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A REVIEW ON CURRENT STATUS OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS

[1]R. Nagaraju, [2]Damineni Saritha*, [3]P. Subhash Chandra Bose*, [3]G. Ravi, [3]Valluru Ravi
[1]Dept. of Pharmaceutics, Sri Padmavati Mahila Visvavidyalayam, Tirupati, Andhra Pradesh, India.
[2]Dept. of Pharmaceutics, Sultan-ul-Uloom College of Pharmacy, Hyderabad-500034, Telangana State, India.
[3]Dept. of Pharmaceutics, MNR College of Pharmacy, Sangareddy, Telangana State, India.

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Address for Correspondence: Dr. Damineni Saritha, Dept. of Pharmaceutics, Sultan-ul-Uloom College of Pharmacy, Hyderabad, Telangana State, India.
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Abstract

The modern drug delivery system of hydrophobic drugs presents a main challenge because of the poor aqueous solubility of such compounds. Self emulsifying drug delivery systems (SEDDS) are usually used to enhance the bioavailability of hydrophobic drugs. SEDDS can be administered orally in soft or hard gelatin capsules and form fine relatively stable oil in water (o/w) emulsions upon aqueous dilution due to the gentle agitation of the gastrointestinal fluids. From time to time so many workers have claimed different rational applications of Self-emulsifying formulation for increcing bioavailability and site-specific targeting of highly lipophilic drugs. Significant improvement in the oral bioavailability of these drug compounds has been demonstrated for each case. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SEDDS will continue, and more drug compounds formulated as SEDDS will reach the pharmaceutical market in the future. The present article gives an overview of the Composition, mechanism, advantages, disadvantages, characterization, recent advancements, patents related information of SEEDS and commercial products approved for oral transmucosal administration.

INTRODUCTION

Oral intake is the most convenient and commonly employed route of drug delivery by the patients as well as the manufacturers for the treatment of diseases due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints and flexibility in the design of dosage form. As a result, many of the drug formulations available in the market are oral dosage forms[1]. About 90 % of all compounds in today's pharmaceutical drug delivery pipelines are reported to be poorly soluble in water[2]. This poses enormous problems for the industry; for an active pharmaceutical ingredient that cannot reach its molecular target in the body if drug remains undissolved in the GIT and is eventually excreted. *"Drugs that don't dissolve will not heal you"*. It is well known that drug efficacy can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus results in low absorption in the gastrointestinal tract after oral administration hence comprising less oral bioavailability. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy of certain drugs[3]. So, solubilisation techniques that overcome this issue by increasing the solubility of drugs are becoming more and more important to pharmaceutical industry.

The barriers that a dosage form has to overcome before it can reach the systemic circulation involve dissolution in the GIT, instability in the GI tract, and permeation through the gut wall. And after that there is a first pass at the liver. If the compound itself is stable in GI environment – in the lumen or in the gut wall – intestinal absorption is affected mainly by dissolution, solubility or permeation. The schematic diagram of Potential barriers to oral bioavailability was depicted in Figure 1.

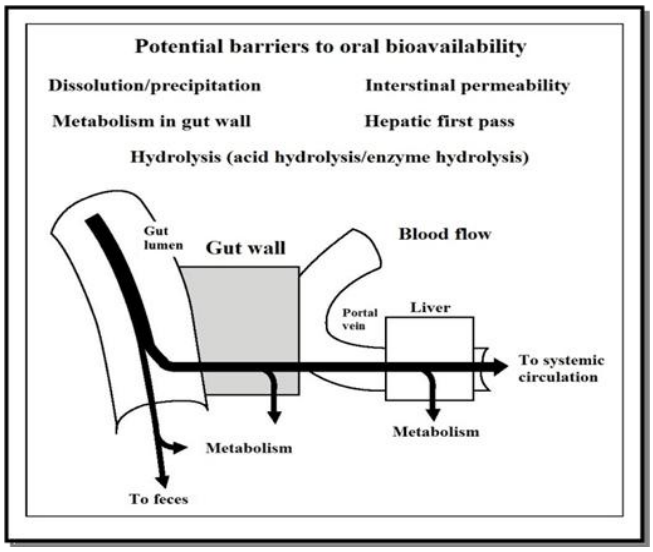

Figure 1: Potential barriers to oral bioavailability

Classification of poorly soluble drugs: The Biopharmaceutical Classification System (BCS):

From a very rough perspective, drug candidates can suffer from two main problems: solubility and permeability. These represent the basis used to classify drug candidates into four fundamental classes, a methodology known as the biopharmaceutical classification system (BCS)[4]. Biopharmaceutical Classification Systems based on dose to solubility ratio and permeability was showed in Table 1. The Biopharmaceutical Classification System and percentage of new chemical entities in individual cases was depicted in Figure 2.

Table 1: Biopharmaceutical Classification Systems based on dose to solubility ratio and permeability[18]

BCS Class	Apparent permeability coefficient values	Dose/ solubility ratio	Hurdles overcome by SEDDS
I	$>1\times10^{-5}$	≤0.5	Gut wall efflux and enzyme degradation
II	$>1\times10^{-5}$	>1	Solubilisation and bioavailability
III	$<2\times10^{-6}$	≤0.5	Gut wall efflux, enzyme degradation and bioavailability
IV	$<2\times10^{-6}$	>1	Gut wall efflux, enzyme degradation, solubilisation and bioavailability.

