

Self-emulsifying Drug Delivery Systems and their Marketed Products: A Review

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Abstract

Self-emulsifying drug delivery systems (SEDDS) are one of the proven methods to increase solubility and bioavailability of poorly soluble drugs. SEDDS are isotropic mixtures, consisting of oils, surfactants, and sometimes cosolvents. Designed formulations are used to improve the oral absorption of highly lipophilic compounds. Multiple lipid-based drug delivery systems are widely reported in literature and they include simple oil solutions, coarse, multiple and dry emulsions, and more complex self-emulsifying, microemulsifying or nanoemulsifying drug delivery systems. The process of self-emulsification is dependent on diverse factors such as the nature of oil, surfactant, cosurfactant, oil/surfactant ratio, and the polarity of the emulsion. Considering the ease of large-scale production and the robustness of SEDDS, several formulations are commercially available which utilize this technology. This article attempts to present an overview of SEDDS along with their applications, compiled literature data, commercially available products, and their descriptions.

Key words: Commercial products, Lipid formulations, Lipophilic drugs, Oral bioavailability, Oral delivery, Self-microemulsifying drug delivery systems

INTRODUCTION

Self-emulsifying system (SES) is one of the most prevalent and commercially feasible oil based approaches for the delivery of drugs that show dissolution speed limited absorption. SES is an isotropic mixture of oils, surfactants, cosurfactants, and at times cosolvents, which emulsify extemporaneously to produce oil-in-water or water-in-oil emulsion when introduced into the gastrointestinal tract (GIT).^[1] Based on the droplet size after emulsification, they are classified into two broad classes, namely self-emulsifying drug delivery systems (SEDDS) with a droplet size range of 100–300 nm and self-microemulsifying drug delivery systems (SMEDDS) with a droplet size range <50 nm.^[2] As a result of the lower globule size, the micro/nanoemulsified drug can be taken up efficiently through lymphatic pathways, where it bypasses the hepatic first-pass effect.^[3] Larger lipid droplet which represents SMEDDS or microemulsions is converted into smaller micelles on coming in contact with bile salts and lipases. These micelles, on absorption through intestinal villi and microvilli help enhance the absorption of the drug which is

distributed in the body through the lymphatic system in the form of chylomicrons as shown in Figure 1. In addition, SEDDS are easy to manufacture and physically stable formulations and may enhance the rate and the extent of absorption for lipophilic drug compounds where dissolution rate is the deciding factor. SEDDS approach can be used for all categories of the biopharmaceutics classification system (BCS). Although multiple reviews have been published on SEDDS/SMEDDS, a review with a focus on commercial aspects is not available which calls for an updated review.

The process of self-emulsification depends on multiple factors such as the nature of oil, surfactant, and cosurfactant and on oil to surfactant ratio or oil to surfactant and cosurfactant ratio, the self-emulsification temperature, the polarity of the emulsion, and droplet size and charge. From multiple studies, it was evident that only a specific combination of drug and excipients lead to efficient SES.^[4]

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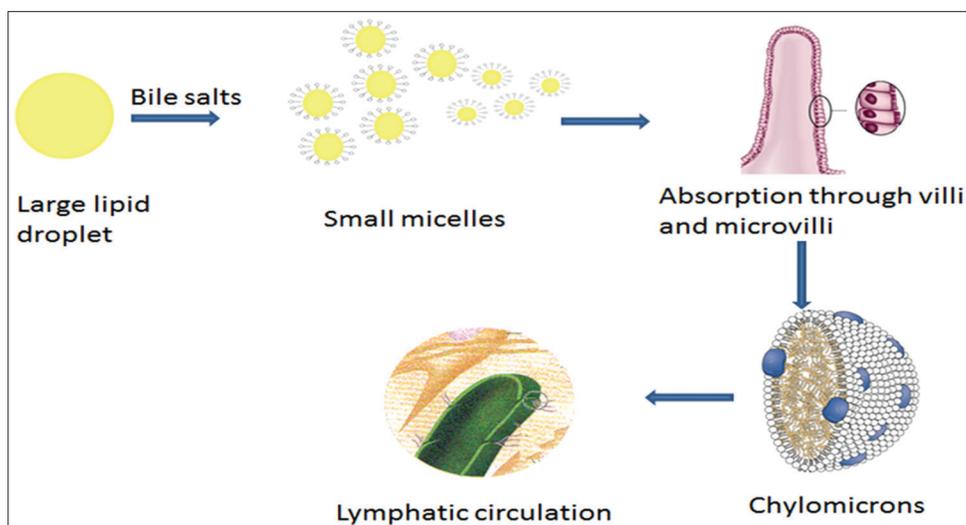


