



## A REVIEW: SELF EMULSIFYING DRUG DELIVERY SYSTEM

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## ABSTRACT

Lipid formulations for oral administration of drugs generally consist of a drug dissolved in a blend of two or more excipients, which may be triglyceride oils, Partial glycerides, Surfactants or co-surfactants. The primary mechanism of action, which leads to improved bioavailability, is usually avoidance, or partial avoidance, of the slow dissolution process, which limits the bioavailability of hydrophobic drugs from solid dosage forms. Ideally the formulation allows the drug to remain in a dissolved state throughout its transit through the gastrointestinal tract. The availability of the drug for absorption can be enhanced by presentation of the drug as a solubilizer within a colloidal dispersion. This objective can be achieved by formulation of the drug in a self-emulsifying system or alternatively by taking advantage of the natural process of triglyceride digestion. In practice 'Lipid' formulations range from pure oils, at one extreme, to blends which contain a substantial proportion of hydrophilic surfactants or co-solvents.

**Keywords:** Self emulsifying drug delivery system (SEDDS), Surfactants, Co solvent.

## INTRODUCTION

Self emulsifying lipid formulations have improved the bioavailability of poorly water soluble & highly permeable compound. This bioavailability enhancing property has been associated with a number of in vivo properties of lipid formulation including:

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

Within these oral dosage forms, lipids are simple emulsions, self-emulsifying and self-micro-emulsifying formulations. SELF systems comprise a defined mixture of lipid excipients, including simple oils, nonionic surfactants and co-surfactants. SELF-systems act as carriers for drugs by forming fine emulsions, or micro-emulsions,

under gentle stirring when diluted in water or physiological media with physiological motion. Drug molecules are either dissolved or suspended in the SELF system, which maintains the drug in very fine dispersion droplets inside the intestinal lumen, providing optimal conditions for absorption. SELF-system exists: self emulsifying drug delivery systems (SEDDS)-micro-emulsifying drug delivery systems (SMEDDSs). Both SEDDSs and SMEDDSs have distinct features associated with improved drug delivery properties.

SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SMEDDS requires the use of a co-surfactant to generate a micro-emulsion. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm–5 μm and the dispersion has a turbid appearance. SMEDDSs, however, have a smaller lipid droplet size (<200 nm) and the dispersion has an optically clear-to-translucent appearance. Both systems are associated with the generation of large surface area dispersions that provide optimum conditions for the increased absorption of poorly soluble drugs. The choice of whether a SEDDS or a SMEDDS is the preferred formulation option often depends on the interplay between the intrinsic properties of the drug compound and its solubility and dissolution profile during in vitro screening with a number of excipients<sup>1</sup>.

