SELF EMULSIFING DRUG DELIVERY SYSTEM (SEDDS) -A REVIEW

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ABSTRACT:

Self-emulsifying drug delivery systems instigated as an oral lipid-based drug delivery system with the sole purpose of improving delivery of highly lipophilic drugs. The innovatory drug delivery possibilities presented by these distinctively simplified systems in terms of muco-adhesiveness and zeta-potential changing capacity lead the way forward to ground-breaking research. Contrarily, SEDDSs destined for topical/transdermal drug delivery has received limited attention. Therefore, this review is focused at utilizing principles, established during development of oral SEDDSs, and tailoring them to fit evaluation strategies for an optimized topical/transdermal drug delivery vehicle. This includes a detailed discussion of how the authentic pseudo-ternary phase diagram is employed to predict phase behaviour to find the self-emulsification region most suitable for formulating topical / transdermal SEDDSs. Additionally, special attention is given to the manner of characterizing oral SEDDSs compared to topical/transdermal SEDDSs, since absorption within the gastrointestinal tract and the multi-layered nature of the skin are two completely diverse drug delivery territories. Despite the advantages of the topical/transdermal drug administration route, certain challenges such as the relatively undiscovered field of skin metabolomics as well as the obstacles of choosing excipients wisely to establish skin penetration enhancement might prevail. Therefore, development of topical/transdermal SEDDSs might be more complicated than expected.

Keywords. Self-emulsifying drug delivery systems.

1. BACKGROUND OF SEDDS.

SEDDS are promising approach for oral delivery of poorly water-soluble compounds. It can be achieved by pre-dissolving the compound in a suitable solvent. The oral drug delivery of hydrophobic drugs can be made possible by SEDDS. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used. If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favors the drug remaining in the lipid droplets. SEDDS are used as potential drug delivery vehicles because of their thermodynamic stability; reversibility, simple manufacturing, and scale up feasibility, and do not

require any special equipment. Oil-in-water (o/w) SEDDS is the most suitable formulation and are potential in improving the bioavailability of poorly water soluble drugs by enhancing their solubility by dissolving the compounds with low water solubility into an oil phase, dissolution rate and ultimately the oral bioavailability by increasing the membrane permeability. Thus, the main purpose of this work is to develop SEDDS which have the potential to enhance the solubility of poorly soluble Clarithromycin drugs (BCS class-II) and overcome the dissolution related bioavailability problems. These system provides protection against oxidation, improve drug dissolution, enzymatic hydrolysis, fast absorption, improves the solubilisation of lipophilic drugs thereby enhance bioavailability and enables reduction in doses.

2. INTRTODUCTION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM

Self-emulsifying drug delivery systems (SEDDS) or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsions (SMEDDS). Self-emulsifying formulations spread readily in the GI tract and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm**.**

These systems advantageously present the drug in dissolved form and the small droplet size which provides a large interfacial area for the drug absorption. When compared with emulsions, which are sensitive and meta-stable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles. The drug in the oil droplet may partition out in the intestinal fluid as presented in Figure.