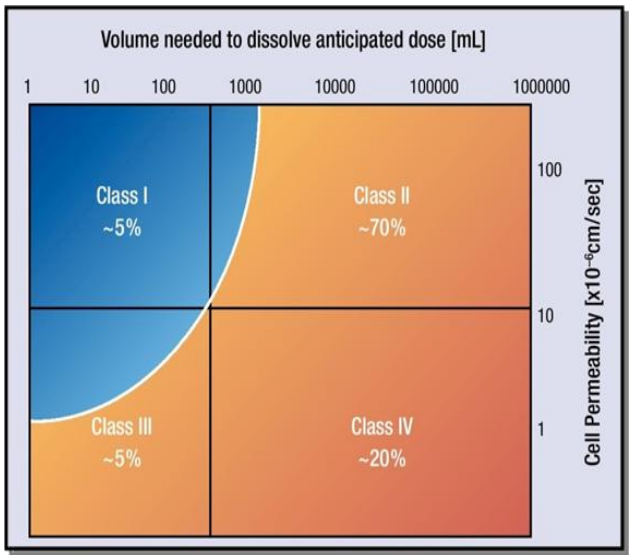

Figure 2: The Biopharmaceutical Classification System and percentage of new chemical entities in individual cases

Class I: In this class, we find drugs (or rather: drug candidates) with both high solubility and high permeability. They dissolve fast and quantitatively are readily taken up by the intestine, eventually reaching their target in the body.

Class II: These are drugs which would easily penetrate the relevant physiological barriers but suffer from poor solubility in the aqueous body fluids. Their share in the modern drug delivery pipeline is continuously growing.

Class III: These actives are soluble in the GIT, but they are not taken up by the body. Like class II actives, they have risk in being excreted without exercising any physiological effect.

Class IV: This is the nightmare for the medicinal chemist: drugs that neither dissolve nor penetrate physiological barriers.

All these drugs pose particular problems in the development cycle.

Class I drugs do not normally have bioavailability problems.

Actives in class II represent the majority of new chemical entities in pharmaceutical development pipelines. However, if it proves possible to increase their solubility in the GIT, they can be formulated into marketable products. The schemetic diagram of BCS class membership was depicted in Figure 3.

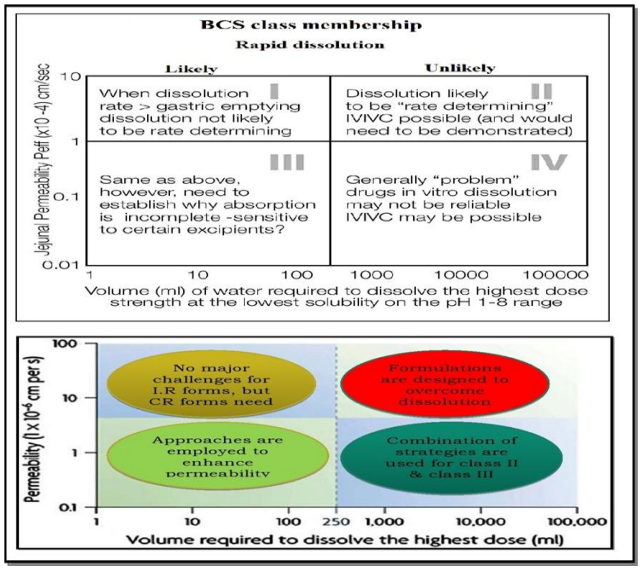

Figure 3: BCS class membership

Class III drugs represent the real challenge. In the scientific literature, there are continuous discussions about the use of penetration enhancers, and there are definite mechanisms that increase the permeation of molecules through the gastrointestinal wall. However, the intestine is usually full of substances that the body does not want to penetrate into the portal vein – for good reasons – and unselective enhancement of penetration of this fundamental membrane implies the risk of significant side effects.

Class IV actives are usually outside of what is called the "drugable space". They combine the problems of class II and class III drugs, and often the best way to get out of such a situation is to send the candidate back to the pharmaceutical chemist and ask for chemical alternatives. If there are reasons to believe that this active will have an excellent performance at the target, e. g. based on in-silico modeling, prodrugs with enhanced dissolution and permeability that will be converted into active agents under physiological conditions are certainly an option to consider. As mentioned above, class II actives represent the largest class of substances in today's drug delivery pipelines. In some cases, this is due to a large portion of hydrophobic moieties in the molecules. Evidently, molecules that consist of carbon and hydrogen only will be so non-polar that miscibility with water will be extremely low.

Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. Various formulation strategies reported in the literature include, incorporation of a drug in oil[5], solid dispersions[6], emulsions[7], liposomes[8], use of cyclodextrins[9], coprecipitates[10], micronization[11], nanoparticles[12], permeation enhancers[13] and lipid-based vehicles[14, 15].

One of the most popular approaches of oral bioavailability and solubility enhancement is the utilization of lipid-based drug delivery systems (LBDDS). LBDDS offer an excellent platform to improve bioavailability of BCS class II (low solubility & high permeability) and class IV (low solubility & low permeability) drugs. The formulation approaches to improve the solubility of the poorly soluble drugs was depicted in Figure 4. LBDDS includes oil solutions, emulsions, microemulsions, self-emulsifying/microemulsifying/nanoemulsifying drug delivery system (SEDDS/SMEDDS/SNEDDS) and micellar systems [16, 17].

SEDDS are proportionate newer LBDDS with huge promise in oral bioavailability enhancement of drugs. These formulations avoid the slow and incomplete dissolution of a drug, increase the extent of its transportation and bypass the P-gp efflux, thereby strengthen drug absorption from the GI tract[19]

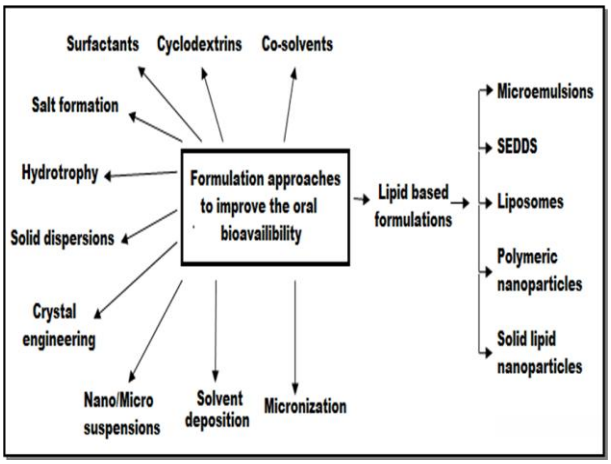

Figure 4: Formulation approaches to improve the solubility of the poorly soluble drugs