Figure 1: Absorption mechanism of lipid-based systems

Advantages of SEDDS over the conventional emulsion

As compared to conventional emulsions which require high shear to form a dispersion, SEDDS preparation involves a simple process of dissolving the drug in oil followed by mixing it with surfactants and cosurfactants.^[5] Conventional emulsions display multiple instabilities such as creaming, coalescence, breaking, and phase inversion. On the other hand, SEDDS formulations are physically stable as they are clear, isotropic mixtures immune to small changes in temperature. In addition, the final dosage forms of SEDDS formulations are presented as patient compliant soft or hard gelatin capsules, which are compatible with strip or blister packing and assure dose uniformity. Large containers required for conventional formulations are cumbersome to carry, and dose nonuniformity of the droplets and dispersion media can lead to decreased efficacy (Khedekar and Mittal, 2013). Another advantage of SEDDS is the amenability to be manufactured by the basic equipment whereas emulsion and suspension need specialized high-cost equipment to monitor the critical processes such as intensity, rate, and duration of mixing.

EXCIPIENT SELECTION

Drug solubility plays a pivotal role in the selection of excipients in SEDDS formulation.^[6] The lipids used generally consist of a fatty acid ester or a medium/long chain saturated, partially unsaturated or unsaturated hydrocarbon chain. Examples include mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil, fatty acids, corn oil, peanut oil, soybean oil, fatty alcohols, and mono-/di-/tri-glycerides.^[7] The oil plays a key role in the drug bioavailability and its lymphatic transportation. The solubility and the bioavailability of the drug are enhanced as the presence of lipidic system in the GIT enhances secretion of lipases and cholic acids, which form a colloidal micelle resulting in lymphatic absorption. In the case

of surfactants for oil-in-water emulsion, a high hydrophilic-lipophilic balance (HLB) is preferred as it ensures efficient self-dispersibility and stability of the formed emulsion. For a stable SEDDS, an optimum concentration of surfactant in the range of 30%–60% (w/w) is required.^[4] Examples include Span 80, Tween 80, Tween 20, and Cremophor RH40.

Cosurfactants play an important role in decreasing the surfactant related gastrointestinal distress and lowering the interfacial tension to a small or negative value. They also improve the penetrability of the dispersion media and decrease the shear required to disperse globules. Widely used cosurfactants include glycerin, propylene glycol, and ethanol.^[8]

FACTORS AFFECTING SEDDS

Critical factors affecting SEDDS include drug dose, the drug solubility in the oil phase, and the drug log P value. It is crucial to consider these factors as high dose drugs are not suitable for SEDDS due to the restricted amount of lipid phase being used and drugs with log $P < 2$ are more challenging to deliver by SEDDS. If surfactant or cosurfactant is contributing to a higher amount for drug solubilization, then there may be a higher chance of precipitation on dilution.^[9] However, in some cases, ion pairing agents have been utilized to enhance the oil solubility of peptides with very low log P values such as desmopressin (log $P = -6.13$) and enhance the oral bioavailability by prevention against glutathione and α -chymotrypsin mediated presystemic inactivation.^[10]

LIPID FORMULATION CLASSIFICATION SYSTEM

Lipid classification is introduced in 2000,^[11] which is used to interpret *in vivo* studies and to enable the identification of thermostable formulations for specific drugs in relation to

their physicochemical properties.^[12] It is classified into four different classes depending on the concentration of the lipids and the surfactant types used.

Type I: Type I formulation almost entirely consists of the actives solubilized in oil/lipid phase. These are simple, non-dispersing systems, which need digestion by pancreatic lipases in the GIT to provide more amphiphilic digestion products such as chylomicrons and micelles. This is an excellent system, which depending on the oil phase can have generally recognized as safe status and displays compatibility with capsules (such as vegetable oil/fractionated coconut oil). Type I systems make the dissolution step redundant by presenting the drug in solubilized form. The major disadvantage of this system includes its suitability only for potent drugs or highly lipophilic compounds and enzyme level dependent absorption, which can lead to variable bioavailability.

