

**A REVIEW ON: SOLID SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM**

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**ABSTRACT**

Poorly water soluble drug candidates are becoming more prevalent and it has been estimated that 40-50% of drug molecules are poorly soluble in aqueous media or have a low permeability which does not allow for their adequate absorption from gastrointestinal tract following by oral administration. Formulation scientists have to adopt different strategies to enhance their absorption. Lipid formulations are seen to be a promising approach to combat the challenges and especially self-microemulsifying drug delivery (SMEDDS) system approach are used to increase the absorption of poorly absorbed drug which ultimately increased their bioavailability. The liquid SMEDDS are converted to solid SMEDDS by using liquid solid compact technique in which amount of carrier materials are calculated that maximum amount of non-volatile liquid can be retained inside its bulk [w/w] while maintaining an acceptable flowability.

**KEYWORDS:** Self-microemulsifying, liquid solid compact technique, surfactant, poorly water soluble drug, bioavailability, absorption, ternary phase diagram.

**INTRODUCTION**

The advancement in combinatorial chemistry and screening resulted in development of new chemical entities. As increased in use of these technologies, the screening of new chemical entities shift the identification of lead compounds of higher molecular weight and high lipophilicity which ultimately leads to poor aqueous solubility.<sup>[1]</sup> The solubility behaviour is one of the key determinants for oral bioavailability. In recent years number of poorly solubility drugs has increased significantly.<sup>[2]</sup> For researchers and scientist it is most important challenge for formulation of poorly soluble drugs. The most widely oral route is preferred compared to others route due to better patient compliance and economical cheap. The drug should be dissolved in gastric fluid to be absorbed from systemic circulation.<sup>[3]</sup> The dissolution step acts as the rate-controlling step for hydrophobic drugs which ultimately determine the rate and extent of absorption. The drugs to absorb through gastrointestinal tract, the molecules should present minimum solubility in physiological media and should present in dissolved state at site of absorption.<sup>[4]</sup> The development in new chemical entities, severe limiting factors must be overcome like poor solubility in GI fluid, stability and reasonable intestinal permeability.<sup>[5]</sup> More than 40% of new chemical entities are of poor water soluble or insoluble drugs. Also up to 50% of orally administered drugs substance suffers from

formulation problem of low solubility and high lipophilicity.<sup>[6]</sup> The few studies have been made for micronization of medication by diminishing the molecular size but problem occur in physical and chemical stability of drugs and thus faced difficulties in formulation design and development. There are certain drugs molecule whose bioavailability and absorption is solubility dependent. In order to design a better delivery system which provides required bioavailability, the poor water solubility of drugs should be improve.<sup>[7]</sup>

**Lipid Formulation Classification System<sup>[8,9]</sup>**

The number of possible combination in liquid formulation especially self-emulsifying system, the Lipid formulation classification system (LFCS) was introduced by Poultan in 2000 and updated in 2006. Based on the composition, effect of dilution and digestion ability to prevent drug precipitation, the LFCS classified lipid-base formulation into four major parts.

**Type I** system comprise of formulation in which drug is solubilised in triglycerides and/or mixed glycerides or in oil water emulsion stabilized by low amount of emulsifiers as 1% w/v polysorbate 60 and 1.2% w/v lecithin. Moreover this system exhibit poor initial aqueous dispersion and need digestion by pancreatic lipase/co-lipase in GIT for more amphiphilic lipid digestion products and the transfer of drug into colloidal aqueous phase is promoted.

**Type II** lipid formulation system also known as non-water soluble component system in which self-emulsification is obtained at surfactant content above 25% w/w, but higher surfactant content of 50-60% w/w cause formation of viscous liquid crystalline gels at oil/water interface. The slow dissolution step in solid oral dosage form can be overcome by type II lipid based formulation.

**Type III** lipid based formulation known as self-microemulsifying drug delivery system are made by inclusion of hydrophilic surfactant having HLB>12 and co-solvent like ethanol, propylene glycol and PEG.

These systems are further differentiating into type IIIA and type IIIB formulation in order to known specific hydrophilic system.

**Type IV** system is recently added system to LFCS which exclude natural lipid from the formulation and represent hydrophilic formulation. Due to maximum solubility of drug in surfactant and co-solvent, the drug payload is increased in these formulations. Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These system produce very fine dispersion in aqueous media compared to simple glycerides containing formulation.