Formulation aspects:

Lipid based drug delivery system includes triglycerides, diglycerides, monoglycerides, lipophilic surfactants, hydrophilic surfactants and co-solvents. The SEDDS have been classified as Type I, II, IIIA, IIIB and IV. Schematic diagram of mechanisms of intestinal drug transport from SEDDS formulations was depicted in Figure 5, Lipid digestion and drug solubilisation process in the small intestine was showed in Figure 6 and Fate of lipids in the gut diagram was represented in Figure 7.

- Type I formulations are oils which require to be digested,
- Type II formulations are water-insoluble self-emulsifying drug delivery systems (SEDDS),
- Type IIIA systems are SEDDS or SMEDDS which contain some water-soluble surfactants and/or co-solvents
- Type IIIB systems are SEDDS or SMEDDS which contain some water-soluble surfactants and/or co-solvents and with less oil components
- Type IV systems which do not contain oils, but contains only hydrophilic surfactants and co-solvents. The composition and salient features of various types of SEDDS formulations was showed in Table 2.

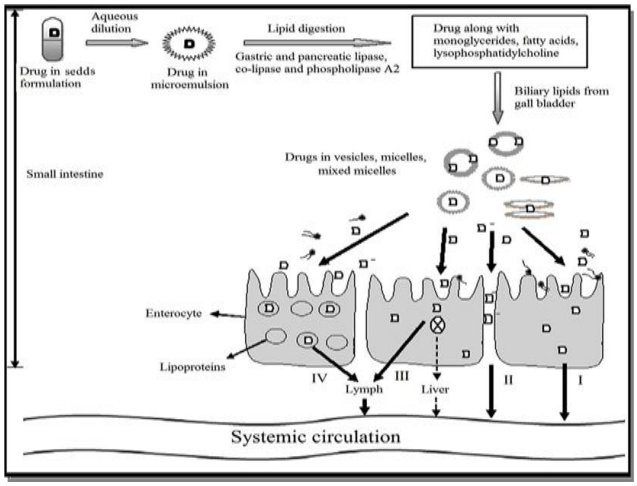

Figure 5: Schematic diagram of mechanisms of intestinal drug transport from SEDDS formulations.

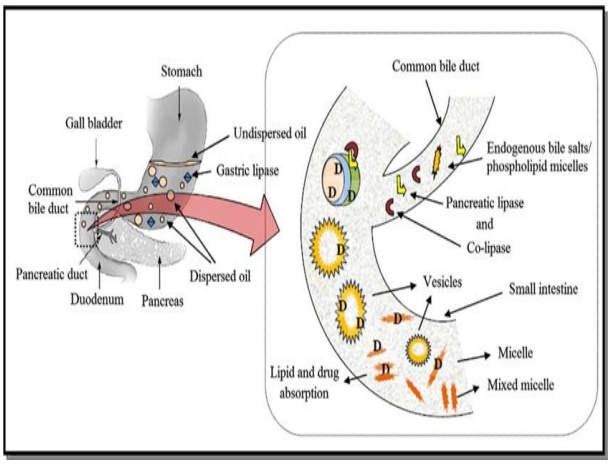

Figure 6: Lipid digestion and drug solubilisation process in the small intestine

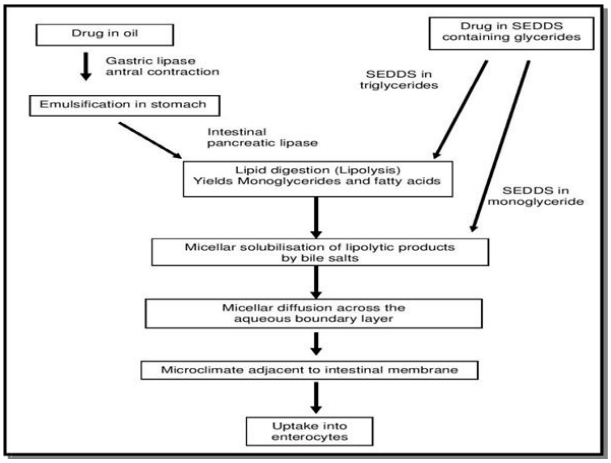

Figure 1.7: Fate of lipids in the gut

Table 2: Composition and salient features of various types of SEDDS formulations[20, 21]

Constituents	Type I	Type II	Type IIIA	Type IIIB	Type IV
Triglycerides or mixed glycerides	100%	40-80%	40-80%	<20%	--
Water insoluble surfactants	--	20-60%	--	--	0-20%
Water soluble surfactants	--	--	20-40%	20-50%	30-80%
Hydrophilic co solvents	--	--	0-40%	20-50%	0-50%
Particle size of dispersion (nm)	Coarse	100-250	100-250	50-100	<50
Significance of aqueous dispersion	Limited importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity	--

Significance of digestibility	Crucial requirement	Not crucial, but is likely to occur	Not crucial, but may be inhibited	Not required, but is unlikely to occur	--
Characteristics	Non-dispersing, requires digestion	SEDDS without water-soluble components	SEDDS/ SMEDDS with water-soluble components	SMEDDS with water-soluble components and low oil content	Oil-free formulation based on surfactants and co solvents
Advantages	*GRAS status; simple; excellent capsule compatibility	Unlikely to lose solvent capacity on dispersion	Clear to almost clear dispersion; drug absorption without digestion	Clear dispersion; drug absorption without digestion	Good solvent capacity for many drugs; disperses to micellar solution
Pitfalls	Formulation has 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

***GRAS: Generally recognized as safe**

Self emulsifying drug delivery systems (SEDDS):

The major technique for enhancing bio-availability is SEDDS, which uses lipophilic, pre-concentrated solutions of the API and excipients (a liquid carrier, a surfactant and a cosurfactant). They emulsify spontaneously when, come in contact with fluids of GIT to form oil-in-water emulsions or microemulsions under mild agitation[22].