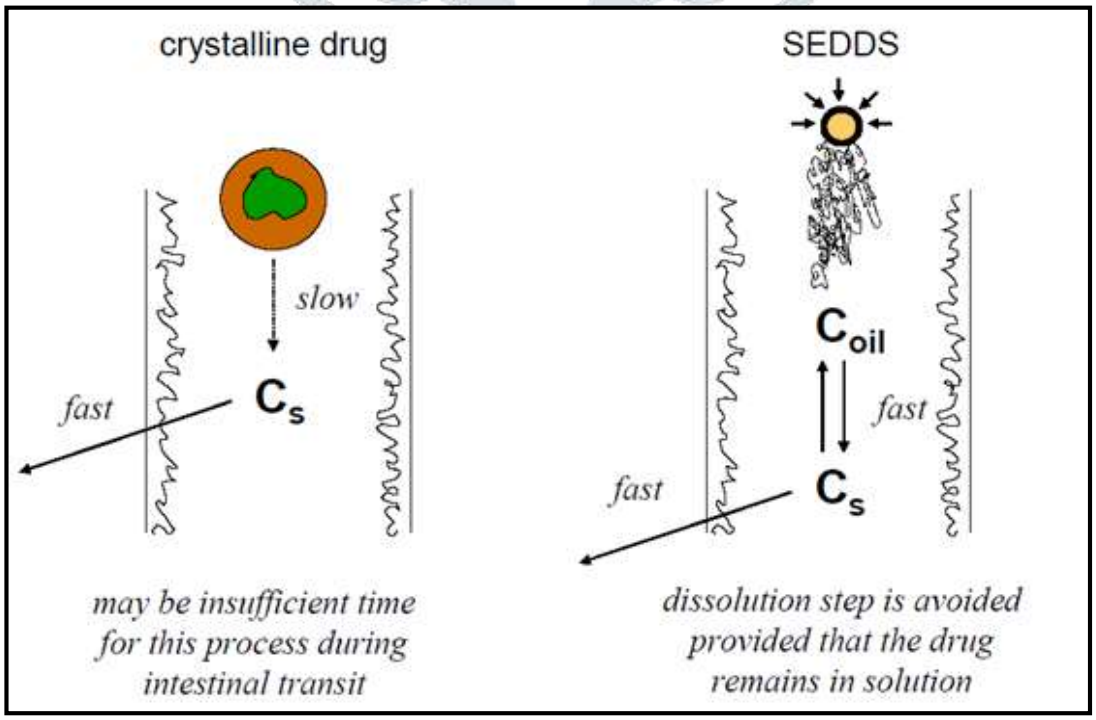

Figure 1: Comparison study of drug partitioning in crystalline drug and SEDDS

3. WHY SEDDS ARE NEEDED.

SEDDS are promising approach for oral delivery of poorly water-soluble compounds. It can be achieved by pre-dissolving the compound in a suitable solvent and fill the formulation into capsules. The oral drug delivery of hydrophobic drugs can be made possible by SEDDS. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used.

4. ADVANTAGES OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS OVER CONVENTIONAL DRUG DELIVERY SYSTEMS.

- Emulsions are sensitive and metastable dispersed forms, whereas S-(M)EDDS are physically stable formulations that are easy to manufacture.
- Fine oil droplets of these SEDDS would pass rapidly and encourage extensive distribution of the drug all the way through the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.
- While compared with oily solutions, these SEDDS afford a large interfacial area for partitioning of the drug between oil and water.
- Consequently, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles.
- Enhanced oral bioavailability enabling reduction in dose.
- Control of delivery profiles.
- Reduced variability including food effects.
- High drug payloads.
- Liquid or solid dosage forms

A COMPARATIVE ACCOUNT OF FORMULATION OF SEDDS & SMEDDS

Table 1: A Comparative Account of Formulation of SEDDS and SMEDDS

SEDDS	SMEDDS
Can be simple binary formulation with the drug and a lipidic excipient able to self-emulsify in contact with gastrointestinal fluids (GIF) or A system comprising drug, surfactant and oil	Are composed of the drug compound, surfactant, co-surfactant and oil (or lipid phase)

SEDDS and SMEDDS Form a fine oil-in-water dispersion in contact with GIF	
Lipid droplet size in the dispersion ranges from 200nm -5 µm providing a large surface area for absorption. The dispersion has a turbid appearance.	Lipid droplet size in the dispersion is < 200nm providing a large surface area for absorption. The dispersion has an optically clear to translucent appearance.
SEDDS and SMEDDS **Have high solubilizing capacity** **High dispersibility capacity**	
SEDDS systems are less thermodynamically stable in water or physiological conditions. Developed/ optimization of SEDDS may require the development of ternary phase diagram.	SMEDDS systems are thermodynamically stable in water or physiological conditions. Pseudo-ternary phase diagram are required optimize SMEDDS
SEDDS and SMEDDS **Formulation can be prepared as liquid and semi-solid for capsule dosage forms and solid dosage form for tableting**	

5. MECHANISM OF SELF-EMULSIFICATION

According to Reiss, the energy required to increase the surface area of the dispersion for self-emulsification process bear less importance when compared to the entropy change that favors dispersion. Self emulsifying process is related to the free energy. The free energy of a conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases. The thermodynamic relationship for the net free energy change is described by Equation.

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

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

Where, N = Number of droplets with radius r

σ = Interfacial energy.