Type II: Type II emulsions or water-insoluble SEDDS consists of formulations in which oils such as medium chain triglycerides and water-insoluble surfactants such as diglycerol monooleate are used. The system, on dispersion in the aqueous phase, provides a coarse emulsion having globule size in between 0.25 and 2.0 μ . The solvent capacity of the system is unaffected by aqueous dilutions as the formulation consists of water-insoluble components. Another major advantage is its enzyme independent absorption. These systems provide a large interfacial area, which offers enhanced partitioning of the drug between oil droplets and they are responsible for absorption. This may result in turbid o/w emulsion.^[13]

Type III: Along with oils, Type III formulations include hydrophilic (HLB >12) surfactants in addition to cosolvents such as ethanol and polyethylene glycol (PEG). According to the oil and the surfactants concentrations, Type III SEDDS are further classified as Type IIIA (oil content ~ 60%, 0–40% cosurfactants, e.g. NEORAL) and Type IIIB (oil content <20%, surfactant 20–50%, and cosurfactant 20–50%). Major advantages of Type III formulations include the formation of a clear dispersion on aqueous dilution and drug absorption without digestion. These systems are often referred to as SMEDDS, as they provide microemulsions with globule size ranges from 20 to 200 nm. A ternary or a pseudoternary diagram helps plot the concentrations best suited for the drug. However, as Type III formulations utilize water-soluble surfactants and cosurfactants, they are likely to lose solvent capacity post aqueous dilution, further results in drug precipitation and variable bioavailability.

Type IV: Type IV systems contain predominantly hydrophilic surfactants and cosolvents without oils. These formulations represent the most hydrophilic formulations of all the emulsions. Such formulations offer a higher post-dilution solubilization capacity of the drugs by virtue of micellar encapsulation, and the globule/particle size of the diluted system is in the range of ~50nm. Such formulations find application in their ability to deliver drugs, which are

hydrophobic but not lipophilic. However, it is necessary to note that the high concentration of surfactants used may lead to gastric distress on chronic usage.

FORMULATION ASPECTS OF SEDDS

The preparation of SEDDS is an uncomplicated process, which involves the mixing of oils, surfactants, and cosurfactants followed by the drug to the mixture and vortexing until transparent. In certain cases, the drug is dissolved in the excipient/s, which is mixed with the remaining components. A critical point of the SEDDS stability evaluation is the sign of turbidity. To obtain a clear solution, it can be heated after equilibration at room temperature for 48 h. Final dosage form depends on the final volume of the formulation; however, the preferred dosage form is soft gel capsules.^[14,6] Solid SEDDS can be prepared using techniques such as spray drying, adsorption to solid carriers, melt granulation, and melt extrusion.

CHARACTERIZATION

Visual evaluation

Self-emulsification assessment is done by visual observation. Post water dilution of SEDDS presence of a clear, isotropic, transparent solution points to microemulsion formation and an opaque; milky white appearance indicates a macroemulsion.^[15,4] The absence of precipitation and/or phase separation indicates the stability of the formulation.

Droplet size analysis

The nature and concentration of surfactant determine the droplet size.^[16] After dilution of SMEDDS with water, the microemulsion formed has a very narrow droplets size distribution, which plays a pivotal role in effective drug release, *in vivo* absorption, and stability. Dynamic light scattering techniques are used for droplet size analysis.^[12]

Zeta potential measurement

Zeta potential indicates the stability of emulsion after appropriate dilution. The formulation remains stable if it has higher zeta potential.^[14,17] However, a zwitterion charge is shown to have better biocompatibility and a higher blood residence time as compared to the particles displaying either surface charge.

Emulsification time

Time needed for emulsification of formulations depends on the oil phase and the oil/surfactant ratio.^[14] This is assessed using basket dissolution apparatus, wherein the formation of

the clear solution under agitation is observed after dropwise formulation addition to the basket containing water.

