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## SELF EMULSIFYING DRUG DELIVERY SYSTEM: A REVIEW

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**ABSTRACT:** The oral route is easiest and most convenient route for drug administration. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor water solubility. This may leads to higher inter subject and intra subject variability and therapeutic failure. The improvement of compounds solubility and bioavailability are the greatest challenges in formulations. The self emulsifying drug delivery system (SEDDS) is a novel approach for enhancing the solubility of formulations; by this approach it is also possible to prolong the release of drug via incorporation of polymers in SEDDS composition which appears to be unique and industrially feasible approach. The SEDDS is an isotropic mixture of oils, surfactants, co-surfactants, co-solvents, etc. It can be used for designing the formulations such as tablets, capsules, pellets, etc. The SEDDS will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

**INTRODUCTION:** The oral route is the preferred route for chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties. For this class of compounds, Amidon *et al.* gives the “low solubility/high permeability” class II, dissolution in the environmental lumen is the rate controlling step in the absorption process<sup>1</sup>. The major problem in oral drug formulation is low erratic bioavailability. This may lead to high inter and intra variability, lack of dose proportionality and therapeutic failure. Improvement of bioavailability of drug is one of the greatest challenges in drug formulation<sup>2</sup>.

Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation<sup>3</sup>. The theory behind dissolution rate improvement by means of SEDDS is the spontaneous development of the emulsion in the gastrointestinal tract with mild agitation provided by gastric mobility, which presents the drug in solubilised form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption<sup>4</sup>.

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### Need of SEDDS:

Self emulsifying formulation spread readily in gastro intestinal tract (GIT) and GI motility of stomach and the intestine provide the necessary agitation for self emulsion. SEDDS are promising approach for oral delivery of poorly water soluble

compounds. It can be achieved pre-dissolving the compounds in suitable solvents and fill the formulations into capsules. Pre-dissolving the compounds overcome the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract<sup>5</sup>.

#### Properties of SEDDS:

1. They are able to self emulsify rapidly in GI fluids & under the influence of peristaltic and other movements of GIT and form a fine o/w emulsion.
2. They can effectively incorporate drugs (hydrophobic or hydrophilic) within the oil surfactant mixture.
3. They can be used for liquid as well as solid dosage forms like suspension, emulsion, tablets, pellets, and suppositories.
4. They require lower dose of drug with respect to conventional dosage forms<sup>6</sup>.

#### Advantages of SEDDS:

1. Oral Bioavailability Improvement: The ability of lipid based formulations which present the drug to GIT in solubilised and micro emulsified form i.e., 10-100 nm globule size and increase in specific surface area which leads to more efficient transport of drug through intestinal aqueous boundary layer and through the absorptive brush border membrane, leading for upgrading the drugs bioavailability. E.g. ketoprofen, improved bioavailability relative to the suspension formulations for either or both of the liquid micro emulsion and SEDDS formulation in all cases<sup>1</sup>.
2. Prevention of enzymatic hydrolysis in GIT: SEDDS has ability to deliver macromolecules like peptides, hormones, enzyme, substrate and inhibitors with ability to offer protection from enzymatic hydrolysis.
3. Reduction in inter-subject and intra-subject variability and food affects E.g. cyclosporine<sup>7</sup>.

4. SEDDS are used for both liquid and solid dosage forms. E.g. progesterone.

5. They can be produced at large scale<sup>8</sup>.

#### Disadvantages of SEDDS:

1. There may be chances of instabilities of drugs, due to presence of high surfactant concentrations.
2. The high content of surfactant in self emulsifying formulations irritates the gastrointestinal tract.
3. Sometime co-solvents remain into the formulation and cause degradation of drugs.
4. While formulating the SEDDS it may allow low drugs loading which can affect dose frequency<sup>9</sup>.

#### Types of SEDDS:

According to water solubility of compound and composition of oil, surfactant and co-solvent the SEDDS can be classified as per **Table 1**.