**Table 1: Lipid based classification system.**

Lipid system	Characteristics	Advantages	Disadvantages
<b>Type I</b>	Non-dispersing: Requires digestion	Excellent capsule compatibility; simple	Formulations have poor solvent capacity until drug is highly lipophilic.
<b>Type II</b>	Self-emulsifying drug delivery system (SEDS) without water soluble component.	Unlikely to lose solvent capacity on dispersion.	Turbid o/w dispersion.
<b>Type IIIA</b>	Self-microemulsifying drug delivery system (SMEDS) with water soluble components.	Almost clear dispersion solution; drug absorption without digestion.	Loss of solvent capacity on dispersion; less easily digested.
<b>Type IIIB</b>	SMEDS with water soluble component and less oil content.	Drug absorbed without digestion; clear dispersion solution.	Likely loss of solvent capacity on dispersion.
<b>Type IV</b>	Oil free based formulation contains surfactants and co-solvent.	Good solvent property for many drugs; disperse to micellar solution.	Loss of solvent capacity on dispersion; may not be digestible.

### Self-Microemulsifying Drug Delivery System

Self-microemulsifying are defined as a physically stable isotropic mixtures of oils, surfactants, co-surfactants and dissolve drug substance which upon contact with aqueous phase with gentle agitation, spontaneously emulsify to form fine oil in water emulsion. Therefore upon administration to GI tract it readily dispersed due to agitation provided by the motility of stomach and small intestine.<sup>[10]</sup> Depending on screening and selection of oil, surfactant and co-surfactant and their relative composition, aqueous dilution will result in spontaneous generation of globule size of SEDDS produce emulsion and SMEDS produce clear transparent micro emulsion.<sup>[11]</sup> The optimum concentrations of oil, surfactant and co-surfactant which are responsible to promote self-emulsification are obtained by constructing Pseudo-ternary phase diagram. The affection of drug loading of micro emulsification is also assessed.<sup>[12]</sup> In SMEDS the globule size is less than 50 nm produce a large surface area which facilitates drug release and drug absorption.<sup>[13]</sup> The drugs are present in dissolve state in oil phase in liquid SMEDS which avoid slow and rate-limiting dissolution process for hydrophobic drugs. The liquid SMEDS are encapsulating in soft and hard gelatine capsules which is administered as oral dosage form. The ability to form fine oil-in-water microemulsion upon gentle agitation is a principle

behind SMEDS.<sup>[14]</sup> The poorly soluble drugs formulated as Self-microemulsifying drug delivery system increased the drug absorption through enhancement in dissolution rate of drugs, promote intestinal lymphatic transport of drugs, prevents from enzymatic degradation and inhibitory effect of P-glycoprotein (Pgp).<sup>[15]</sup> The conventional emulsions prepared are not stable as they are sensitive and metastable dispersed forms and require high shear of agitation to form emulsion. While in SMEDS simple mixing is required and does not require a high agitation to form microemulsion, also they are physically stable, manufacturing is easy and simple and are convenient for oral delivery in soft and hard gelatine capsules. But in formulation of liquid SMEDDS in soft and hard gelatine capsules, the incompatibility problem arises with the shells of soft gelatine capsules. Therefore a solid SMEDS was introduced which shows a good patients acceptability. Some of the problems which can be overcome by SMEDDS.<sup>[16,17]</sup>

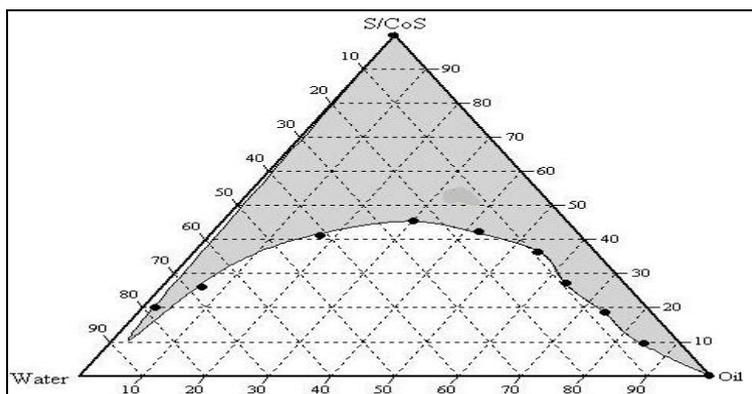


Figure 1: Pseudo-ternary phase diagram.