Cloud point determination

Cloud point is the temperature above which the homogenous solution loses its transparency. The surfactant usually loses its micelle forming capacity above the cloud point. It is determined by gradually increasing the temperature of the formulation and measuring the turbidity spectrophotometrically. The temperature at which percentage transmittance is decreased is considered as the cloud point of the surfactant. Formulations should exhibit a cloud point greater than 37.5°C to retain its self-emulsification property.^[18]

Viscosity measurements

The viscosity of diluted SMEDDS formulation that is microemulsion is generally determined by rheometer such as Brookfield cone and plate rheometer fitted with cone spindle^[19] or rotating spindle Brookfield Viscometer.^[20]

Impact of dilution-induced stress

Dilution studies help to understand the effect of dilution-induced stress on the physicochemical properties of the pre-diluted emulsions. These studies are performed by diluting the microemulsion to various dilution ratios with distilled water, simulated gastric fluid, or simulated intestinal fluid. If the emulsion shows no turbidity, which indicates the absence of drug precipitation, the formulation is considered as a stable formulation.

Refractive index

Refractive index (RI) can be used as an important tool to investigate the microemulsion structure. It is evaluated by recording the RI of samples stored at 4°C and 25°C at multiple time intervals till 6h. Insignificant changes in the RI at these time points indicate constant microemulsion structure. The constant RI also indicates the thermodynamic stability of the formulation.^[20]

Percentage transmittance

Percentage transmittance is determined following the dilution of the formulation and recording the transmittance with water as a blank. A percentage transmittance value closer to 100% indicates a clear and transparent microemulsion formation.^[8]

Transmission electron microscopy (TEM)

TEM is mainly used to investigate the structure and morphology of microemulsions that are formed by dilution of SES.^[21]

Thermodynamic stability

Diluted SEDDS are centrifuged either at 3500rpm for 30min or 15,000rpm for 15 min. Subsequently, these formulations are subjected to freeze-thaw cycles (−20°C and 40°C temperature, respectively) and observed visually. If there is no change in the visual description (creaming or phase separation), then the formulation is considered to be stable.^[21]

In vitro dissolution profile

Drug release from formulation can be evaluated after filling the formulation in a hard gelatin capsule or as other dosage forms using USP XXIII apparatus I (100rpm) or USP XXIII apparatus II (50rpm) or with dialysis method at 37°C. Samples at regular intervals are withdrawn from the medium and drug content is estimated and compared with the control.^[22]

Stability assessment

These studies are performed according to the international conference on harmonization guidelines. Samples are tested for appearance, color, drug content, pH of the diluted formulation, and dissolution profile. If these properties match the initial formulations, it can be concluded as a stable formulation.^[23,24]

RELEASE MECHANISM OF THE DRUG FROM SEDDS

The release from the microemulsion depends on the lipid phase polarity, which is affected by factors such as HLB, fatty acid length and number of double bonds, hydrophilic portion molecular weight, and the emulsifier concentration. The drug polarity is an indicator for its affinity toward oil and/or water and provides an idea of the forces involved. Although higher polarity will enhance the drug release rate in the aqueous media, it may have an adverse effect on the drug solubility.

FORMULATION OPTIMIZATION OF SEDDS

The quality by design (QbD) is a systematic pharmaceutical approach toward formulation development that is initiated with preset objectives and lays stress on product and process understanding and process control through robust science and quality risk management. QbD helps in building excellent products and to recognize critical process parameters affecting the drug products fabrication. It also helps in designing approaches to retain quality throughout its life cycle. QbD is majorly applied through design of experiment which uses multiple designs such as plackett-Burman, Box–Behnken design, fractional factorial design, central composite design,

and mixture design for either screening or optimization of the variables.^[25] A detailed discussion of these designs and their applications is beyond the scope of this review. The readers are directed to a few successful formulations using factorial design.^[26]

MECHANISM OF SEDDS

A brief review of literature reveals multiple mechanisms for microemulsion formation. It is considered that the surfactant-mediated intricate film formation at the oil-water interface leads to the microemulsion droplets formation [Figure 2]. As per the thermodynamic theory of microemulsion formation, the emulsification ensues as soon as the change in entropy favoring dispersion is higher than the energy necessary for the dispersion surface area amplification and the free energy (ΔG) is negative.^[27] The free energy in the microemulsion formation is related to the energy required to create a new surface between the two phases as given in the below equation:

$$\Delta G = \sum N r^2 \sigma$$

Where ΔG is the free energy associated with the process (where free energy of the mixing was ignored), “N” is number of droplets, “r” is radius, and “ σ ” is the interfacial energy, respectively. The two emulsion phases are likely to separate to reduce the interfacial area, which subsequently, decreases the free energy of the system. The emulsion resulting post aqueous dilution is stabilized by surfactants, by forming a single layer surrounding the emulsion droplets, which results in the reduction of the interfacial energy, and provides a barrier against coalescence.^[16]