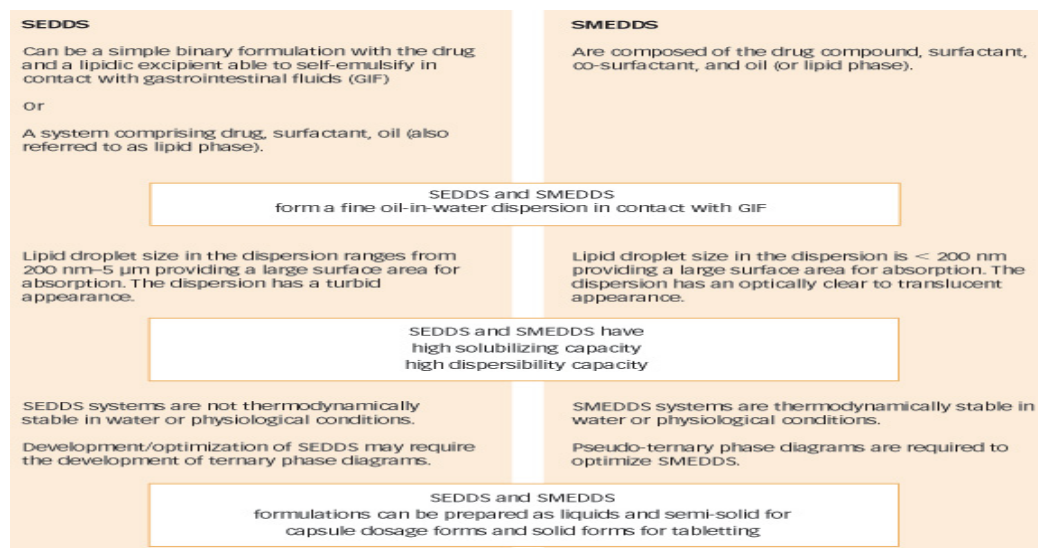


Fig. 1: Schematic diagram of SEDDS and SMEDDS

**Table 1: Examples of pharmaceutical products formulated as self-emulsifying systems**

Drug name	Compound	Dosage form	Company
Neoral	Cyclosporine	Soft gelatin capsule	Novartis
Norvir	Ritonavir	Soft gelatin capsule	Abbott laboratories
Fortovase	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche Inc.
Agenerase	Amprenavir	Soft gelatin capsule	Glaxosmithkline
Solufen	Ibuprofen	Hard gelatin capsule	Sanofi- Aventis
lipirex	Fenofibrate	Hard gelatin capsule	Sanofi- Aventis

In terms of dosage form, SELFs are principally liquid or semi-solid formulations and, therefore, ideal for soft or hard capsule filling. Currently, drugs that utilize SEDDs are exclusively developed in soft or hard gelatin capsules (Table 1). This is because, until recently, getting a SELF into tablet form was a formulation challenge because of the nature of excipients and formulation techniques. That is not to say that formulating for a solid dosage form that utilizes a SELF is impossible, but the starting point for such a formulation requires the use of semi-solid excipients<sup>2</sup>. SELFs have been transformed into solid dosage forms using techniques such as melt granulation, where the lipid excipient acts as a binder and solid granules are produced on cooling. Solvents or supercritical fluids can be used with semi-solid excipients, which are solubilized and then the solvent evaporated to produce a waxy powder. Spraying techniques can be used to produce powder form formulations. These techniques enable the production of granules or powders that can then be compressed into a tablet form or filled into capsules. In all cases, the lipid excipients used must be semi-solid at room temperature.

However in many cases, because of the nature of lipid excipients, the SELF system is a liquid-based formulation rather than a semi-solid formulation and, therefore, an alternative approach are required. This article describes the development and optimization of a solid SELF system to produce a tablet from a liquid SELF<sup>3</sup>. The concept works by the adsorption/absorption of a liquid SELF onto a neutral carrier (i.e., neutral silicate). Although surprisingly straightforward, developing this solid dosage form technique has required extensive investigation of critical success parameters including:

- Extensive screening of different neutral carriers to evaluate their ability to adsorb maximum levels of the liquid SELF.
- Maximum loading value of the carrier and effect on tablet compression.
- Absorption onto the carrier and effect on flow ability — an essential feature for tablet compression.
- Evaluation of the integrity of the system with a poorly soluble API to examine the effect of transforming a liquid into a powder on drug solubility and dissolution rate<sup>4</sup>.

#### Excipient Class

##### Semi synthetic lipid excipient

Several semi-synthetic liquid and thermo-softening (semi solid) excipients, most commonly prepared by chemically combining medium-chain saturated fatty acids or glycerides derived from natural product plant oils, with one or more hydrophilic chemical entities are currently available as pharmaceutical excipients for oral formulation development. These excipients find application as drug-solubilizing vehicles, surfactants and wetting agents and as emulsifiers and co-emulsifiers in SEDDS and self-micro emulsifying drug delivery systems (SMEDDS). They are gelatin well-suited for filling into both soft and hard gelatin or into HPMC capsules. Thermo-softening excipients, which melt in the range of 26-70 °C and exist as waxy semi-solids at ambient room temperatures, are typically filled into capsules in the molten state, with the excipient melting temperature limiting their use to hard gelatin capsules<sup>5</sup>.

##### Natural product oil

A number of natural product oils, derived primarily from plant sources and processed to remove impurities or to isolate various fractions of the original product, are available and suitable for use in encapsulated oral formulation product. Naturally occurring oils and fats comprised of mixture of triglycerides which contain fatty acids

of varying chain lengths and degrees of un-saturation. The melting point of a particular oil increases with increasing degree of un-saturation, which also increases the relative susceptibility to oxidation. Triglycerides are classified as short (<5 carbons), medium (6-12 carbons), or long chain (>12 carbons) and may be synthetically hydrogenated to decrease the degree of un-saturation, thereby conferring resistance to oxidative degradation. Separation is used to prepare excipients that maximize desirable physical and drug absorption-promoting properties while minimizing such issues as susceptibility to oxidation<sup>6</sup>.