Composition of SEDDS

Lipid

- The most significant excipient in the formulation of SEDDS is lipid.
- It can solubilize significant amounts of the hydrophobic drug.
- Facilitate self emulsification.
- It can take up the fraction of lipophilic drug transported through the lymphatic system, and hence improving absorption from the GIT confide on the molecular nature of triglyceride.

In preparation of SEDDS, long and medium chain triglyceride oils with different degrees of saturation are used preferably edible oils/ natural oils. But they are not regularly selected because of their poor capability to dissolve large amounts of lipophilic drugs. In the design and development of SEDDS, modified long and medium chain triglyceride oils, with different degrees of saturation or hydrolysis are widely used because they offer definite physiological and formulation related advantages, as their degradation products simulate that of the natural end products of intestinal digestion[20, 23, 24]. The general strategy of formulating SEDDS and their subsequent conversion to emulsions was depicted in Figure 8.

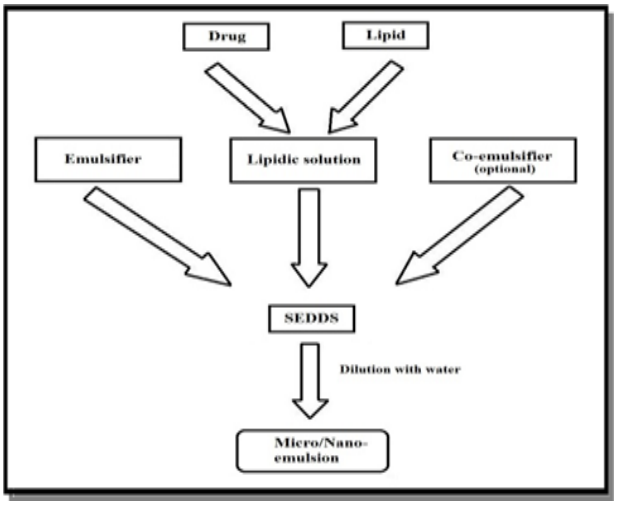

Figure 8: General strategy of formulating SEDDS and their subsequent conversion to emulsions

Hydrogenated vegetable oils, modified triglycerides further its fatty acid composition and molecular structural features are shown in Table 3. Unsaturated and saturated fatty acids have been extensively used in the formulation of lipidic systems. Nonetheless, the SEDDS, in distinct, constitute of saturated fatty acids like, caproic, caprylic, lauric acid, oleic, stearic, linoleic, palmitic, myristic acid etc., Based on potential utilities, physical sate and HLB, one can select one amongst these looking into their composition.

Table 3: Fatty acid composition (%) of vital hydrogenated vegetable oils and semi-synthetic triglycerides employed in SEDDS[21, 25-27]

Oil	Fatty Acid										
	Caproic	**Caprylic**	**Capric**	**Lauric**	**Myristic**	**Myristoleic**	**Pentadecanoic**	**Palmitic**	**Palmitoleic**	**Margaric**	**Margaroleic**
Number of carbons	**6**	**8**	**10**	**12**	**14**	**14**	**15**	**16**	**16**	**17**	**17**
Number of double bonds	**0**	**0**	**0**	**0**	**0**	**1/9**	**0**	**0**	**1/9**	**0**	**1**
Canola oil	-	-	-	-	0.1	-	-	4	0.3	0.1	
Castor oil	-	-	-	-	-	-	-	2	-	-	-
Cocoa butter	-	-	-	-	0.1	-	-	26	0.4	0.3	-
Coconut oil	0.5	7	6	47	19	-	-	9			-
Corn oil	-	-	-	-	-	-	-	11	0.2	0.1	-
Cotton seed oil	-	-	-	0.1	0.7	-	-	22	0.6	0.1	0.1
Lard	-	-	0.1	0.1	2	-	-	-	-	0.4	0.3
Olive oil	-	-	-	-	-	-	-	9	0.6	-	-
Palm kernel oil	0.2	3	3	48	16	-	-	8	-	-	-
Palm oil	-	-	-	0.1	1	-	-	44	0.2	0.1	-
Peanut oil	-	-	-	-	0.1	-	-	11	0.2	0.1	0.1
Rapeseed oil	-	-	-	-	0.1	-	-	4	0.3	-	-
Soya been oil	-	-	-	-	0.1	-	-	11	0.1	0.1	-
Sun flower oil	-	-	-	-	0.1	-	-	7	0.1	0.1	-
Tallow	-	-	-	0.1	0.3	0.9	0.5	24	4	2	0.8
Oil	**Fatty Acid**										
	Stearic	**Oleic**	**Ricinoleic**	**Linoleic**	**Linolenic**	**Ecosanoic**	**Ecosenoic**	**Ecosadienoic**	**Behenic**	**Erucic**	**Tetracosanoic**
Number of carbons	**18**	**18**	**18**	**18**	**18**	**20**	**20**	**20**	**22**	**22**	**24**
Number of double bonds	**0**	**1**	**1**	**2**	**3**	**0**	**1**	**2**	**0**	**1**	**0**
Canola oil	2	61		21	9	0.7	1		0.3	0.7	0.2
Castor oil	1	7	87	3	-	-	-	-	-	-	-
Cocoa butter	34	34	-	3	-	1	0.1	-	0.2	-	-
Coconut oil	3	7	-	2	0.1	0.1	-	-		-	-
Corn oil	2	25	-	60	1	0.4	-	-	0.1	-	-
Cotton seed oil	3	19	-	54	0.7	0.3	-	-	0.2	-	-
Lard	14	44	-	10	0.4	0.2	0.7	0.1	-	-	-
Olive oil	3	80	-	6	0.7	0.4	-	-	-	-	-
Palm kernel oil	3	15	-	2	-	0.1	0.1	-	-	-	-
Palm oil	4	39	-	10	0.4	0.3	-	-	0.1	-	-
Peanut oil	2	47	-	32	-	1	2	-	3	-	1
Rapeseed oil	1	19	-	14	11	0.7	7	0.7	0.5	41	1
Soya been oil	4	23	-	54	8	0.3	-	-	0.3	-	-
Sun flower oil	5	19	-	68	0.8	0.4	0.1	-	0.7	-	-
Tallow	19	43	-	3	0.7	0.2	0.3	-	-	-	-