### Advantages<sup>[18]</sup>

- Increased the bioavailability of the drugs.
- Globule size of less than 50 nm is achieved.
- May enhanced the oral bioavailability which enables of active ingredients.
- Dose of active ingredients is reduced.
- More consistent temporal profiles of drug absorption is achieved.
- Provide 100% drug entrapment efficiency capacity.
- Drug targeting of drug can be achieved to site specific absorption site.
- Provide a protection of drugs from hostile environment in gut.
- Decreased the variability of food effects.
- Thermodynamically stable system can be achieved for long time without creaming and phase separation
- Manufacturing process and scale-up is easy and simple as it does not demand high force of agitation compared to normal emulsion to for micro emulsion.
- No specific condition of storage is required.
- Can preserve protein and peptides in microemulsion form.
- No dissolution step is required after oral administration because drug is in solubilise form and thus it ultimately increased rate of absorption rate.

### Disadvantages<sup>[19]</sup>

- Require comparatively high amount of surfactants which may be toxic in certain cases.
- For unit dosage preparation in gelatin capsules, it may produce softening or hardening effect on capsule shell, so for long term storage it is undesirable.
- In microemulsion there is presence of oil with its own odour or taste so for oral delivery it may produce patient noncompliance.
- Drug precipitation after long term storage may be a problem with certain component system.
- It may form bulky dosage form compare to solid oral dosage, so storage & transportation may be a problem.

### Mechanism of self-microemulsion<sup>[20]</sup>

The mechanism involves in formation of self-microemulsion is not very well clarified and understood. From the surface free energy of emulsion formation, It can be understood that the change in the Gibbs free energy of the system ( $\Delta G$ ), produced by dispersing procedure at constant composition and pressure, can be expressed by following equation:

$$\Delta G = \Delta H - T \Delta S$$

Where  $\Delta G$  = change in free energy

$\Delta H$  = change in enthalpy

$\Delta S$  = change in entropy

T = absolute temperature

The change in entropy ( $\Delta S$ ) is defined as a measure of the extent of disorder in the physical system and thus measures the extent of size reduction of the oil phase (or increase in droplet number). As the increased in disorder in system during the formation of an emulsion means a positive  $\Delta S$  value which contribute the stability of prepared microemulsion. The  $\Delta H$  means the change in enthalpy of the system and can be considered as the binding energy of the oil phase or the energy input required to achieve a optimum average globule size (surface area). Thus it has been suggested that self-emulsification process takes place when the entropy change favoring dispersion ( $\Delta S$ ) is greater than the energy required to increase the surface area of the dispersion ( $\Delta H$ ). On the other hand, emulsification occurs spontaneously with SEDDS because the free Energy which is necessary to form the emulsion is either low and positive or negative. According to Reiss equation, the spontaneous formation of microemulsion can be achieved if free energy change ( $\Delta G$ ) of system must become negative in order to fulfill the thermodynamic requirement of SMEDS.

$$\Delta G = \sum N_i \pi r_i^2 \sigma$$

Where N = number of droplets of radius r  $\sigma$  = represents the interfacial energy.

Thus it has been suggested that self-emulsification process takes place when the entropy change favoring dispersion ( $\Delta S$ ) is greater than the energy required to increase the surface area of the dispersion ( $\Delta H$ ). The free energy required in conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases. Thus two phases of the emulsion tend to separate with time to reduce the interfacial tension and free energy of systems. In conventional emulsion, emulsifying agents stabilize emulsions resulting from aqueous dilution by forming a monolayer around the emulsion droplets, decreasing the interfacial energy and forming a barrier to provide from coalescence of droplets. On the other hand, emulsification occurs spontaneously with SEDDS because the free Energy which is necessary to form the emulsion is either low and positive or negative. According to Reiss equation, the spontaneous formation of microemulsion can be achieved if free energy change ( $\Delta G$ ) of system must become negative in order to fulfill the thermodynamic requirement of SMEDDS,

$$\Delta G = \sum N_i \pi r_i^2 \sigma$$

Where N = number of droplets of radius r  
 $\sigma$  = represents the interfacial energy.

#### Excipients Used In Smedds

The preliminary studies and screening are performed for selection of oil, surfactant and co-surfactant which is an important and critical component for formulation of

SMEDDS. SMEDDS comprise of oil, surfactant and co-surfactant. The Solubility of drug is carried in various oils and surfactants. The Pharmaceutical acceptability for excipients and the toxicity issues of components used makes the selection of excipients more critical. There is a great restriction as which excipients should be used so it does goes out to its toxic level.<sup>[21]</sup>