#### Theory of SEDDS:

Self Emulsifying Drug Delivery Systems (SEDDS) are formed using surfactants of HLB < 12. These are the stable preparations which improve dissolution of the drug due to increased surface area on dispersion and therefore, they are not dependent on bile secretion for absorption as its emulsified form itself is readily absorbable. This ensures a rapid transport of poorly soluble drugs into the blood. 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. For selecting a suitable self-emulsifying vehicle, drug solubility in various components, identification of emulsifying regions and resultant droplet size distribution need careful monitoring<sup>11</sup>.

#### Mechanism of self emulsification:

In emulsification process the free energy ( $\Delta G$ ) associated is given by the equation:

$$\Delta G = \Sigma N \pi r^2 \sigma \dots\dots\dots (1)$$

'N' is Number of droplets with radius 'r' 'σ' is interfacial energy.

**TABLE1: FORMULATION TYPES OF SEDDS <sup>10</sup>.**

Formulation Type	Composition	Characteristics
Type I	Oils without surfactants	Non-dispersing ,poor solvent capacity except for highly lipophilic drugs, requires digestion to release drug
Type II	Oils and water insoluble surfactants	SEDSS, turbid o/w dispersion (particle size 0.25-2µm),unlikely to lose solvent capacity on dispersion, possible loss of solvent capacity on digestion
Type III	Oils, water-soluble surfactants and co-solvents	SEDSS/SMEDDS, slightly bluish to clear dispersion, possible loss of solvent capacity on dispersion ,less easily digested, possible loss of solvent capacity on digestion
Type IV	Water-soluble surfactants and co-solvents (oil free)	Forms a clear micellar solution on dispersion ,likely loss of solvent capacity on dispersion ,unlikely to be digested

From the equation the spontaneous formation of the interface between the oil and water phases is energetically not favoured. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. The emulsification process may be associated with the ease with which water penetrates the oil-water interface with the formation of liquid crystalline phases which shows swelling at the interface thereby resulting in greater ease of emulsification. However, for the system containing co-surfactant, significant partitioning of components between the oil and aqueous phases may take place leading to a mechanism described as "diffusion and stranding", where by the oil is solubilised, leading to migration in to the aqueous phase <sup>12</sup>.

Self-emulsification occurs when the entropy change that favours dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation. The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents, who form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence.

The specificity of surfactant combination required to allow spontaneous emulsification may be associated with a minimization of the phase

inversion temperature, thereby increasing the ease of emulsion. Phase studies are also necessary for liquid crystal formation in self emulsification. These indicate that good formulations are usually operating close to a phase inversion region and in a region of enhanced close to a phase inversion region and in a region of enhanced aqueous solubilisation<sup>13</sup>. Emulsification requiring 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 shearing. In the case of self emulsifying systems, the free energy required to form the emulsion is either very low or positive, or negative then, the emulsification process occurs spontaneously<sup>14</sup>.

### Formulation of SEDDS:

Depending upon requirement and type of SEDDS following components are used in the formulation.

### Composition:

1. Oils
2. Surfactants
3. Co-solvent
4. Co-surfactant
5. Drug

### 1] Oils:

The oily component is generally a fatty acid ester or a medium or long chain saturated, partially unsaturated hydrocarbon, in liquid, semisolid or solid form at room temperature. Examples are

mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil, fatty acids, fatty alcohols, and mono-/di-/triglycerides. 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-emulsification markedly reduce their use in SEDDS<sup>9</sup>. Oils can solubilise 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<sup>15</sup>.

## 2] Surfactant:

The 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 30–60% 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 solubilise relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules<sup>16,2</sup>.

## 3] Co-solvents:

Co-solvents like ethanol, propylene glycol, polyethylene glycol, polyoxyethelene, propylene carbonate tetrahydrofurfuryl alcohol, Glycofurool etc. help in dissolve a large amount of hydrophilic surfactant or hydrophobic drugs in lipid phase<sup>2</sup>.

