SEDDS & SMEDDS

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Introduction

Challenge in development of optimum oral solid dosage form in terms of formulation design and bioavailability of new pharmaceutical products as

- 40% of new drug candidates exhibit **low solubility in water**
- oral delivery of 50% of the drug compounds is hampered because of the **high lipophilicity** of the drug itself

Introduction

- lipid solutions, emulsions and emulsion pre-concentrates, which can be prepared as physically stable formulations suitable for encapsulation of such poorly soluble drugs.
- use of surfactants, cyclodextrins, micronization, liquisolid techniques, salt formation, pH change, nano size delivery, solid dispersions and permeation enhancers
- Emulsion systems are associated with their own set of complexities, including **stability** and **manufacturing problems** associated with their commercial production.

DEFINITION:

- SEDDS or self-emulsifying oil formulations (SEOP) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants and co-solvents/surfactants.

- SEDDSs emulsify spontaneously to produce fine oil in- water emulsions when introduced into an aqueous phase under gentle agitation and spread readily in the gastro intestinal tract.

- SEDDSs typically produce emulsions with a droplet size between 100–300 nm while self-micro-emulsifying drug delivery systems (SMEDDSs) form transparent micro-emulsions with a droplet size of less than 50 nm.

Self-emulsifying drug delivery systems (SEDDS)

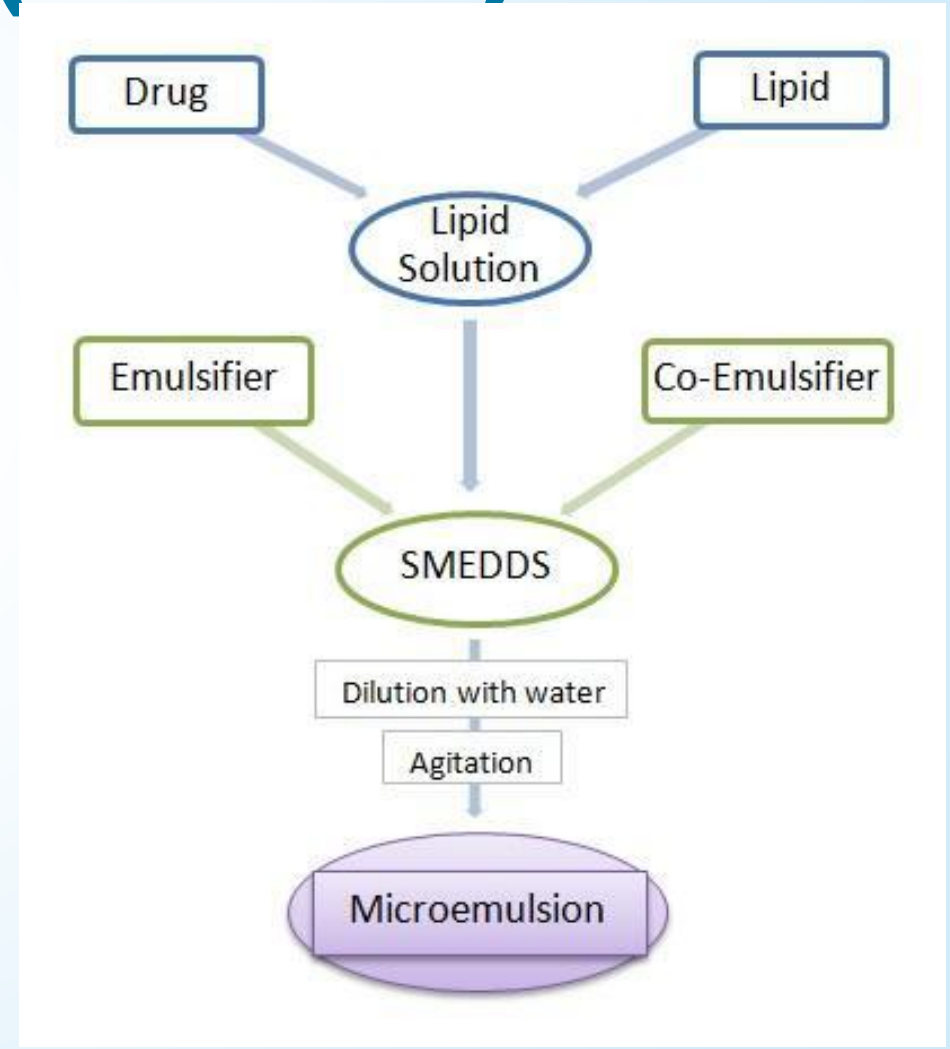
- improve the bioavailability of poorly water-soluble compounds.
- SEDDS are isotropic mixtures of **drug, lipids and surfactants**, usually with one or more hydrophilic co.
- Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously.
- The size of the droplet formed is between **100 and 300 nm**