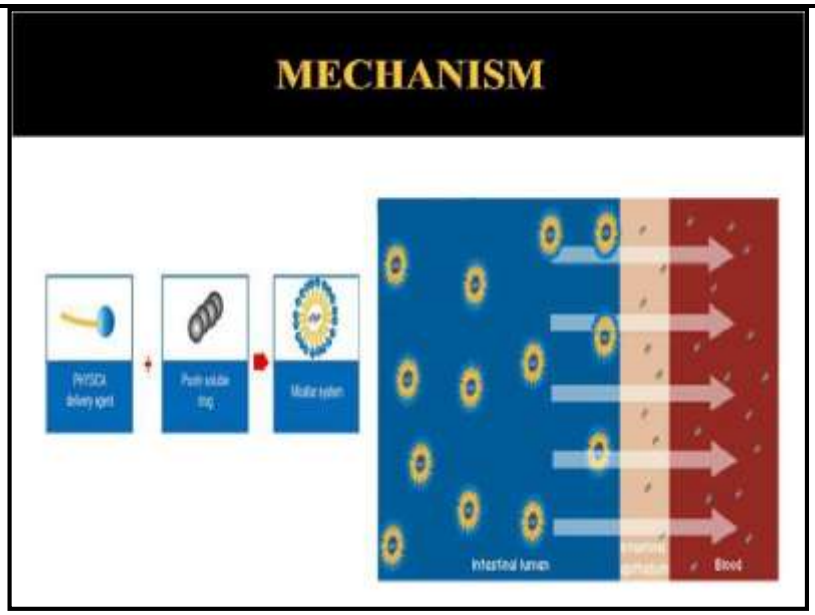

Figure 1.4: Characterization of Self-Emulsifying Drug Delivery Systems

6. APPLICATION OF SEDDS/SMEDDS FORMULATION

A. Improvement of oral absorption:

SEDDS partially avoids the additional drug dissolution step prior to absorption in the GI tract. They increase the amount of solublized drug in the intestinal fluids resulting in good drug absorption. Apart from this, absorption of the drug may also be enhanced by using lipid based excipients in the formulation. There are several mechanisms through which increased absorption can be achieved.

B. Retardation of gastric emptying time:

Surfactants are believed to play a role in retardation of gastric transit time, thereby increasing the time available for the drug to dissolve and get absorbed. Surfactants may show down gastric empting for a period of time by formation of viscous mass in the gastric and intestinal lumen. Labrasol shows improved bioavailability of an investigational compound by retarding gastric empting time.

C. Increase in effective drug solubility in lumen:

The pathway of lipidic transport from the GI lumen to the systemic circulation is of paramount significance for interpretation of the biopharmaceutical properties of oral lipid-based formulations and successful product development. On oral administration, the SEDDS formulation undergoes digestive, absorptive and circulatory phases. Figureure 1.6 presents a comprehensive pictorial view of such pathways through which the drug molecules form self-emulsifying systems tend to get absorbed into the circulatory system.