## 4] Aqueous phase:

The droplet size and stability of W/O emulsion is influenced by the nature of aqueous phase by which the self emulsifying formulations are designed. Hence, the pH and ionic content of aqueous phase is of prime importance when designing. The physiological milieu has a diverse pH range varying from a pH of 1.2 (stomach) to around 7.4 (blood and intestine). The presence of electrolytes has been found to have an impact on emulsion characteristics such as droplet size and physical

stability. Hence, it is advisable to evaluate the self-emulsification of the SEDDSs and the characteristics of resultant w/o emulsion in aqueous phases with varying pH and electrolyte concentration depending upon the type of application. In addition to plain water, ringer's solution, simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 6.8) and phosphate buffer saline can be used as aqueous phase to evaluate spontaneous emulsification of SEDDSs<sup>17</sup>.

## 4] Co-surfactant:

In SEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of SEDDS. Examples of co-surfactants are:

- Polyoxyethylated glycerides (Labrafil M 2125 Cs)
- Polyoxyethylated oleic glycerides (Labrafil M1944 Cs)
- D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)<sup>11</sup>.

## 5] Drug:

The drug is important therapeutic agent in the formulation so the Physiochemical properties of the drug, such as log P, pka, molecular structure and weight, presence of ionisable groups and their quantity all have considerable impact on the formation of SEDDS because every factor affect on formulation. The BCS class-II drugs mostly selected for SEDDS. The Drugs showing surface activity, such as sodium salicylate, ascorbic acid and tricyclic amines, may show different behaviour with an increasing concentration in SEDDS<sup>17</sup>.

## Formulation:

- Preliminary studies are performed for selection of oil, which is an important and critical requisite for formulation of SEDDS. SEDDS contain oil, a surfactant and a co-surfactant. Solubility of drug is determined in various oils and surfactants.
- Prepare a series of SEDDS system containing drug in various oil and

surfactant. Then, in vitro self-emulsification properties and droplet size analysis of these formulations upon their addition to water under mild agitation conditions is studied.

- Pseudo-ternary phase diagram is constructed, identifying the efficient self-emulsification region. From these studies, an optimized formulation is selected and its bio-availability is compared with a reference formulation.
- 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.

When developing lipid based formulations the following parameters are considered:

- The solubility of drug in the formulation as such and upon dispersion (for SEDDS).
- The rate of digestion (for formulations susceptible to digestion) and possibly.
- The solubilisation capacity of the digested formulation<sup>18</sup>.

### Evaluation of SEDDS:

The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

#### 1] Visual assessment:

This may provide important information about the self-emulsifying and micro emulsifying property of the mixture and about the resulting dispersion in SEDDS.

#### 2] Zeta potential measurement:

This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil

droplet is negative due to presence of free fatty acids.

#### 3] Determination of emulsification time:

Determine the time required to form micro emulsion upon dilution of SEDDS with water. Self-emulsification time, dispersibility, appearance and flow ability was observed in SEDDS<sup>10,19</sup>.

#### 4] Thermodynamic stability measurement:

The physical stability of a lipid based formulation is a Prime importance, 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 formulation, affecting not only formulation performance, but also visual appearance. Also the, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

**1. Heating cooling cycle:** Six cycles between refrigerator temperature 4<sup>0</sup>C and 45<sup>0</sup>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.

#### 2. Centrifugation:

Passed formulations are centrifuged thaw cycles between 21<sup>0</sup>C and 25<sup>0</sup>C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

#### 3. Freeze thaw cycle:

Three freeze thaw cycles between -21<sup>0</sup>C and +25<sup>0</sup>C with storage at each temperature for not less than 48 hours was done for the formulations. Three freeze formulations taken for study, those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

#### 5] Turbidometric Evaluation:

Nepheloturbidometric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying 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 turbidometer. 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).

#### 6] Dispersibility test:

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One millilitre of each formulation was added to 500 mL of water at  $37 \pm 0.5$  °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

**Grade A:** Rapidly forming (within 1min) 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, greyish 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.

#### 7] Viscosity Determination:

The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it can 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 are w/o type of the system.

#### 8] Droplet Size Analysis Particle Size Measurements:

The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water.

#### 9] Refractive Index and Percent Transmittance:

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing a drop of solution on slide and compares it with water (1.333). The percent transmittance of the system is measured at a 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<sup>1, 15, 20</sup>.