#### Oils

The oil is an important component as it facilitate the self-micro emulsion formation. The lipophilic drug can be solubilise in oils and increase the drug transport across intestinal lymphatic system and increased the drug absorption rate. Hydrogenated vegetable oils have many advantages as the foundation of lipid-based delivery systems. They are frequently ingested with food as they are fully digested and absorbed without any safety issues.<sup>[22]</sup> Vegetable oils are glyceride product of glycerolysis esters of mixed containing unsaturated long-chain fatty acids which is commonly known as long-chain triglycerides (LCT). The Oils from different vegetable sources have different proportions of each fatty acid. The Coconut oil is carry over distillation to produce the 'medium-chain triglycerides' (MCT) (also known as glyceryl tricaprlylate/caprante) which is available from several suppliers and commonly comprises glyceryl esters containing saturated C8 (50–80%) and C10 (20–45%) fatty acid.<sup>[23]</sup> Castor oil is common source of Glyceryl ricinoleate, which uniquely has a hydroxyl group coupled to the alkyl chain.<sup>[24]</sup>

**Table 2: Oils used in Smedds.**

LIPIDS	Chemical name	Regulatory status
Vegetable oils	Long chain TAG	FDA IIG
Miglyol 812	Medium change TGA caprylic/capric TAG	GRAS IIG
Inwitor 988	Caprylic/capricglycerides	USP
Maisine 35-1	Glyceryl mono-oleate	Oral product, GRAS, EP, USP-NF
Captex 355	Glycerolcaprylate caprate	GRAS, FDA IIG
Labrafac CC	PG dicaprylocaprante	USFA, JSFA, EP
Peceol	Glyceryl mono-oleate	GRAS, EP, USP-NF, FDA IIG

#### Surfactants

The choice of surfactant and its concentration range are very important for formation of microemulsion. The surfactant lowers the interfacial tension and upon the mild agitation produce by the digestive motility of stomach and small intestine is sufficient to achieve microemulsion.<sup>[25,26]</sup> Many compounds exhibit surfactant properties as they are employed for the design of self-microemulsifying systems, but the selection of surfactant is limited as only very few surfactants are orally. The choices of surfactant are mainly control by two parameter: (a) hydrophilic-lipophilic balance, (b) safety.

Usually surfactant should have high HLB value. Non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) are most widely acceptable for microemulsion formation.<sup>[27]</sup> The most widely used emulsifiers/surfactant are various solid or liquid

ethoxylated-polyglycolized glycerides and polyoxyethylene 20oleate (Tween 80). The safety of the surfactant is very important factor while choosing and selection of surfactant. Generally the surfactant concentration ranges between 30 and 60% w/w in order to form stable SMEDDS. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS.<sup>[28]</sup>

Table 3: Surfactants used in SMEDDS.

Chemical name	Trade name
Sorbitan monostearate	SPAN® 60
Sorbitan monopalmitate	SPAN® 40
Polyoxyethylene20 sorbitan monostearate	Polysorbate60 (Tween® 60)
Saturated polyglycolized glycerides	Gelucire® 44/14
Polyoxyethylene 20 sorbitan monooleate	Polysorbate80 (Tween® 80)
Polyoxyl 35 castor oil	Cremophor® EL
Polyoxyl 40 hydrogenated castor oil	Cremophor® RH40
Unsaturated polyglycolized glycerides	Labrafil® M2125, M1944 4
PEG-8 Caprylic/Capric glycerides	Labrasol®

### Co-surfactant

In order to prepare optimum SMEDDS, it requires relatively high concentrations (generally more than 30% w/w) of surfactants but at high concentration it may irritate to GI tract and cause toxicity. Thus the concentration of surfactant can be minimize by incorporation of co- surfactant in the formulation. The selection of surfactant and co-surfactant is crucial step not only for formation of SMEDDS, but also for solubilisation of drug in the SMEDDS.<sup>[29,30]</sup>

### Solid Self-Microemulsifying Drug Delivery System<sup>[31,32]</sup>

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquid solid systems has been developed. This approach is based on the flowable liquid retention ( $\Phi$ -value). The  $\Phi$ -value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of slide.

$$\Phi \text{ value} = \frac{\text{Weight of Non Volatile Liquid}}{\text{Weight of carrier material}}$$

### Determination of Angle of Slide

The required amount of carrier was weighed and placed at one of a metal plate with a polished surface and it is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. It was used to measure the flow properties of powders. A value of 33° for angle of slide gives an optimum flowability to the powders. Keeping constant weight of carrier/ coating material, increasing amount of solvent was incorporated and on each addition, angle of slide was determined. The flowable liquid retention potential ( $\Phi$  -value) of each liquid/powder admixture was calculated using the following equation.

$$\Phi \text{ -value} = \text{weight of liquid/weight of solid}$$

The  $\Phi$  -values were plotted against the corresponding angle of slide (for optimal flowproperties).