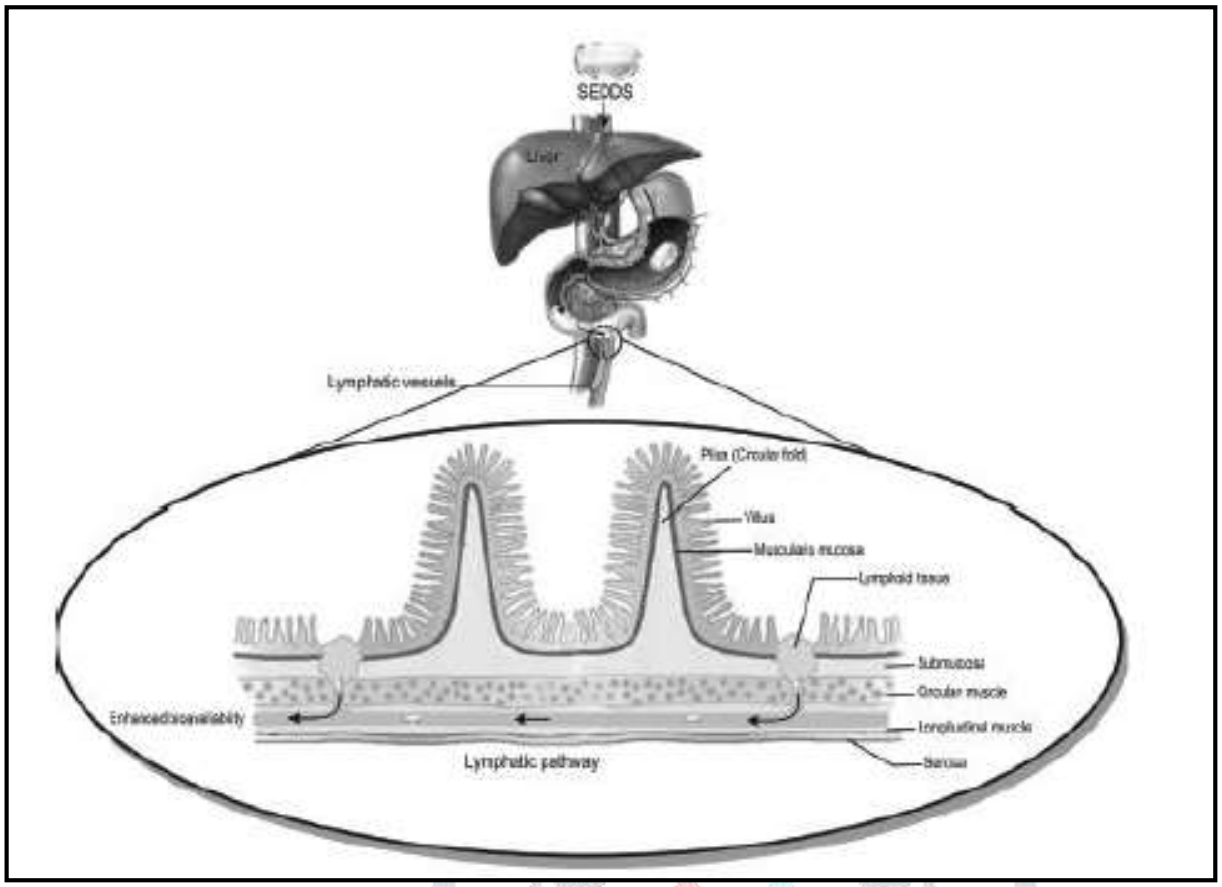

Figure 2. The self-emulsifying formulations enhancing the oral bioavailability of drugs through lymphatic pathways bypassing the hepatic first-pass effect

D. Lymphatic Pathway

Most of the drug deliveries using SEDDS are absorbed systematically via portal vein except for certain type of drugs. The lymphatic system is an extensive drainage network spread throughout the body. It shadows the blood circulation system and functions mainly to return fluid, which has leaked into the interstitial space, back to the blood. The intestinal lymphatics also play an essential role in the absorption of products from lipid digestion e.g., long chain fatty acids and lipid-soluble vitamins.

E. Effect of P-glycoprotein (P-gp) Inhibition:

There may be other possible reasons for enhanced uptake of hydrophobic and/or lipophilic drugs formulated as SEDDS from the GI tract, like a decrease in the P-gp drug efflux. In addition to a multidrug efflux pump, phase I metabolism by the intestinal cytochrome P450's is now becoming recognized as a significant factor in oral drug bioavailability. In some cases, as shown recently, excipients incorporated in SEDDS/SMEDDS can inhibit both presystemic drug metabolism and intestinal efflux mediated by P-gp, resulting consequently in an increased oral absorption of cytotoxic drugs.

7. METHOD OF FORMULATION OF SEDDS

The formulation of a self-emulsifying drug delivery system with a view for increasing the bioavailability of a drug and/or pharmaceutical ingredient by emulsifying the drug with the self-emulsifying excipient includes various steps as described below:

- Preparation of phase diagram.

- Poorly water-soluble drug and/or pharmaceutical ingredient are solubilised in a mixture of surfactant, co-surfactant and solvent. The oil phase prepared was mixed with the solubilized drug formulation and if necessary, by heating or other preparatory means.
- The emulsion thus obtained can then be added to a suitable dosage form such as soft or hard-filled gelatin capsules and allowed to cool.