##### Surfactants

Various non-ionic surfactants such as the polysorbates and polyoxylys, which cover the HLB range from 2 to 18, may be used in combination with lipid excipients to promote self-emulsification or micro-emulsification. Due to their relatively low toxicity, the acceptable quantities for use of these surfactants are limited primarily by their tendency, at high concentration, to cause brittleness of hard and soft gelatin capsules due to their dehydrating effects on capsule gelatin. Surfactant have a high HLB & hydrophilic which assist the immediate formation of O/W droplet & rapid spreading of the formation in aqueous media. Surfactants are amphiphilic in nature & they can dissolve or soluble relatively high amount of hydrophobic drug compound. This can prevent precipitations of the drug within the GI lumen & for prolong existence of drug molecules. Due to their relatively low toxicity, the acceptability quality for use of these surfactant are limited primarily by their tendency, at high concentration, to cause brittleness of hard & soft gelatin capsule due to their dehydrating effect on capsule gelatin<sup>7</sup>.

##### Co-solvent

Co-solvent like diethylene glycol monoethyle ether, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydro furfuryl alcohol polyethylene glycol ether, etc, may help to dissolve large amount of hydrophilic surfactant or the hydrophobic drug in the lipid base. The physical state of these excipients at ambient room temperature is determined by their molecular weight. PEG ranging from 200 to 600 in molecular weight is liquid at ambient room temperature where those possessing molecular weight of 1000 or greater exit as thermo softening semi solid. Polymeric liquid and semi-solid excipients, most of which are glycolic in nature and relatively non-toxic, are used as solvents for formulating poorly water-soluble drugs. These excipients can be used alone or in combination with other lipid excipients to improve the overall solubilizing power of the formulation. However, their pronounced water miscibility can compromise formulation performance due to uncontrolled precipitation of the drug substance following dilution in the aqueous contents of the GIT this typically results in dose-dependent bioavailability enhancement.

A few examples of the most commonly applied excipients in this class and their application follows. Among the polymeric glycol-based excipients finding pharmaceutical application, the polyethylene glycols (PEGs) are a versatile, well-characterized and widely applied class of solubilizers which are available as both liquids and thermo softening semi-solid. The physical state of these excipients at ambient room temperature is determined by this molecular weight. In comparison to natural product oils, PEGs have the following disadvantages: They tend to be more chemically reactive; they can be more irritating to the GI mucosa than oils. PEGs are also known to contain varying levels of peroxide impurities and secondary products formed by auto-oxidation, which can contribute

to chemical instability of the incorporated drug substance<sup>8</sup>. These excipients are widely used in soft gelatin capsule formulations but find limited use in conjunction with hard gelatin capsules due their hygroscopic and resultant effects on gelatin moisture content, which can compromise capsule physical integrity. Propylene glycol, a pharmaceutically-acceptable, monomer solvent possessing humectants and plasticizing properties, finds application for soft gelatin capsule formulations of poorly water-soluble drugs. The Poloxamers, which are co-polymers of polyoxyethylene and polyoxypropylene, possess both solvent and surfactant properties and thus find application in the oral delivery of poorly water-soluble drugs. As with the PEGs, they are available in a range of molecular weights which control the physical state of the excipient at room temperature. In addition to improving the bioavailability of poorly water-soluble drugs, they have found application in modified release formulations<sup>9</sup>.

## Formulation

### Single-component lipid solutions

The simplest lipid-based formulation consists of the drug substance solubilized in a single excipient, such plant oil, a fractionated glyceride, or a PEG. The obvious advantage of this formulation approach is its relative simplicity. With the exception of the PEGs, which function primarily as water-miscible solvents, this formulation depend solvent on the gastrointestinal lipid handling pathways to promote emulsification which is essential for facile drug release and absorption. As such, drug absorption may be less than optimal in patients for whom lipid digestion has been compromised by age or disease. Which single-component PEG solutions often have high solubilizing power for poorly water-soluble drugs, they are water miscible which can result in precipitation of the GI tract. Thus, the degree of bioavailability enhancement is dose-dependent, which renders PEG solution formulations poorly effective for high-dose drugs. There are at least 10 commercially available single-component lipid solution formulations. All are marketed in soft gelatin capsules, with most relying on the use of PEGs or medium-chain triglycerides as the primary or sole excipient<sup>10</sup>.