Corresponding to 33° of a liquid/powder admixture represented the flowable liquid-retention potential.

$$\text{Loading factor (Lf)} = \Phi_{\text{car}} + \Phi_{\text{coat}} (1/R)$$

Where,

$\Phi_{\text{car}}$  = liquid retention potential for carrier material

$\Phi_{\text{coat}}$  = liquid retention potential for coating material

R= ratio of carrier to coating material

$$\text{Lf} = W/Q$$

$$Q = W/ \text{Lf}$$

Where,

W= weight of liquid medication

Q= amount of carrier material

$$R = Q/q$$

$$q = Q/R$$

Where,

q= amount of coating material

### Evaluation Parameter Of Self-Microemulsifying Drug Delivery System<sup>[33,34]</sup>

#### 1. Macroscopic evaluation

Macroscopic evaluation is checked by colour transparency or phase separation observed during normal storage condition (37±2°C) in micro emulsion formulation.

#### 2. Robustness to dilution

Robustness to dilution is important in SMEDDS to check the microemulsion formed have similar properties at different dilution to achieve uniform drug release profile and to ensure that the drug will not get precipitated at higher dilution *in-vivo* which retard the significant absorption of the drug from the formulation. The SMEDDS formulation is diluted in various dilution with various diluents to know the effect of dilution on liquid SMEDDS and their effect on the properties of formed emulsion. The diluted SMEDDS were store at room temperature and observed for any phase separation or precipitation occur or not.

#### 3. Self-emulsification test

The self-emulsification of SMEDDS is performed by using a standard USP type II(Paddle) apparatus. The liquid SMEDDS upon dilution with water at 37 ± 0.5°C

at 50rpm; the time required to obtain clear homogenous mixture are recorded as emulsification time.

Grade A: Micro emulsion formed rapidly within 1 min having clear appearance.

Grade B: Micro emulsion formed are less clear rapidly formed having white appearance in less than 2 min.

Grade C: Micro emulsion with white fine milky appearance within 2 min.

#### 4. Cloud point measurement

The cloud point measurement is important factor in SMEDDS as it gives information about the stability of micro-emulsion formed at body temperature. The formulation is diluted in water and kept on water bath and temperature is increase gradually. The point at which cloudiness observed is noted as cloud point.

#### 5. Droplet size and zeta potential

The globule size of formed emulsion is important as it determine the rate and extent of drug release as well as absorption. The globule size of reconstituted formulation is measured after diluting the liquid SMEDDS in distilled water by using Zetasizer. The Zeta potential are carried out to identify charge on the surface of droplet. The liquid SMEDDS containing drug is diluted in distilled water in a flask and were mixed gently by inverting the flask. The particle size occurred are determine by dynamic light scattering spectroscopy by using instrument Zetasizer.

#### 6. % Transmittance

The primary means of self-microemulsion is visual assessment. To avoid any subjective variations, %transmittance of the resulting microemulsion obtained on dilution of self-emulsifying is measured using UV-visible spectrophotometer.

#### 7. In-vitro drug release

The development of dissolution methods for SMEDDS is performed in USP type-II Paddle apparatus using suitable dissolution medium at  $37^{\circ}\text{C}\pm 2^{\circ}\text{C}$  and is compared with standard formulation.

#### 8. Flow and compressibility characteristics

Determination of angle of repose, Carr's index, Hausner's ratio is used to characterize flow properties of the solid powder SMEDDS. The flowability of a powder is critical parameter important in production of pharmaceutical dosage form in order to get uniform feed as well as reproducible filling of the tablet dies.

#### 9. Scanning Electron Microscopy (SEM)

The surface morphology of sample of solid-SMEDDS is determine by using Scanning Electron Microscopy. The sample is sprinkle on aluminium stab and then specimen is coated with gold particles in a high vacuum evaporation at an accelerating voltage of 10 KV.

## CONCLUSIONS

Advancement of the technologies and design and development of new chemical moieties having targeting potential is leading to emergence of new drug molecules having therapeutics effect but unfavourable there drug absorption in the body. This emerges the greatest challenge to the researcher to efficiently deliver such drug molecules which exhibit poor aqueous solubility. Lipid formulations are promising approach for various categories of drug molecules having poor aqueous solubility. Among the various lipid formulation, the self-microemulsifying drug delivery systems offers additionally advantages of increased bioavailability, higher stability, high drug loading capacity, potential for oral drug delivery (solid-SMEDDS), ease of manufacture etc. SMEDDS are mostly investigated for BCS class II drugs having low aqueous solubility for their bioavailability enhancement.

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