#### 10] Equilibrium phase diagram:

The self-emulsification is a dynamic non-equilibrium process involving interfacial Phenomena, information can be obtained about self-emulsification using equilibrium phase behaviour. There seems to be a correlation between emulsification efficiency and region of enhanced water solubilisation and phase inversion region, formation of lamellar liquid crystalline dispersion phase on further incorporation of water. An equilibrium phase diagram enables comparison of different of different surfactants and their synergy with co-solvent or co-surfactant. The boundaries of one phase region can easily be assessed visually. The phase behaviour of a three component system can be represented by a ternary phase diagram.

#### 11] Liquefaction time:

This test is designed to estimate the time required by solid SEDDS to melt in vivo in the absence of agitation to simulated GI conditions. One dosage form is covered in a transparent polyethylene film and tied to the bulb of a thermometer by means of a

thread. The thermometer with attached tablets is placed in a round bottom flask containing 250 ml of simulated gastric fluid without pepsin maintained at  $37 \pm 180^\circ\text{C}$ . The time taken for liquefaction is subsequently noted<sup>21</sup>.

### Factors affecting to SEDDS:

1. Drugs which are administered at a very high dose are not suitable for SEDDS, unless they exhibit extremely good solubility in at least one of the components of SEDDS, preferably lipophilic phase. The drugs exhibit limited solubility in water and lipids are most difficult to deliver by SEDDS.
2. The ability of SEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oily phase. If the surfactant or co-surfactant is contributing to a greater extent for drug solubilisation, then there could be a risk of precipitation, as dilution of SEDDS will lead to lowering of solvent capacity of surfactant or co-surfactant.
3. Equilibrium solubility measurement can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in solubilising and colloidal stabilizing environment of the gut.
4. Studies reveals that such formulations can take up to 5 days to reach equilibrium and that the drug can remain in a super saturated state up to 24 hours after the initial emulsification event. The polarity of lipid phase is one of the factors that govern the release from the micro-emulsion. HLB, chain length and degree or unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces involved. The high polarity will promote rapid rate of release of the drug into the aqueous phase. The highest release was obtained with the formulation that had oily phase with highest polarity<sup>22</sup>.

### Recent techniques used for SEDDS:

#### 1. Adsorption on solid carriers:

##### a. Physical adsorption:

These solid carriers have property to absorb liquid/semisolid formulation as self-emulsifying system (SES). It is a simple procedure, where SES is incorporated into a free flowing powder material which has adsorption quality. The mixture is uniformly adsorbed by mixing in a blender. This solid mixture is filled into capsule or added to more excipient for compression into tablets. The above mixture was solidified to powder forms using three kinds of adsorbents: micro porous calcium silicate (Florite<sup>TM</sup>RE); magnesium aluminium silicate (Neusilin<sup>TM</sup>MUS2) and silicon Dioxide.

##### b. Spray drying:

In this technique first the prepared formulation containing oil, surfactant, drug, solid carrier etc, is sprayed into a drying chamber through a nozzle. The volatile vehicles first evaporate leaving behind small solid particles. These particles are then filled into capsules or compressed into tablets.

#### 2. Self-emulsifying capsules:

After administration of capsules containing conventional liquid self-emulsifying formulations, microemulsion droplets are formed and subsequently get dispersed in the GI tract to reach sites of absorption. Besides liquid filling, liquid self emulsifying ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers). Various researchers have converted liquid SEDDS to solid SEDDS and packed them in capsules.

#### 3. Self-emulsifying tablets:

The liquid SEDDS are first adsorbed on to solid carriers and then compressed into tablets after adding tablet excipient. The newest advance in the research field of self-emulsifying tablet is the self-emulsifying osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SES.

#### 4. Self-emulsifying beads:

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, The loading SEDDS into the micro channels of porous polystyrene beads (PPB) using the solvent

evaporation method was studied. PPB with complex internal void structures is typically produced by copolymerizing styrene and divinyl benzene. They are inert, stable over a wide pH range and to extreme conditions of temperature and humidity. This research concluded that PPB was potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB.