Table 4: Popular lipids employed in the SEDDS formulations

Chemical name	Brand name	HLB
Glyceryl monoleate	Capmul GMO	3
Glyceryl mono- and dioleate	Capmul GMO-50	3-4
Glyceryl monostearate	Capmul GMS-50K	3-4
Glyceryl mono- and dicaprylate/caprate	Capmul MCM	5-6
Glyceryl mono- and dicaprylate	Capmul MCM C-8	6-7
Glyceryl mono- and dicaprate	Capmul MCM C-10	5
Polyglyceryl-6 octastearate	Caprol ET	2.5
Polyglyceryl-6 dioleate	Caprol MPGO	10
Polyglyceryl-10 mono, dioleate	Caprol PGE 860	11
Polyglycerol-3 oleate	Caprol 3GO	6.5
Polyglyceryl-3 stearate	Caprol 3GS	7
Polyglyceryl-10 decaoleate	Caprol 10G10O	10
Glyceryl tricaprylate/ caprate	Captex 300	11
Glyceryl tricaprylate/ caprate/ laurate	Captex 350	11
Glyceryl triacetate	Captex 500 P	--
Glyceryl tricaprylate/ caprate/ linoleate	Captex 810D	--
Glyceryl tricaprate	Captex 1000	--
Glyceryl tricaprylate	Captex 8000	7
Glyceryl triundecanoate	Captex 8227	--
PEG-35 castor oil	Cremophor EL	12-14
PEG-40 hydrogenated castor oil	Cremophor RH 40	14-16
Glyceryl mono-, di-tribehenate	Compritol 888 ATO	2
Glyceryl trilaurate	Dynasan 112	--
Glyceryl trimyristate	Dynasan 114	--
Glyceryl trip releasesalmitate	Dynasan 116	--
Glyceryl trioleate	Emerest 2423	--
Hard fat	Gleurice 33/01	1
PEG-32 Glyceryl laureate	Gleurice 44/14	14
PEG-32 glyceryl palmitostrearate	Gleurice 50/13	13
Glyceryl mono-, di-, and tristearate	Imwitor 900	3
PEG-4 glyceryl caprylate/ caprate	Labrafac Hydro WL 1219	5
PEG-6 glyceryl linoleate	Labrafil M 2125 CS	3-4
PEG-6 glyceryl oleate	Labrafil M 1944 CS	3-4
PEG-8 glyceryl caprylate/ caprate	Labrasol	14
PEG-40 castor oil	Marlower R40	13
Glyceryl	Maisine 35-1	4
Glyceryl tricaprylate/ caprate/ succinate	Miglyol 829	7
Glyceryl palmitostearate	Pericol ATO 5	2
Polyglycerl-3 diisostearate	Plurol oleique CC	6-7
Polyglyceryl-3 dioleate	Plurol oleique CC497	6
PEG-6 glyceryl caprylate/ caprate	Softigen 767	18
Glyceryl tricaprylate/ caprate/ stearate	Softisan 378	--

Novel semi synthetic medium chain derivatives and amphiphilic compounds having surfactant properties, are regularly and completely substituting the regular medium chain triglyceride oils[17]. The globule size of the emulsion depends on the lipophilicity of the oil and concentration of oil in SEDDS. So, it may be difficult for a single oily component to contain maximum properties with respect to emulsification. Commonly employed oils used in the formulation of SEDDS are shown in Table 4. In some cases, mixture of oils can also be used to get desired properties of the oily phase[28]. Hence, the choice of the oil depends on its capacity of solubilisation of drug and facilitates formation of emulsion with desired characteristics[29].

Emulsifier:

The other most vital component of the SEDDS is an emulsifier. An emulsifier, habitually a surfactant, is mandatory to provide the necessary emulsifying characteristics to the SEDDS. Popular emulsifiers employed in the SEDDS formulations were showed in Table 5.

Table 5: Popular emulsifiers employed in the SEDDS formulations

Chemical name	Brand name	HLB
PEG-4 lauryl ether	Brij-30	9.7
PEG-35 castor oil	Cremophor-EL Cremophor-ELP	12-14
PEG-35 hydrogenated castor oil	Cremophor RH 40	13
PEG-40 hydrogenated castor oil	Cremophor RH 40	13
Polyoxyl-40-hydrogenated castor oil	Cremophor RH 40	13
Ethoxylated castor oil	Emulphor El-620	12-15
PEG-6 corn oil	Labrafil M 2125 CS	4
PEG-6 apricot kernel oil	Labrafil M1944CS	4
PEG-8 caprylic/capric glycerides	Labrasol	14
PEG-8 caprylic/capric glycerides	Labrafac CM 10	>10
PEG-8 corn oil	Labrafil WL 2609 BS	6-7
L-a-Phosphatidylcholine	Lecithin	4-9
Glyceryl monooleate	Peceol	3-4
Polyoxyethylene-polyoxypropylene copolymers	Pluronic F 127	18-23
Methyl-oxirane polymer with oxirane	Pluronic L-64	12-18
PEG-25 hydrogenated castor oil	Simulsol 1292	11
PEG-25 trioleate	Tagat TO	11
PEG-20 sorbitan monooleate	Tween-80	15
PEG-20 sorbitan trioleate	Tween-85	11
PEG-20 sorbitan monolaurate	Tween-20	17
PEG-20 sorbitan tristearate	Tween-65	11