### Self-emulsifying formulations

Self-emulsifying drug delivery systems (SEDDS) are physically stable, isotropic mixtures of oil, surfactant, co-surfactant and solubilized drug substance that are suitable for oral delivery in soft and hard gelatin (or hard hydroxypropyl methylcellulose) capsules. Depending on the excipient selection and relative composition of the formulation, aqueous dilution will result in spontaneous formation of lipid droplets ranging in size from approximately 100 nm (SEDDS) to less than 50 nm (SMEDDS).

The optimum concentrations, or concentration ranges, of oil, surfactant and co-surfactant necessary to promote self-emulsification. Which should also assess the effect of loading on the efficiency of self-emulsification? Since droplet surface area is inversely proportional to diameter, smaller lipid droplets with their associated, greater surface area are thought to facilitate digestion, resulting in more lipid and uniform drug release and absorption.

The improved drug absorption provided by self-emulsifying for utilization is contingent upon the maintenance of the drug in the solubilized state until it can be absorbed from the GIT. Indeed the amount of water-miscible surfactant necessary to promote the self-emulsification of these formulations can occasionally be problematic in that it results in drug precipitation upon dilution *in vivo*. In some instances, SMEDDS formulations have proven useful in mitigating the enhancing effect that food can have on the absorption of poorly water-soluble drugs, as the case for the neural formulation of cyclosporine<sup>11</sup>.

### Self-emulsifying solid dispersion formulations

Liquid self-emulsifying formulations rely on micelle or solvent/co solvent systems to fully solubilize the drug dose, which helps to ensure optimal absorption. However the usefulness of these formulations can be limited by their inability to solubilize the entire drug dose in the volume of a single oral capsule. In these instances,

solid dispersion formulations, which may not fully solubilize the drug in the excipient matrix, can provide a viable, although not necessary as effective, alternative oral formulation. These formulations consist of a dispersion of the drug in an inert excipient matrix, where the drug could exist in either the finely divided crystalline, solubilized or amorphous states or a mixture thereof. This can increase the dissolution rate of the drug and subsequent absorption from, the GI tract relative to the stable crystalline drug substance.<sup>12</sup> These excipient have the potential to further increase the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending prior to filling.

### Mechanism of self-emulsification

Self-emulsification occurs when the entropy change that favors 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:

$$DG = S N_i p r_i 2s$$

Where,

"DG" = free energy associated with the process (ignoring the free energy of mixing),

"N" = number of droplets; "r" = radius of droplets and "S" = interfacial energy.

The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence.<sup>7</sup>

### Characterization

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.

### Visual assessment

This may provide important information about the self-emulsifying and micro-emulsifying property of the mixture and about the resulting dispersion<sup>13</sup>.

### Turbidity measurement

This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time<sup>14</sup>.

### Droplet size

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques are mainly used for the determination of the emulsion droplet size. The reduction of the droplet size to values below 50 μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions

### 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.

### Determination of emulsification time

Self-emulsification time, dispensability, appearance and flow ability was observed<sup>3</sup>.

### Biopharmaceutical aspects

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed and the interested reader is directed to these references for further details. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability *via* a number of potential mechanisms, including <sup>8</sup>.

1. Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution
2. Increases in effective luminal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micelle structures and a further increase in solubilization capacity.
3. Stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly *via* a reduction in first-pass metabolism.
4. Changes in the biochemical barrier function of the GI tract. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism.
5. Changes in the physical barrier function of the GI tract. Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs.

### Enhanced drug absorption by lymphatic delivery

Lymphatic transport should have a log *P* >5 and, in addition, a triglyceride solubility >50 mg/ml. The importance of lipid solubility was illustrated by a comparing the lymphatic transport of DDT (log *P* 6.19) with hexachlorobenzene (HCB, log *P* 6.53). While both compounds have similar log *P* values, the difference in lymphatic transport on administration in oleic acid, 33.5% of the dose in the case of DDT and 2.3% with HCB, was attributed to the 13-fold difference in triglyceride solubility. However, combination of a high log *P* and high triglyceride solubility does not always guarantee significant lymphatic transport. Penclomedine, an experimental cytotoxic agent with a log *P* of 5.48 and a triglyceride solubility of 175 mg/ml, was poorly transported in the intestinal lymph, ~3% of the dose. Significant lymphatic transport of the poorly lipid soluble (~1 mg/ml) HCl salt of halofantrine (Hf-HCl), following oral post-prandial administration to dogs.

