. The development of **SEDDS**, however, is still largely empirical and *in vitro* models that are predictive of oral bioavailability enhancement are lacking. There is a need for *in vitro* methods for predicting the dynamic Changes involving the drug in the gut in order to monitor the solubilisation state of the drug *in vivo*. Attention also needs to be paid to the interactions between lipid systems and the components of the capsule shells. The characteristics of various lipid formulations also need to be understood, so that guidelines can be established that allow identification of Suitable candidate formulations at an early stage. Future research should involve human bioavailability studies, as well as more basic studies on the mechanisms of action of this fascinating and diverse group of formulations.

## CONCLUSION

Self-emulsifying drug delivery systems are a hopeful approach for the formulation of lipophilic drugs. Several studies have been confirmed that **SEDDS** provides significantly improved solubility/dissolution, absorption and bioavailability of hydrophobic drugs. As improvements or alternatives of conventional liquid **SEDDS, S-SEDDS** are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance.

The oral delivery of hydrophobic drugs can be made possible by **SEDDS,** which have been shown to substantially improve oral Bioavailability. Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested using in vivo and in vitro methods. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable.

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