Self-emulsification

- is a term used to describe emulsification which occurs with little or no input of energy .
- The process may be **spontaneous** or may require low levels of shear
- but will contrast with Conventional Emulsification which requires high shear.
- SMDDS & SMEDDS form fine oil-in-water (o/w) emulsions or micro emulsions (SMEDDS)upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids.
- The drug, therefore, remains in solution in the gut, avoiding the dissolution step that frequently limits the absorption rate of hydrophobic drugs from the crystalline state.

Self-micro Emulsifying Drug Delivery Systems (SMEDDS)

- these are physically stable,
- easy to manufacture,
- can be filled in soft gelatin capsules and
- then will generate a drug containing micro-emulsion with a large surface area upon dispersion in the gastrointestinal tract.
- droplet size of less than 50 nm



INTRODUCTION

Emulsion: White- semi white look

- Oil
- Surfactant
- Water

Microemulsion: Uni phasic System: Transperancy

- Oil
- Surfactant
- Co-surfactant
- Water

Self emulsifying drug delivery system (SEDDS)

- Oil
- Surfactant
- Co-surfactant

Self micro emulsifying drug delivery system (SMEDDS)

- Oil
- Surfactant
- Co-surfactant

SEDDS Vs SMEDDS

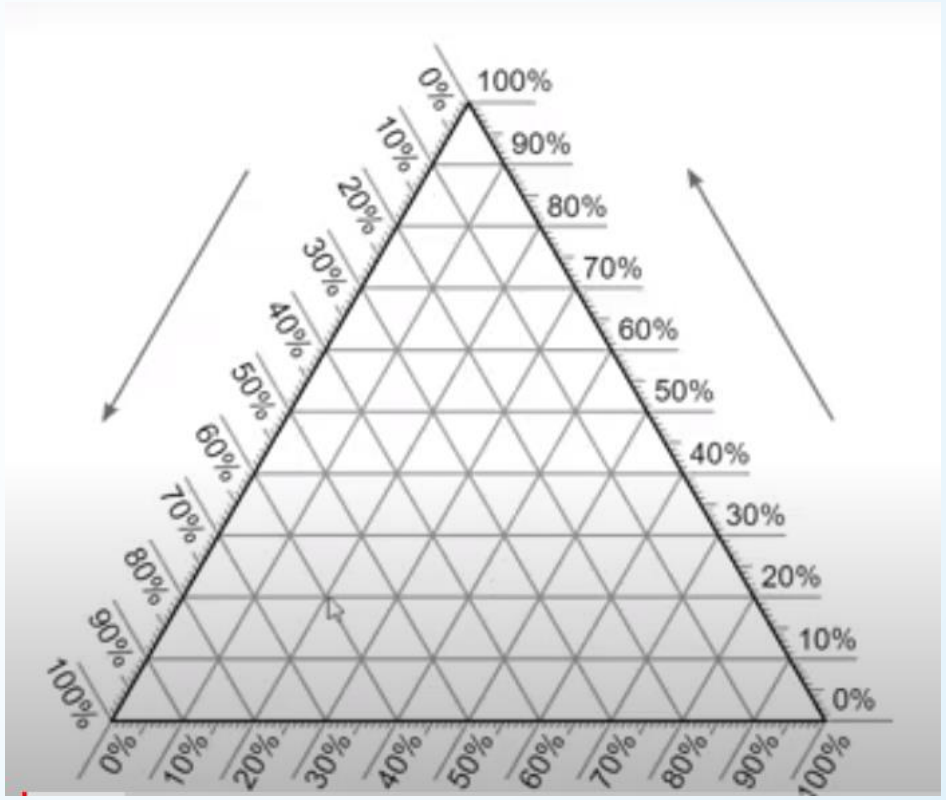
SEDDS

- produce opaque emulsions
- with a droplet size 100 and 300 nm
- concentration of oil 40-80%