The authors suggest that the high level of lymphatic transport of Hf-HCl (43.7% of dose), which was similar to that of the lipid soluble Hf base, was due to conversion of Hf-HCl in the intestinal lumen, during lipolysis, to the more lipophilic free base, which then becomes associated with chylomicron production.<sup>15</sup> Ontazolast undergoes extensive hepatic first-pass metabolism and it has solubility in soybean oil of 55 mg/ml, and a log *P* of 4. The formulations of ontazolast investigated included a suspension (lipid-free control), a 20% soybean o/w emulsion, two SEDDS containing Gelucire 44/14 and Peceol in the ratios 50:50 and 80:20, respectively, and a solution of the drug in Peceol alone. All the lipid formulations increased the bioavailability of ontazolast relative to the control suspension, while the SEDDS promoted more rapid absorption. Maximum lymphatic transport occurred with the emulsion and the Peceol solution. The emulsion prolonged lymphatic transport and this may be related to the need for pre-absorptive lipolysis of the triglyceride vehicle and an associated slower gastric emptying time. The Peceol solution provided the highest rate of lymphatic triglyceride transport thus

resulting in greater partitioning of the drug into the lymph. The SEDDS formulations resulted in the highest concentration of ontazolast in the chylomicron triglyceride. The authors suggest that SEDDS, which promote more rapid absorption of ontazolast, could produce higher concentrations of the drug in the enterocyte during absorption and hence improve lymphatic drug transport by a concentration-partitioning phenomenon <sup>15</sup>.

### The effect of excipients on efflux transport

Drug efflux mediated by broad-specificity xenobiotic transporters present in the intestinal epithelium may be an important factor in the poor or variable absorption of orally administered drugs. In the search for less toxic multidrug resistance (MDR) modulators. Bile salts, fatty acids, phospholipids, and surfactants were potent absorption enhancers and efflux-reducing agents in Caco-2 cells and the rat intestine. Other researchers also investigated the non-ionic surfactants, such as Tween 80, Pluronic P85, and Cremophor EL *in vitro* and *in vivo* in animals and in humans for their potential ability to reverse MDR caused by p-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRP).

Cremophor, Tween 80, and Solutol HS-15 have been proven to reverse the MDR phenotype in cultured cells at concentrations likely to be achieved clinically. TPGS (d- $\alpha$ -tocopheryl polyethylene glycol 1000 succinate) has been shown to be an effective inhibitor of P-gp mediated drug resistance and has been used to enhance the bioavailability of CsA in liver transplant patients as well as significantly improving absorption and reducing the daily drug cost. Inhibition of MDR-related pumps by various permeability enhancers has been proposed to occur due to binding competition, ATP depletion, and membrane perturbation. For example, Tween 80 has been shown to modulate anthracycline and Vinca alkaloid resistance in MDR cells by inhibiting the binding of these drugs to the pumps. The ability of Pluronic copolymer, one poly (ethylene oxide) block copolymer, to antagonize P-gp and sensitize MDR cells appears to be a result of ATP depletion, and inhibition of P-gp and MRP drug efflux proteins. Studies with MDR modifiers such as bile salts indicated that perturbations of the cell membrane structure may influence P-gp-mediated drug transport.

These modifiers may influence cytotoxic drug action by producing structural changes to the lipid domains in the plasma membrane. The membrane perturbation caused by pharmaceutical excipients, such as Tween 20, Tween 80, Brij 30, and Myrj 52, may result in a change in the fluidity of Caco-2 cell membranes, and thus inhibit the activity of membrane-spanning proteins, such as P-gp and MRPs which substantially reduce the basolateral to apical efflux of epirubicin across Caco-2 monolayers. Tween 20, Tween 80, Brij 30, and Myrj 52 may also inhibit protein kinase C (PKC) activity, reduce phosphorylation of P-gp, and modulate P-gp mediated drug efflux <sup>16</sup>. Inhibition of the efflux and/or enterocyte-based metabolism will increase the concentration and residence time of the intact drug in the cell. This may result in increased drug available for partitioning into the lymphatic.