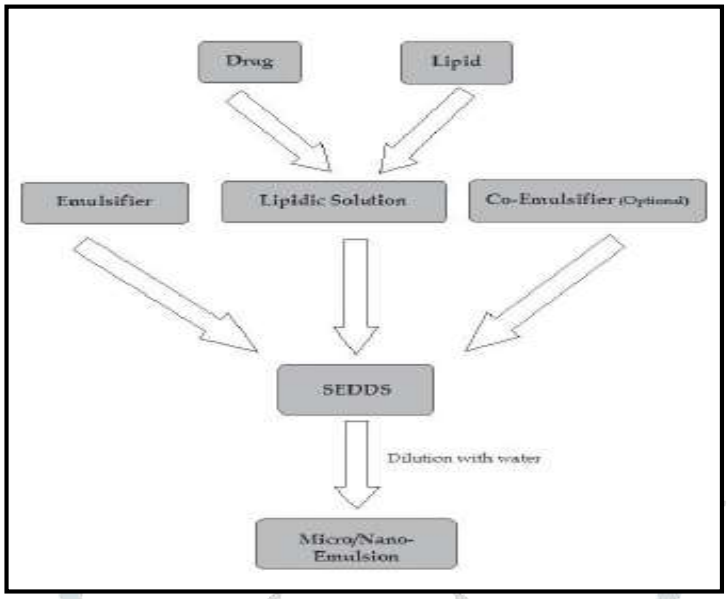

Figure3. Schematic flowchart on the general strategy of formulating self-emulsifying systems and their subsequent conversion to micro/nano emulsions

8. SELECTION OF EXCIPIENTS FOR LIPID BASED FORMULATIONS

Chemically, lipids are considered as one of the most versatile excipients class available today. There are various subcategories of lipids available and there is a constant influx of new lipid based excipients in the market. It provides flexibility to the formulator in terms of selecting suitable particular excipients.

A. OIL PHASE

The oil is one of the most important excipients because it can solubilize the required dose of the lipophilic drug or facilitate self-emulsification as well as increases the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride oils used in self-dispersing systems can be classified into following categories:

I. **Triglyceride vegetable oils**

They are easily ingested, digested and absorbed presenting no safety issues. Depending on the vegetable source, they can have different proportions of long chain triglycerides (LCT) and medium chain triglycerides (MCT). Generally vegetable oils are rice in unsaturated LCT with the exception of coconut oil and palm kernel oil which are rich in saturated MCT. They are highly lipophilic and their effective concentration of ester group determines its solvent capacity.

II. **Vegetable oils derivatives**

Popular vegetable oil derivatives are hydrogenated vegetable oil, mixed glycerides, polyoxylglycerides, ethoxylated glycerides and esters of fatty acids with various alcohols. Hydrogenated vegetable oils are produced by hydrogenated before they are transformed into their derivatives since hydrogenation increases

chemical stability. Examples of such oils are hydrogenated cottonseed oil 10 (Lubritab), hydrogenated plam oil (Dynasan), hydrogenated castor oil (Cutina HR) and hydrogenated soybean oil (Lipo).

III. Mixed partial glycerides

They are formed by partial hydrolysis of triglycerides present in the vegetable oil resulting in a mixture of mono-, di- and tri-glycerides. The physical state, melt characteristics and the bHLB of the partial glycerides depend on the nature of the fatty acid present and the degree of esterification. Glycerides with medium chain or unsaturated fatty acids are used for improving bioavailability, while once with saturated long chain fatty acids are used for sustained-release purposes. Examples of glycerides with medium chain fatty acids are Glyceryl monocaprylocaprate (Capmule MCM) and ones with long chain fatty acids are glyceryl monoleate (Peceol) and Glyceryl monolinoleate (Maisine 35-1).

B. SURFACTANTS

Numerous compounds exhibiting surfactant properties might be working for the design of self-emulsifying systems, but the choice is limited at the same time, a very few surfactants are orally suitable, because safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactant. The most extensively suggested ones being the non-ionic surfactants with a relatively high hydrophiliclipophilic balance (HLB) (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The strength of surfactant usually ranges between 30–60%w/w of the formulation for the formation of stable SEDDS. Surfactants contain high HLB and hydrophilicity, which assists the instantaneous formation of o/w droplets and fast dispersion of the formulation in the aqueous media.