SMEDDS

- form transparent micro emulsions
- with a droplet size of less than 50 nm
- concentration of oil is less than 20 %

Development of Ternary and Pseudo Ternary Phase Diagram

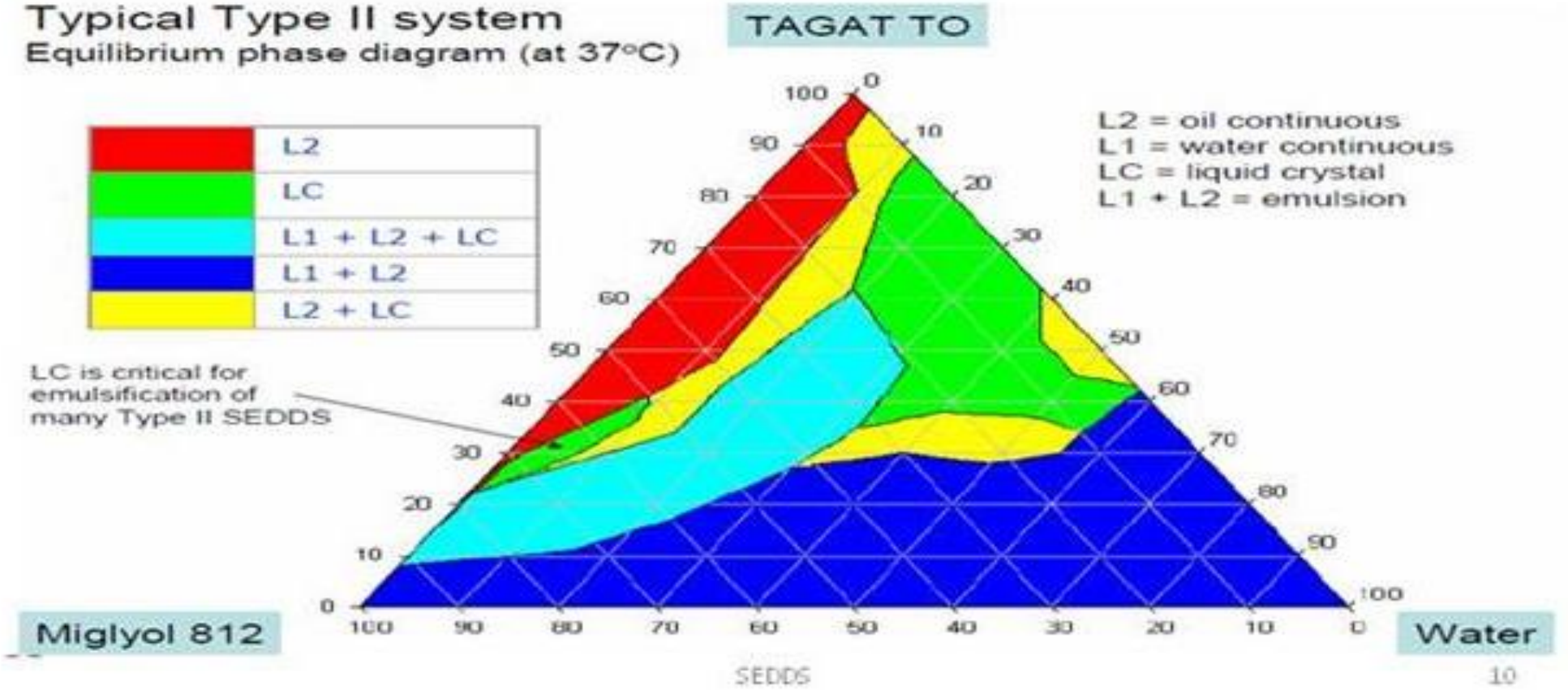


Ternary and Pseudo Ternary Phase Diagram

- is used to map the **optimal composition range** for three key excipients according to the resulting droplet size following self emulsification, stability upon dilution and viscosity.
- **Titration method** is employed to construct phase diagram.
- Mixture of oil with surfactant is prepared at different ratios (e.g. 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10) into different vials.
- A small amount of water in 5 % (w /w) increments is added into the vials. Following each water addition the mixture in vials is centrifuged for 2 to 3 minute and is incubated at 25 ^{0} C or 48 hrs with gentle shaking.