PERFORMANCE OF SEDDS IN BIOLOGICAL SYSTEMS

Lipid-based formulations help in increasing solubilization capacity and prevent drug precipitation post intestinal dilution. Although this issue is not extensively investigated, it is reported that the absorption of the drugs through SMEDDS/ SEDDS is dependent on the globule size of the formulation. A formulation with a lower globule size (~200 nm) displays enhanced bioavailability as compared to formulation with relatively higher globule size (~800 nm).^[28] However, there have been some contrary reports which downplay the effect of globule size on the bioavailability of the SEDDS/SMEDDS. SEDDS and SMEDDS of halofantrine having significantly different globule size did not affect the halofantrine absorption from the gut.^[29] The influence of globule size on the absorption and bioavailability needs to be studied while maintaining the concentrations of the lipids and surfactants at the same level.

As mentioned earlier, SMEDDS have been utilized for augmenting the stability and improving the bioavailability of peptides and drugs by decreasing the presystemic metabolism and enhancing bioavailability. Drugs entrapped in the globules of emulsions formed from SMEDDS/ SEDDS are protected against the proteases such as trypsin and chymotrypsin and the gastric acids, which are capable of degrading it. Entrapment of the peptides in the globules also offers protection against the biological thiols, which can degrade the intramolecular disulfide bonds and disrupt the 3-D structure of peptides. In addition, the globules also enhance the drug and peptide bioavailability by increasing membrane fluidity, the opening of tight junctions, inhibition of P-gp and CYP450.^[30] As mentioned previously, the SEDDS/SMEDDS lead to the formation of chylomicrons,^[31]

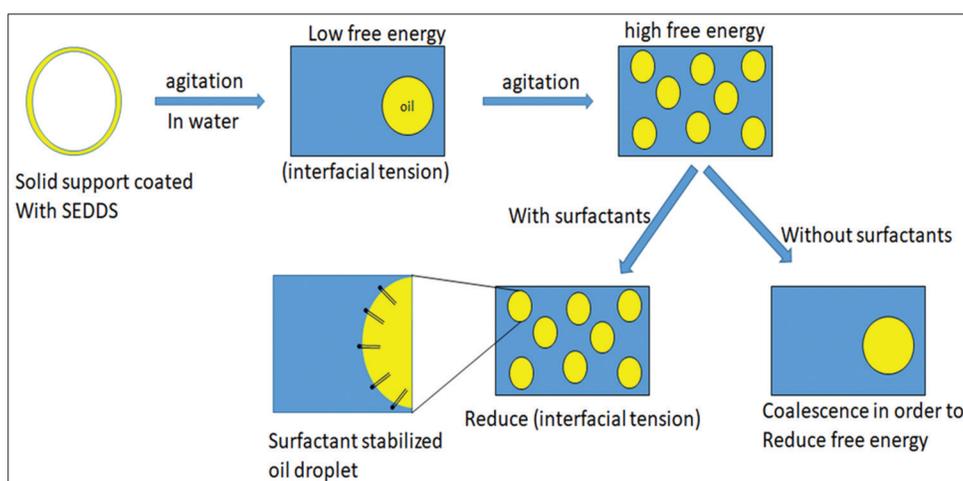


Figure 2: Mechanism of emulsion formation after interaction with aqueous media. Initial agitation dislodges the oil from the solid support to form a system, which has low free energy, due to low interfacial tension. After further agitation, the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion and the free energy (ΔG) is negative. The surfactants decrease the interfacial tension, thus reducing the free energy while maintaining the reduced droplet size. In absence of surfactants, the oil droplets coalesce thus reducing the free energy of the system