### 5. Self-emulsifying liposphere:

The poorly a water soluble drug, piroxicam, was incorporated into self-emulsifying lipospheres consisting of a mixture of a homolipid from *Capra hircus* and Tween 65. Various solid self-emulsifying lipospheres were formulated having different ratios of the homolipid and Tween 65 to contain piroxicam. The self-emulsifying lipospheres were evaluated using the following parameters: particle size, absolute drug content, and dissolution profile. The pharmacodynamics of the drug from the lipospheres was also evaluated using anti nociceptive activity on albino mice. These lipospheres gave best therapeutic effects.<sup>23</sup>

### 6. Melt granulation:

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a 'one-step' operation, melt granulation offers several advantages compared with conventional wet granulation, since liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent.

The melt granulation technique, also described as "thermoplastic pelletization", is easily adaptable to lipid-based excipients that exhibit thermoplastic properties. A wide range of solid and semi-solid lipids can be used as a meltable binder for solid dispersions. Generally, lipids with a low HLB and high melting point are suitable for sustained release applications. Semi-solid excipients with high HLB, on the other hand, may be used for immediate release and bioavailability enhancement. Other lipidbased excipients evaluated for melt granulation

to create solid SES include lecithin, partial glycerides, or polysorbates. The melt granulation process is usually used for adsorbing SES onto solid neutral carriers like silica and magnesium alumino meta-silicate. The main parameters that control the granulation process are the impeller speed, mixing time, binder particle size, and the viscosity of the binder.

### 7. Supercritical fluid based methods:

Lipids may be used in supercritical fluid based methods either for coating of drug particles, or for producing solid dispersions. The coating process entails dispersing the drug particles as powder in a supercritical fluid containing one or more dissolved coating materials. The solubility of the coating material is sustained initially by elevated pressure and temperature conditions. The coating process is subsequently facilitated by a gradual reduction in pressure and temperature leading to reduced solubility of the coating material in the supercritical fluid allowing gradual deposition onto the drug particles, to form coating layer. The supercritical fluid of choice is supercritical carbon dioxide.

The process for obtaining solid particles entails dissolving the drug and lipid-based excipients in an organic solvent such as methanol and then in a supercritical fluid, followed by lowering the temperature and pressure conditions to reduce their solubility in the fluid. Examples of lipid-based or lipid-related excipients that have been studied with this process for controlled-release applications include glyceryl trimyristate (Dynasan™ 114). The important considerations with this formulation technique are:

- The solubility of the formulation components in the supercritical fluid,
- The integrity stability of the active substance under the process conditions,
- The energy or environmental concerns relating to the evaporation of solvents if applicable.
- Compared with other methods, it has one of the highest potentials for lipid Exposure and a relatively lower drug loading capacity so



they are best suited for highly potent, low-dose drugs.

### 8. Self-emulsifying nanoparticles:

Nano particle techniques have been used in the production of SE nanoparticles. Solvent injection is one of these techniques in which the lipid, surfactant and drugs are melted together, then injected drop-wise into a stirred non-solvent. The resulting self emulsifying nanoparticles are then obtained by filtration and dried. This approach produced nanoparticles of about 100 nm with a high drug loading efficiency of 74%. A second technique involves sonication emulsion-diffusion-evaporation, which allowed the co-loading 5-fluorouracil and antisense epidermal growth factor receptor plasmids in biodegradable nanoparticle.

The mixture of poly-lactide-co-glycolide and *O*-carboxymethyl-chitosan exhibited an SE effect, without surfactant stabilizer. A novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate for the delivery of paclitaxel was developed with bio adhesive properties and increased cellular association were prepared by the multiple emulsions (O/W/O) solvent evaporation method.

### 9. Self-emulsifying suppositories:

Some investigators have shown that SEDDS can increase not only GI adsorption but also rectal/vaginal adsorption. Glycyrrhizin given by the oral route barely achieves therapeutic plasma concentrations, but satisfactory therapeutic levels for the treatment of chronic hepatic diseases can be achieved by the use of either vaginal or rectal SE suppositories.