### Role of lipolysis

Digestion of dietary triglyceride in the small intestine is very rapid, and many other non-ionic esters, such as mixed glycerides and surfactants, will be substrates or pancreatic lipase. Digestion of formulations will inevitably have a profound effect on the state of dispersion of the lipid formulation, and the fate of the drug. Fortunately, the liberation of free fatty acid during lipolysis can be titrated using NaOH in a pH stat, allowing quantitative data about the kinetics of digestion to be obtained. The location of the drug can be assayed in various fractions after ultracentrifugation of the products of digestion, which allows investigation of the likely fate of the drug after lipolysis <sup>17</sup>. The inclusion of highly lipophilic compounds in SEDDS is often reported to result in strongly enhanced oral absorption although it is still controversial whether further lipolysis of the dispersed lipid material is required for final transfer to the enterocyte membranes. In order to assess the relative roles of lipid vehicle dispersion and vehicle digestibility in the oral absorption of penclomedine (Pcm), a series of formulations of Pcm in medium chain triglyceride (MCT)/ TPGS was developed having

three sizes (160 nm, 720 nm, and mm-sized ('crude' oil)); with or without the inclusion of tetrahydrolipstatin (THL), a known lipase-inhibitor. Oral absorption of Pcm was studied after administration of small volumes of these formulations to conscious rats. Formulations with a particle size of 160 nm had the highest relative bioavailability (set at  $F = 1$ ), whereas administration in particle 720 nm in size resulted in a slightly lower bioavailability ( $F = 0.79$ ). Co-inclusion of THL yielded similar bioavailability for these two SEDDS. 'Crude' oil formulations had an  $F = 0.62$  (without THL) and 0.25 (with THL). Only in the case of Pcm administered as un-dispersed MCT was the absorption more dependent on the action of lipase as the bioavailability was inhibited two-fold by the co-incorporation of THL<sup>6</sup>.

#### Positively charged SEDDS

More recently, it has been shown that the enhanced electrostatic interactions of positively charged droplets with the mucosal surface of the everted rat intestine are mainly responsible for the preferential uptake of the model drug cyclosporine A (CsA) from positively charged droplets. The Caco-2 cell model was used for the investigation of the charge-dependent interactions of the SEDDS with human intestinal epithelial cells. The positively charged

emulsions affected the barrier properties of the cell monolayer at high concentrations and reduced the cell viability. However, at the dilution with aqueous phase used in the study (1:2000), the positively charged SEDDS did not produce any detectable cytotoxic effect. The binding of the fluorescent dye DiI(18(3)) was much higher from the positively charged SEDDS, compared with the negatively charged formulation, suggesting increased adhesion of the droplets to the cell surface due to electrostatic attraction<sup>18</sup>.

#### Application

SEDDS formulation is composed of lipids, surfactants, and co-solvents. The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation. SEDDSs present drugs in a small droplet size and well-proportioned distribution, and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the pre-systemic clearance in the GI mucosa and hepatic first-pass metabolism. Table shows the SEDDSs prepared for oral delivery of lipophilic drugs in recent years.

Table shows-- Application of self-emulsifying drug delivery systems

Type of delivery system	Drug	Oil	Surfactant	Cosolvent	Improvement
SEDDS(Gelled)	Ketoprofen	Captex 200	Tween 80	Capmul MCM	Silicon dioxide was used for gelling agent. As the concentration of silicon dioxide increases, it causes an increase in the droplet size of emulsion and slows the drug diffusion <sup>19</sup> .
SEDDS	Carvedilol	Labrasol	Labrafil M 1944CS	Transcutol P	It improves the oral bio availability of carvedilol up to 413% when compare to conventional tablet <sup>20</sup> .
SMEDDS	Simvastatin	Caproyl 90	Crempophore EL	Carbitol	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>21</sup> .
Self- emulsifying tablet	Diclofanac 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 better release rate <sup>22</sup> .
Self- emulsifying pellets	Methyl and propyl parabens	Mono and di glycerides of capric and caprylic acids.	Tween 80	-----	The self emulsifying formulation improves 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 <sup>23</sup> .

#### CONCLUSION

From the above review we can 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.

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