Table 1: Commercial products description

Product name/ drug	Use	BCS class	Strength (mg)	Dosage form	Inactive ingredients	Manufactured by/for
Sandimmune® (cyclosporine A/I)	Indicated for the organ rejection prophylaxis in allogenic transplants of kidney, liver, and heart	IV	25/100	Soft gelatin capsule	Corn oil, linoleoylmacrogol glycerides, and sorbitol	Novartis pharmaceuticals corporation
Neora® (cyclosporine)	Systemic immunosuppressant	IV	10/25/50/100	Soft gelatin capsule	Corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil NF, DL- α -tocopherol USP	Novartis Pharmaceuticals Corporation
Gengraf® (Cyclosporine A/III)	Systemic immunosuppressant	IV	25/100	Hard gelatin capsule	Polyethylene glycol NF, polyoxyl 35 castor oil NF, polysorbate 80 NF, propylene glycol USP, sorbitan monooleate NF, titanium dioxide	AbbVie Inc.
Norvir® (Ritonavir)	Combination with other antiretroviral agents for the treatment of HIV-1 infection	II	100	Soft gelatin capsule	Butylated hydroxytoluene, ethanol, oleic acid, polyoxyl 35, and castor oil	AbbVie Inc.
Fortovase® (Saquinavir)	Inhibitor of the human immunodeficiency virus (HIV) protease	IV	200	Soft gelatin capsule	Medium chain mono- and diglycerides, povidone, and dl-alpha-tocopherol	Roche Laboratories Inc.
Agenerase® (Amprenavir)	Inhibitor of the human immunodeficiency virus (HIV) protease	II	50	Soft gelatin capsule	d-alpha tocopheryl PEG 1000 succinate (TPGS), PEG 400, and propylene glycol	GlaxoSmithKline
Depakene® (Valproic acid)	Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures	II	250	Soft gelatin capsule	Corn oil, glycerin, methylparaben, and propylparaben	AbbVie Inc.
Rocaltro® (Calcitriol)	Management of secondary hyperparathyroidism and management of hypocalcemia	II	0.25/0.5	Soft gelatin capsule	Triglyceride of coconut oil	Roche Products Limited
Targretin® (Bexarotene)	Treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy	II	75	Soft gelatin capsule	Polyethylene glycol 400, NF, Polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF	Ligand Pharmaceuticals/ Eisai Ltd.

(Contd...)

Table 1: (Continued)

Product name/ drug	Use	BCS class	Strength (mg)	Dosage form	Inactive ingredients	Manufactured by/for
Vesanoid® (Tretinoin)	Retinoid that induces maturation of acute promyelocytic leukemia (APL)	II	10	Soft gelatin capsule	Beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils, and soybean oil	Roche Laboratories Inc.
Accutane® (Isotretinoin)	Severe recalcitrant nodular acne	II	10/20/40	Soft gelatin capsule	Beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil	Roche Laboratories Inc.
Aptivus® (Tipranavir)	Combination antiretroviral treatment of HIV-1	II	250	Soft gelatin capsule	Dehydrated alcohol (7% w/w or 0.1 g per capsule), polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid	Boehringer Ingelheim Pharmaceuticals, Inc.

BCS: Biopharmaceutics classification system, PEG: Polyethylene glycol

which are absorbed, through the lymphatic system. This lymphatic system mediated absorption is beneficial for drugs which display high first-pass effect.^[32] Readers are directed to some excellent reviews on this subject published elsewhere.^[33]

DOSAGE FORM OF SEDDS

Most of the commercially approved SEDDS dosage forms are available as soft gelatin capsules and a few are as hard gelatin capsules. SES can be prepared as powders by adsorbing on to adsorbents such as microcrystalline cellulose. Orit can be formulated as granules using a wet granulation technique, where the SES will be used as a binder or granulating media.^[34] Dough masses consisting of SES can be converted to pellets by extrusion and spheronization. Even though self-emulsifying tablets and pellets have been extensively investigated and published in literature, no commercial products were available in these forms. Manufacturers are researching on some other new technologies such as liquid-filled hard capsules and lipid multi-particulate technologies.

Self-emulsifying capsule

Conventional soft gelatin capsules filled with SEDDS or SEDDS loaded powders filled in capsules consequently scatter in the GIT to reach the absorption site. Enhancement of drug

absorption is not possible if irreversible phase separation of microemulsion occurs in the GIT. The best-known example of this type of formulation is Neoral. Sodium dodecyl sulfate can be added to the system to prevent irreversible phase separation.