### 10. Self-emulsifying implants:

Research into SE implants has greatly increased the use and application of S-SEDDS. As an example, 1, 3-bis (2-chloroethyl)-1-nitrosourea (Carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumours. Its effectiveness was hindered by its short half life. In order to enhance its stability compared with its release from poly (D, L-lactide-co-glycolide) (PLGA) wafer implants, SES was formulated with tributyrin, Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil 1944 (polyglycolized glycerides). Then, the self-emulsified BCNU was fabricated into

wafers with a flat and smooth surface by compression moulding. Ultimately, SES increased the *in vitro* half-life of BCNU up to 130 min compared with 45 min with intact BCNU. The copolymers having a bioresorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain was developed, Such copolymers exhibit SE properties without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses<sup>24, 21</sup>.

### 11. Melt extrusion/extrusion spheronization:

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions. The size of the extruder aperture will determine the approximate size of the resulting spheroids. The extrusion-Spheronization process is commonly used in the pharmaceutical industry to make uniform sized spheroids (pellets). The extrusion Spheronization process requires the following steps: The dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with binder; extrusion into a spaghetti-like extrudate; Spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating (optional). In the wet masses comprising SES (polysorbate 80 and mono-/di-glycerides), lactose, water and MCC, the relative quantities of SES and water had a significant effect on the extrusion force, size spread, disintegration time, and surface roughness of pellets.

Studies suggested that the maximum quantity of this SES that can be solidified by extrusion Spheronization occupies 42% of the dry pellet weight. Generally, the higher the water level, the longer the disintegration time. The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SES containing wet mass with a wide range of rheological characteristics can be processed, but a single rheological parameter cannot be used to

provide complete characterization of how well it can be processed by extrusion–speronization<sup>25</sup>.

## 12. Dry emulsions:

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/water (O/W) emulsions containing solid carrier lactose, maltodextrin in the aqueous phase by rotary evaporation, freeze-drying or spray drying.

The technique of spray drying is more frequently used in preparation of dry emulsions. The O/W emulsion was formulated and then spray-dried to remove the aqueous phase. The most exciting finding in this field ought to be the newly developed enteric coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of a surfactant, a vegetable oil, and a pH-responsive polymer, by lyophilisation technique<sup>26, 27</sup>.

**TABLE 2: APPLICATIONS OF SEDDS:**

Delivery system	Drug Used	Lipids	Surfactant	Improvement
SEDDS	Griseofulvin	Myvacet	Capmul GMO-50	Increase in solubility due to the presence of hydrochloric Acid.
SEDDS	Puerarin	Oleic acid	Tween80	Significant in bioavailability
SEDDS	Simvastatin	Lauraglycol: Capatex(1:1)	CremophoreEL: Capmul MCM	Hypolipidimic activity is increased.
SEDDS (gelled)	Ketoprofen	Capatex200	Tween 80	Silicon dioxide was used as a gelling agent, As a concentration of silicone dioxide Increases the droplet size of emulsion increase and slows The drug release.
SEDDS	Celecoxib	Capmul PG8	Tween 80	Improvement in Bioavailability <sup>28</sup> .
SEDDS	Danazol	Soyabean oil: maisine	Cremophor EL	Decrease in lipid content reduces danazol Bioavailability.
SMEDDS	Paclitaxel	Vitamin E	DOC-Na, TPGS, Cremophor RH 40	Higher bioavailability <sup>29</sup> .
SEDDS Tablet	Diclofenac sodium	Goat fat	Tween 65	SEDDS tablets were formulated by pour molding using plastic mould. The tablet containing higher tween 65: goat fat content ratios give release rate.
SMEDDS	Simvastatin	caproyl 90	Cremophore EL	The release rate of Simvastatin from SMEDDS was higher than conventional tablet. The oral bio availability of SMEDDS is about 1.5- fold higher than conventional tablet <sup>19</sup> .
SEDDS Pellets	Sodium Diclofenac	Lemon oil	Tween 80	Improved dissolution of diclofenac sodium <sup>30</sup> .

**CONCLUSION:** From the above review we conclude that Self-emulsifying drug delivery systems are approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made

possible by SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the

delivery of poorly soluble drugs. The SEDDS also provide new recent techniques to convert liquid SEDDS into solid forms such as spray dryer, extrusion sponization, etc.

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