Construction of phase diagram

- The resulting mixture is evaluated by visual and microscopy observation. For phase diagram the micro emulsion is the region of clear and isotropic solution.
- Coarse emulsion is the region of cloudy dispersion.



OILS

- Oils can solubilize the lipophilic drug in a specific amount.

  It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract.
- Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs.
- EG.mono-di-tri-glycerides DL-alpha-Tocopherol,
- Fractionated triglyceride of coconut oil(medium-chain triglyceride)
- Corn oil, Olive oil, Oleic acid, Sesame oil, Hydrogenated soya bean oil, Hydrogenated vegetable oils,Soyabean oil, Peanut oil, Beeswax

Surfactant

- 1: Anionic Surfactants, where the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphonate (RSO3 -) or sulphate (ROSO3 -).

  Examples: Potassium laurate, SLS
- 2: Cationic surfactants, where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.
- 3: Ampholytic surfactants (also called zwitterionic surfactants)

  Example: sulfobetaines.
- 4: Nonionic surfactants, where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH2CH2O).

  Examples: Sorbitan esters (Spans), Polysorbate (Tween).

- Nonionic surfactants with high Hydrophilic Lipophilic Balance (HLB) values are used in formulation of SEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.).
- 30–60% w/w is used of the formulation in order to form a stable SEDDS. Surfactants have a high HLB(>12) and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media

Cosolvents/Cosurfactant

- Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG) polyethylene glycol (PEG), etc) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self emulsifying drug delivery systems

Other components

- These may be pH adjusters,
- flavors,and
- Antioxidant agents.
- Lipophilic antioxidants(E.g. alpha tocopherol, propyl gallate,ascorbyl palmitate) may be required to stabilize the oily content of SMEDDS formulation.
- Consistency builder

self-emulsifying formulation depends

(1) physicochemical properties of the drug, such as pKa, polarity and solubility in various components

(2) physicochemical nature of oily phase, surfactant and co-surfactant

(3) the area of the self-emulsifying region as obtained in the phase diagram,

(4) the ratio of the components, especially oil to surfactant ratio and

(5) the droplet size distribution of the resultant emulsion following self-emulsification.

Table 2: The lipid formulation classification system [5, 26]

		Type I	Type II	Type III A	Type III B	Type IV
Composition	Oils	100 %	40–80%	40–80 %	<20%	0%
	Water-insoluble surfactants (HLB < 12)	0%	20-60%	0%	0%	0-20%
	Water-soluble surfactants (HLB > 12)	0%	0%	20–40%	20–50%	30–80%
	Hydrophilic co-solvents (e.g. PEG, propylene glycol, transcutol)	0%	0%	0–40%	20–50%	0–50%
Particle size		Coarse	100-250	100–250	50–100	<50
Characteristics		Non-dispersing	Emulsion (SEDDS)	SEDDS/ SMEDDS formed with water-soluble components	SEDDS/ SMEDDS formed with water-soluble components and low oil content	Disperses typically to form a micellar solution
Digestibility		Requires digestion	Will be digested	Digestion may not be necessary	Digestion may not be necessary	Limited digestion
Advantages		GRAS status; simple; excellent capsule compatibility	Unlikely to lose solvent capacity on dispersion	Clear or almost clear dispersion. Absorption without digestion	Clear dispersion. Absorption without digestion	Good solvent capacity for many drugs; disperse to micellar solution
Disadvantages		Poor solvent capacity (unless drug is highly lipophilic)	Turbid o/w dispersion	Possible loss of solvent capacity on dispersion. Less easily digested	Likely loss of solvent capacity on dispersion	Loss of solvent capacity on dispersion; may not be digestible