Surfactants, being amphiphilic in nature, can solubilize high amounts of lipophilic drugs. The natural emulsifiers are safer than the synthetic ones. However, as the former possess only limited self-emulsification properties, these are sometimes employed for the preparation of SEDDS. Usually surfactants will be selected based on HLB values and safety[30]. The HLB value provides important information on potential utility of surfactant in the formulation of SEDDS. To get high self-emulsifying properties, the emulsifier should have high HLB value for the formation of o/w globules, and/or rapid dispersion of formulation in aqueous media[31].

Commonly employed emulsifiers used in the formulation of SEDDS are shown in table 1.5. Surfactant maintains the drug at absorption site for prolonged period for effective absorption, by which the precipitation of drug

within the GIT can be prevented[6, 32]. The most widely recommended emulsifiers include the non-ionic surfactants with relatively high HLB values. Non-ionic surfactants are considered as safer than the ionic ones[33-36].

Co-emulsifiers/Cosolvents:

Co-emulsifiers/Cosolvents are commonly used to enable the dissolution of large quantity of hydrophilic surfactant in SEDDS. Commonly employed co-emulsifiers used in the formulation of SEDDS are shown in Table 6. Traditional cosolvents like ethanol, propylene glycol and PEG will have tendency to evaporate from the shells of sealed gelatin capsules, which leads to precipitation of drug inside the shell. Cosolvents like transcutol and glycofurol have numerous advantages over the traditional ones, including better stability and less volatility[37, 38].

Table 6: Popular co-emulsifiers employed in the SEDDS formulations

Chemical name	Brand name	HLB
Caprylic/ Capric glycerides	Akoline MCM	5-6
Di-methyl isosorbide	Arlasolve DMI	--
Diethylene glycol monoethyl ether	Carbitol	4
PEG-60 hydrogenated castor oil	HCO-60	14
Polyglyceryl-6 dioleate	Hodag PGO-62	6
Propylene glycol monolaurate	Lauroglycol 90	5
PEG-6 apricot kernel oil	Labrafil 1944	4
Polaxomer 188	Lutrol F 68	29
Block copolymer of ethylene oxide & propylene oxide	Pluronic L44	12-18
Methyl-oxirane polymer with oxirane	Pluronic L64	12-18
Sodium lauryl sulfate	SLS	40
Sorbitan monooleate	Span 80	4.3
Diethylene glycol mono ethyl ether	Transcutol P	4

Mechanism of self emulsification:

There are many theories which explain the self emulsification process. No single theory describes all aspects of emulsion formation.

According to Reiss -Self-emulsification occurs when the entropy change that favours dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by equation

$$\Delta G = \Sigma N \pi r^2 \sigma$$

Where, ΔG - Free energy associated with the process

N - Number of globules

r - Radius

σ - Interfacial energy

With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems.

Advantages of SEDDS over conventional DDS[40-44]

1. Protection of drugs from hostile environment in the gut.

2. Compared with oily solutions, SEDDS provide a large interfacial area for drug loading.

3. Wide distribution of the drug throughout the GIT leads to reduction in gastric irritation.

4. Emulsions are metastable dispersed forms and are very sensitive where as SEDDS are physically stable formulations.

5. SEDDS shows more consistent drug absorption.

6. SEDDS show enhanced oral bioavailability.

7. Drug targeting towards a specific absorption window in the GIT.

Disadvantages of SEDDS[45, 46]

Lack of good relative dissolution models for assessment of the formulations because traditional dissolution methods do not work, as SEDDS potentially dependent on digestion prior to release of the drug.

Characterization of SEDDS:

The primary means of self-emulsification assessment is visual evaluation[47]. The efficiency of selfemulsification could be estimated by determining the rate of emulsification and droplet size distribution. Turbidity measurements can be carried out to determine the rapid equilibrium reached by the dispersion and the reproducibility of this process[48]. The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption[49,50]. Photon correlation spectroscopy (PCS) is a useful method for determination of emulsion droplet size[47,51] especially when the emulsion properties do not change upon infinite aqueous dilution, a necessary step in this method. However, microscopic techniques should be employed at relatively low dilutions for accurate droplet size evaluation[52,53]. The reduction of droplet size to values below 50 nm leads to formation of SMEDDS, which are stable, isotropic and clear o/w dispersions[54-57]. Pseudo-ternary phase diagrams, in which the ratio of two or more of the components is kept constant while typically three other excipient concentrations are varied, can be constructed to describe such systems[58,59]. Normally, the oil, surfactant and co-surfactant or co-solvent ratios are changed in an attempt to identify the self-emulsifying regions and/or other types of dispersions[60,61]. Finally, appropriate experimental conditions (optimum excipient concentrations) are established by means of ternary diagram studies allowing formulation of the required SEDDS and/or SMEDDS. The characterization of SMEDDS can be made utilizing dye solubilization, dilutability by the dispersed phase excess and conductance measurements[58]. Emulsion droplet polarity is also a very important factor in characterizing emulsification efficiency[49]. The HLB, chain length and degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier have an impact on the polarity of the oil droplets. Polarity represents the affinity of the drug compound for oil and/or water and the type of forces formed. Rapid release of the drug into the aqueous phase is promoted by polarity. The charge of the oil droplets of SEDDS is another property that should be assessed[52,53]. The charge of the oil droplets in conventional SEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1.0−3%, will yield cationic SEDDS. Thus, such systems have a positive n-potential value of about 35−45 mV[52,53,62]. This positive n-potential value is preserved following the incorporation of the drug compounds.