C. CO-SOLVENTS

For effective self-emulsifying system a relatively high surfactant concentrations (usually more than 30% w/w) of cosolvents are needed. Organic solvents such as ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc. are used to dissolve larger amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents play major role of the co-surfactant in the self emulsion systems. Organic solvents are suitable for oral administration are ethanol, propylene glycol, and polyethylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid base. Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents act as co-solvents. Triacetin is suitable since it is miscible in the oil lipid phases and it can be used to solubilize a hydrophobic drug.

Commercially used Surfactants, Co-Surfactant & Co-Solvent used in formulations

Table 2: Example of surfactants, co-surfactant and co-solvent used in commercial formulations

EXCIPIENT NAME (COMMERCIAL NAME)	EXAMPLES OF COMMERCIAL PRODUCTS
SURFACTANTS/CO-SURFACTANTS	
Polysorbate 20	Targreting soft gelatin capsule
Polysorbate 80	Gengraf hard gelatin capsule
Sorbitan monooleate	Gengraf hard gelatin capsule
Cremophor EL	Gengraf hard gelatin capsule, Ritonavir soft gelatin capsule
Polyoxy-40- hydrogenated castor oil	Nerol soft gelatin capsule, Ritonavir oral solution
Polyoxyethylated glycerides	Sandimmune soft gelatin capsules
CO-SOLVENTS	
Ethanol	Nerol soft gelatin Capsule, Nerol Oral Solution, Gengraf hardgelatin Capsule, Sandimmune soft gelatin Capsule
Glycerin	Nerol soft gelatin Capsule, Sandimmune soft gelatin Capsules
Polypylene glycol	Nerol soft gelatin Capsule, Nerol Oral Solution, Lamprene soft gelatin capsule, Agenerage Oral solution , Gengraf hard gelatin capsule
Polyethylene glycol	Targretin soft gelatin capsule, Gengraf hard gelatin capsule, Agenerase soft capsule, Agenerase oral solution
LIPID INGREDIENTS	
Corn oil, mono,di,,tri-glycerides	Nerol soft gelatin Capsule, Nerol Oral Solution
Medium chain mono-and di-glycerides	Fortavase soft gelatin capsule
Olive oil	Sandimmune soft gelatin capsule, Depakene capsule
Oleic acid	Ritonavir soft gelatin capsule, Norvir soft gelatin capsule
Sesame oil	Marinol soft gelatin capsule
Hydrogenated soyabean oil	Accutane soft gelatin capsule,Vesanoid soft gelatin capsule
Hydrogenated vegetable oils	Accutane soft gelatin capsule,Vesanoid soft gelatin capsule
Peanut oil	Prometrium soft gelatin capsule
Beeswax	Vesanoid soft gelatin capsule

SEDDS can exist in either liquid or solid states. SEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SEDDS.

9. DOSAGE FORM DEVELOPMENT OF S-SEDDS

Various dosage forms of S-SEDDS are as listed below:

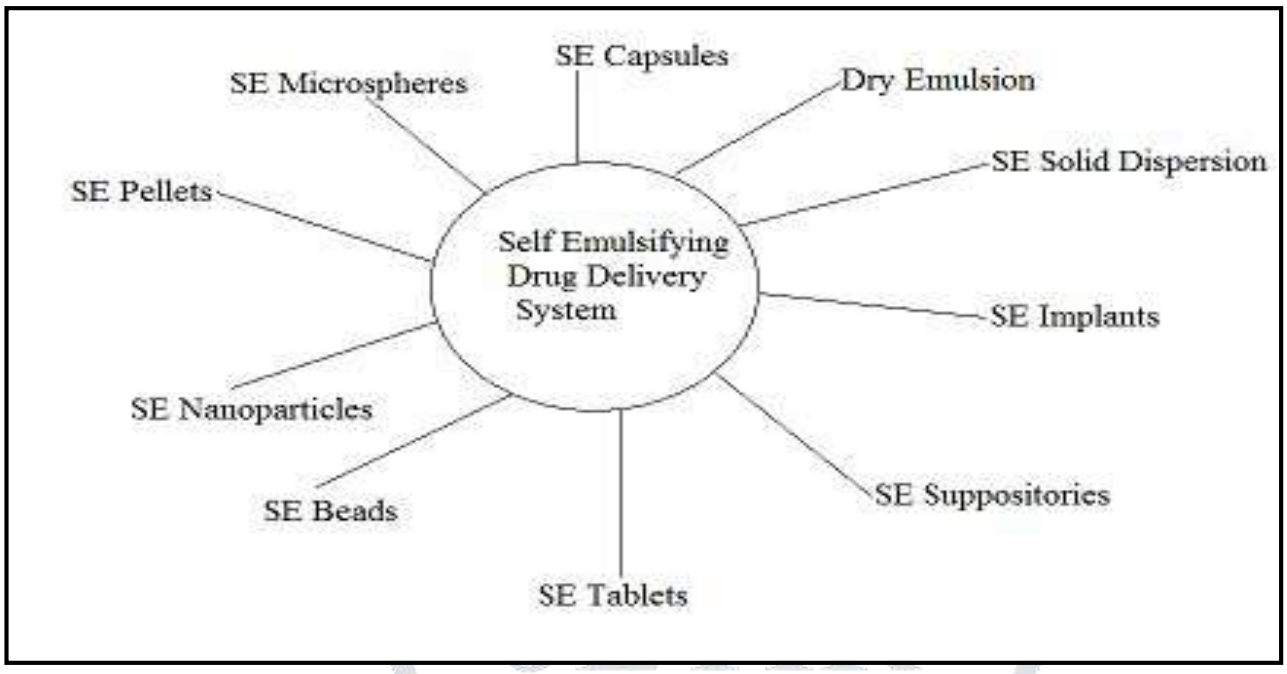

Figure 4: Types of solid SEDDS

A. 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 a solid carrier (lactose, maltodextrin, and so on) 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.

B. Self-emulsifying capsules

Solid SEDDS prepared by various techniques mentioned above can be filled into capsule shell. This prevents physical incompatibility of liquid SEDDS with the capsule shell. After administration of capsules containing conventional liquid SE formulations, micro-emulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. Besides liquid filling, liquid SE ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers.

C. Self-emulsifying sustained/controlled-release tablets

Combinations of lipids and surfactants have presented great potential of preparing SE tablets that have been widely researched. Nazzal et al. formulated eutectic based self-emulsifying tablets in which irreversible precipitation of the drug within the formulation was inhibited. A eutectic forming combination of a drug and suitable semi-solid oil was used in the formulation. Using the melting point depression method the oil phase containing the drug melts at body temperature producing emulsion droplets in the nanometer size range.

D. Self-emulsifying sustained/controlled-release pellets

Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it is very appealing to combine the advantages of pellets with those of SEDDS by SE pellets.

E. Self-emulsifying solid dispersions

Solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs however, some manufacturing difficulties and stability problems existed. *Serajuddin* pointed out that these difficulties could be surmounted by the use of SE excipients. These excipients have the potential to increase further 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 before filling. SE excipients like Gelucire1 44/14, Gelucire1 50/02, Labrasol1, Transcutol1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used. Gelucire1 50/13 was used as the dispersion carrier, whereas Neusilin US2 was used as the surface adsorbent.

F. Self-emulsifying sustained-release microspheres

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions including tumor suppressive, antibacterial, and antithrombotic activity. With ZTO as the oil phase, *You et al*. prepared solid SE sustained-release microspheres using the quasi-emulsion–solvent-diffusion method of the spherical crystallization technique.

G. Self-emulsifying Beads

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients. *Patil et al*., investigated loading SES into the micro-channels of porous polystyrene beads (PPB) using the solvent evaporation method. 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.

H. Self-emulsifying nanoparticles

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant and drugs were melted together and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried by using different techniques like lyophilization. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%. More recently, *Trickler et al*. developed a novel Nanoparticle drug delivery system consisting of chitosan and glyceryl mono-oleate (GMO) for the delivery of paclitaxel (PTX).

I. Self-emulsifying suppositories

Some investigators proved that S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption. Glycyrrhizin, which, by the oral route, barely achieves therapeutic Plasma concentrations, can achieves satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE

suppositories. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester.

J. Self-emulsifying implants

Self-Emulsifying implants has greatly enhanced the utility 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 tumors. However, its effectiveness was hindered by its short half-life. In order to enhance its stability compared with that released 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 (polyglycolyzed glyceride).

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