Self-emulsifying sustained/controlled release

Self-emulsifying tablets can be prepared with a combination of lipids and surfactants, which are used in obviating adverse drug side effect. SES adsorbed on powders or loaded on granules/pellets which can be compressed as tablets, and a sustained or controlled release can be achieved by utilizing a suitable concentration of polymers.

Self-emulsifying sustained/controlled release pellets

Self-emulsifying formulations can be converted into pellets using different coating techniques which can provide multiple advantages over normal solid dosage form, such as manufacturing flexibility, decreased intra- and inter-subject plasma profile variability along with reduced GI irritation without impacting the drug bioavailability.^[35] Pellets of SES can be prepared by extrusion and spheronization and can provide different release profiles such as immediate, delayed and controlled release using a wide variety of spray coating techniques.

Table 2: Literature data for SEDDS/SMEDDS/SNEDDS

Drug/BCS class	Oil, surfactant, and cosurfactant	Result/outcome	Reference
Atorvastatin calcium/II	Sefsol 218, Cremophor RH 40, propylene glycol	Enhanced bioavailability	[22]
Efavirenz/II	Labrafac PG, Tween 80, Labrasol	Better systemic absorption and bioavailability	[36]
Fexofenadine hydrochloride/II	Oleic acid, Aconon MC8, PEG 400	Optimized gave complete drug release in 90 min	[37]
Meloxicam/II	Sunflower oil, Tween 80, PEG 400	Optimized formulation gave faster dissolution than marketed product	[38]
Domperidone/II	Labrafac CC, Tween 80, Transcutol	Enhanced bioavailability and dissolution rate	[39]
Ibuprofen/II	Labrafil M 1944CS Tween 80 as a surfactant, Transcutol P	Enhanced absorption in rats	[40]
Olmesartan Medoxomil/II	Acrysol EL 135, Tween, Transcutol P	<i>In vitro</i> and <i>ex vivo</i> diffusion rate of the drug from the SMEDDS was significantly higher than that of the plain drug suspension	[41]
Dutasteride/II	Capryol TM 90, Cremophor EL, Transcutol HP	Optimized SMEDDS formulation significantly improved the oral absorption of dutasteride	[42]
Fenofibrate/II	Labrafil M 1944 CS, Labrasol, Capryol PGMC	Improved dissolution rate and oral bioavailability	[43]
Glibenclamide/II	Capmul MCM C8, Cremophor RH 40, Transcutol, Aerosil 200	Enhanced dissolution rate	[44]
Carbamazepine/II	Labrafil M 1944 CS, Cremophor RH-40, PEG-400	Enhanced dissolution rate	[45]
Tacrolimus/II	Lauroglycol FCC, Cremophor RH, PEG 400	The optimized liquid and solid SMEDDS showed higher drug release than the marketed capsule and pure drug	[46]
Rosuvastatin calcium/II	Cinnamon oil, Labrasol, Capmul MCM C8	Significant increase in dissolution and bioavailability	[47]
Mebendazole/II	Oleic acid, Tween 80 and Polypropylene glycol	<i>In vitro</i> drug release and <i>in vivo</i> plasma drug concentration of microemulsion and SMEDDS was much higher than that of marketed preparation	[48]
Loratadin/II	Liquid paraffin, Capriole, Span 20, Transcutol Aerosil, Croscarmellose	<i>In vitro</i> release of SNE pellets was higher than the liquid SNE and powder tablets	[49]
Telmisartan/II	Castor oil, Tween 20, propylene glycol	SMEDDS and solid-SMEDDS improved dissolution and oral bioavailability	[50]
Carvedilol/II	Oleic acid, labrafil, and labrafac PG	Enhanced dissolution, bioavailability, and drug permeability through rat intestine	[51]
Rosuvastatin calcium/II	Capmul MCM, Cremophor ELP, Propylene glycol	The solid SEDDS formulations prepared from the optimized liquid SEDDS gave maximum release rate (97.7%) than marketed formulation	[52]
Ritonavir/II	Imwitor988, Cremophor EL and Cremophor RH 40 (1:1), Capmul GMS K-50	Enhanced solubility and relative oral bioavailability	[53]
Glipizide/II	Captex 355, Solutol HS15 and Imwitor 988, Calcium carbonate	Glipizide dissolution was improved significantly from the solid SNEDDS when compared to the pure drug and commercial product (65.82) respectively	[54]
Avanafil/II	Dill oil, Tween 80, propylene glycol	A 1.4-fold increase in bioavailability was achieved when compared with pure drug	[55]
Nevirapine/II	Oleic acid, Tween 20, PEG 600	Increase in dissolution rate when compared to pure drug	[56]

(Contd...)