Drug incorporation into SEDDS:

Drugs with low aqueous solubility present a major challenge during formulation as their high hydrophobicity prevents them from being dissolved in most approved solvents. The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The addition of solvents including ethanol, PG and PEG, may also contribute to the improvement of drug solubility in the lipid vehicle. The efficiency of drug incorporation into a SEDDS is generally specific to each case depending on the physicochemical compatibility of the drug/system. In most cases, there is an interference of the drug with the selfemulsification process up to a certain extent leading to a

change in the optimal oil/surfactant ratio. The efficiency of a SEDDS can be altered either by halting charge movement through the system by direct complexation of the drug compound with some of the components in the mixture through its interaction with the LC phase [63,64], or by penetration into the surfactant interfacial monolayer[63,65,66]. The interference of the drug compound with the self-emulsification process may result in a change in droplet size distribution that can vary as a function of drug concentration[65]. It should be pointed out that emulsions with smaller oil droplets in more complex formulations are more prone to changes caused by addition of the drug compound[56,58]. Hence, the design of an optimal SEDDS requires pre-formulation solubility and phase diagram studies to be conducted.

RECENT ADVANCEMENTS IN SEDDS:

1. Self-emulsifying sustained/controlled-release tablets:

Combinations of lipids and surfactants have presented great potential of preparing self-emulsifying tablets that have been widely researched. After evaluation the effect of some processing parameters (colloidal silicates X1, magnesium stearate mixing time X2, and compression force X3) on hardness and coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X1 = 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face-centered cubic design[67]. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipeints and aiding in slowing down of the drug release[68].

2. Self-emulsifying capsules:

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. However, if irreversible phase separation of the micro emulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation[69]. With the similar purpose, the super saturatable SEDDS was designed, using a small quantity of hydroxyl propyl methyl cellulose (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects[70,71]. The SEDDS formulations, empty soft gelatin capsules were filled with the formulation using a syringe and sealed with hot gelatin. The optimized self-emulsifying formulation contained 30% (w/w) Tagat TO, 67.1°/,) (w/w) Miglyol 812 and 2.9% (w/w) cyclosporin, and each capsule was filled to contain 25 mg of cyclosporine. The limited drug loading capacity and incomplete emulsification characteristics of the EG formulation were improved by developing a surfactant enhanced system (SEEG)[72]. Although the drug loading capacity of these systems is still relatively low, for potent, lipophilic compounds, solid SEEG formulations may provide advantages in administration and chemical stability over traditional formulation alternatives such as emulsions and liquid fill soft gels[73].

3. Self-emulsifying suppositories

Some investigators proved that Solid-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption[74]. Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain 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[75].

4. Microemulsion Drug Delivery

Dioctyl sodium sulfosuccinate (aerosol OT) has proved to increase the intestinal absorption of many drugs[76-77] While the number of publications on the possible application of aerosol OT micro emulsions for topical drug delivery is already extensive, aerosol OT applicability for oral micro emulsion drug delivery still needs to be studied[78,79] Recently, a patent cooperation treaty (PCT) provided a stable, self-emulsifying water/oil micro emulsion in which the surfactant with high Hydrophilic Lipophilic Balance (HLB) comprises a medium-chain alkyl/dialkyl sulfate, sulfonate, or sulfosuccinate salt dissolved in a polyhydric alcohol to improve the delivery characteristics of a therapeutic peptide drug[80].

5. 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. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%[81]. More recently, a novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for

the delivery of paclitaxel (PTX) has been developed. The SE property of GMO enhanced the solubility of PTX and provided a foundation for chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies of PTX. These advantages allow the use of lower doses of PTX to achieve an efficacious therapeutic window, thus

minimizing the adverse side effects associated with chemotherapeutics like PTX[82].

The purpose of the present study was to formulate a selfnanoemulsifying system (SNES) containing model lipophilic drug, felodipine (FLD), to improve its solubility. The SNES was formulated using varying amounts of Miglyol 840 (as an oil), Cremophor EL (as a surfactant), and Capmul MCM (as a co-surfactant). The SNES were characterized for turbidity, droplet size and in vitro FLD release. The SNES containing oil, surfactant, and co-surfactant in the weight ratio of 3.5:1.0:1.0, respectively, showed good emulsification, median droplet size (of 421 nm), and rapid FLD release (more than 90% release in 15 min)[83].

Self-emulsifying sustained/controlled-release pellets: To formulate and prepare SEDDS, there were some basic guidelines needed to conform: safety, compatibility, drug solubility, efficient self-emulsification efficiency and droplet size, etc.[84,85]. Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reduction of intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it seems very appealing to combine the advantages of pellets with those of SEDDS by SE pellets. Spherical pellets with low friability and self-emulsifying properties can be produced by the standard extrusion/spheronization technique. The pellets are capable of transferring lipophilic compounds into the aqueous phase and have a high potential to increase the bioavailability of lipophilic drugs[86]. Formulation of SE controlled-release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release are also very useful. Pellets were prepared by extrusion/spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained mono-diglycerides and Polysorbate 80[87]. The combinations of coating and SES could control in vitro drug release by providing a range of release rates and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution[88].

PATENTS AND COMMERCIAL PRODUCTS APPROVED FOR ORAL TRANSMUCOSAL ADMINISTRATION:

Patents on SEDDS/SMEDDS/SNEDDS were illustrated in Table 7. Commercially available lipid based drug delivery systems were showed in Table 8.

Table 7: Patents on SEDDS/SMEDDS/SNEDDS

Title	Patent number	Inventors
Self microemulsifying drug delivery system of abiraterone acetate[89]	WO2014/009434 A1	Novak Stagoj, Homar Miha, Klancor Uros, Peternel Luka
Self microemulsifying drug delivery system with increased bioavailability[90]	WO2012071043A1	Emadeldin Hassan
Pharmaceutical composition for enhancing anticancer efficacy of tamoxifen[91]	WO2013/008083 A1	Sanyog Jain, Omesh Mallappa, Amith Kumar Jain, Harsha Prakash Harde
Eutectic based self nanoemulsified drug delivery system[92]	US2012/0269792 A1	Mansoor A Khan, Sami Nazzal
Galenic applications of self-emulsifying mixtures of lipidic excipients[93]	US2011/0104268 A1	Jean Pachot, Serge Segot Chicq
Self emulsifying drug delivery system for a curcuminoid based composition[94]	US2011/0294900 A1	Kanchan Kohli, Sunny Chopra, Saurab Arora, Roop K Khar, Kolappa K Pillai
Self micro-emulsifying oral pharmaceutical composition of hydrophilic drug and preparation method thereof[95]	US20100273730 A1	Chang Shan Hsu, Wei-hua HAO, Jong-Jing Wang, Tsung-Hsin Lin
Oral formulations for picoplatin[96]	US20100310661	Andrew Xian, Chen Cheni Kwok, Christopher A Procyshyn
Self-emulsifying pharmaceutical compositions of rhein or diacerein[97]	EP2207531B1	Nakhat Premchand and Mandaogade Prashant
Self-emulsifying formulations of CETP inhibitors[98]	WO2003000295A3	Michael Jon GumkowskiFranco LOMBARDOSharad Balasaheb MurdandeMichael Ellis Perlman
Process for dosing self-emulsifying drug delivery systems[99]	WO2008128960A1	Schwarz, Franz, Xaver
Delivery of tetrahydro cannabinol: A self-emulsifying drug delivery system to improve dissolution, stability, and bioavailability of drug compounds of dronabinol or other cannabinoids[100]	US20070104741	Ram Murty and Santos Murty

Self-emulsifying formulations of fenofibrate and/or fenofibrate derivatives with improved oral bioavailability and/or reduced food effect[101]	WO2004002414A3	Shojaei H Amir, Beth A Burnside, Liang Likan, Ibrahim A Scott
Self-emulsifying formulations of cholesteryl ester transfer protein inhibitors CETP inhibitors have improved solubility and bioavailability in a lipophilic vehicle comprising a digestible oil, a lipophilic solvent, or a surfactant[102]	US20060014788A1	Michael J. Gumkowski, Lombardo Franco, Sharad B. Murdande and Michael E. Perlman
Self emulsifying drug delivery systems for poorly soluble drugs[103]	WO2003074027A3	Simon Benita, Jean-Sebastien Garrigue, Neslihan Gursoy, Gregory Lambert, Alain Razafindratsita, Shicheng Yang
Self emulsifying drug delivery system[104]	US7815933B2	Christina Holmberg

Table 3.1: Commercially available lipid based drug delivery systems[105-109]

Trade name	API	Type of formulation
Agenerase® (GaxoSmithKline)	Amprenavir	Soft gelatin capsule
Targretin® Ligand	Bexarotene	Soft gelatin capsule
Rocaltrol® (Roche)	Calcitriol	Soft gelatin capsule
Coreg CR® (Glaxo SmithKline)	Carvedilol	Hard gelatin capsule
Panimun Bioral® (Panacea Biotec)	Cyclosporine	Soft gelatin capsule
Cyclosporine® Capsules (Sidmak)	Cyclosporine A	Soft gelatin capsule
Gengraf® (Abbott)	Cyclosporine A	Soft gelatin capsule
Neoral ® (Novartis)	Cyclosporine A	Soft gelatin capsule
Sandimmune® (Novartis)	Cyclosporine A	Soft gelatin capsule
Zipsor® (Xanodyne Pharam)	Diclofenac Potassium	Soft gelatin capsule
Fenogal® (Genus)	Fenofibrate	Hard gelatin capsule
Lipirex® (Sanofi-Aventis)	Fenofibrate	Hard gelatin capsule
Solufen® (Sanofi-Aventis)	Ibuprofen	Hard gelatin capsule
Infree® (Eisai Co.)	Indomethacin	Soft gelatin capsule
Accutane® (Roche)	Isotretinoin	Soft gelatin capsule
Kaletra® (Abbott)	Lopinavir & Ritonavir	Soft gelatin capsule
Norvir® (Abbott)	Ritonavir	Soft gelatin capsule
Fortovase (Roche)	Saquinavir	Soft gelatin capsule
Aptivus® (Boehringer Ingelheim)	Tipranavir	Soft gelatin capsule
JuvelaN	Tocopherol nicotinate	Soft gelatin capsule
Vesanoid® (Roche)	Tretinoin	Soft gelatin capsule
Convulex® (Pfizer)	Valproic acid	Soft gelatin capsule
Depakine® (Abbott)	Valproic acid	Soft gelatin capsule

CONCLUSION:

Self-emulsifying drug delivery systems (SEDDS) are a promising approach for the formulation of drug compounds or recently existing moieties with low aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDS, which have been shown to substantially enhance oral bioavailability. The effectiveness of the SEDDS formulation is case specific in most instances; thus, composition of the SEDDS formulation should be determined very carefully. Since a relatively surfactants high concentration is usually employed in the SEDDS formulation, surfactant toxicity being used should be taken into account. In fact, a compromise must be reached between the toxicity and selfemulsification ability of the surfactant that is considered for use. With future improvement of this technology, SEDDS will continue to enable new applications in drug delivery and solve deficiency associated with the delivery of poorly soluble drugs. Thus this technology field required for further exploration and present research so as to bring out commercially available self emulsifying formulation.

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