Table 2: (Continued)

Drug/BCS class	Oil, surfactant, and cosurfactant	Result/outcome	Reference
Dutasteride/II	Capryol 90, Cremophor EL, Transcutol HP	Improved physicochemical property and oral absorption	[57]
Atorvastatin/II	Oleic acid or Capryol 90, Tween 80, 1,2-propylene glycol	Increase in dissolution rate when compared to pure drug	[58]
Simvastatin/II	Capryol 90, Tween 80	SEDDS showed a remarkable reduction in plasma cholesterol level	[59]
Tacrolimus/II	Labrasol, Lauroglycol, Labrafac	Enhanced oral bioavailability in rats due to faster absorption and accelerated dissolution of the drug from the solid SEDDS	[60]
Lornoxicam/II	Labrafil M 1944 CS Kolliphor HS 15, Transcutol H	Improved solubility and bioavailability	[61]
Lovastatin/II	Capmul MCM, Nikkol HCO-50, Lutrol F127	Enhanced drug absorption and the pharmacodynamic potential in regulating serum lipid levels	[62]
Glipizide/II	Phosphatidylcholine, Tween 80, Transcutol P, Syloid 244 FP (adsorbent)	<i>In vivo</i> study demonstrated that blood glucose levels were effectively controlled with S-SEDDS compared with pure drug	[63]
Darunavir/II	Capmul MCM C8, Tween 80, Transcutol P Neusilin US2	<i>In vivo</i> , pharmacokinetic studies in rats resulted in enhanced values of peak drug concentration for L-SNEDDS and S-SNEDDS compared to pure darunavir	[64]
Chlorthalidone/IV	Capmul MCM, Tween 80, PEG 400, Neusilin US2	<i>In vitro</i> dissolution study indicated a high dissolution rate of solid-SMEDDS over the pure drug and marketed formulation	[65]
Etofibrate/II	Oleic Acid, Tween 80 and Isopropanol	Enhanced dissolution rate	[66]
Telmisartan/II	Labrafil 1944, Kolliphor ELP: Span 80 (1:1) and PEG 400: Ethanol (1:1)	Dissolution rate was enhanced when compared to pure drug	[67]
Nateglinide/II	Capryol-90, Tween 80, Transcutol P, Aerosil-200	Enhanced release of the drug from solid-SEDDS when compared to plain drug	[68]
Bosentan/II	Gelucire 44/14, Cremophor EL, and PEG 400 (PEG 400)	Enhanced dissolution rate	[69]

BCS: Biopharmaceutics classification system, PEG: Polyethylene glycol, SMEDDS: Self-microemulsifying drug delivery systems, SEDDS: Self-emulsifying drug delivery systems

COMMERCIALY AVAILABLE PHARMACEUTICAL PRODUCTS

SEDDS is one of the commercially feasible techniques and several products have been filed as new drug application (NDA) and abbreviated new drug application (ANDA). In the current review, we describe some of the approved NDAs and ANDA. Some of the NDAs such as Agenerase, Depakene, Rocaltrol, Targretin, Accutane, and Aptivus are filed under sub-classification as Type 1 – new molecular entity. Other NDAs such as Sandimmune, Neoral, Norvir, Fortovase, and Vesanoid are filed under sub-classification as Type 3 – new dosage form. Depakene and Rocaltrol were approved in the year 1978. Gengraf is filed as an ANDA and is available as a hard gelatin capsule. Some of the commercially available pharmaceutical products formulated as SEDDS are presented in Table 1. From the tabular data, it is evident that SEDDS

strategy is a commercially viable system for drugs from BCS Class II and IV.

LITERATURE DATA

In this section, attempts were made to provide the list of SEDDS/SMEDDS/SNEDDS and their components along with their outcomes with respect to drug release, dissolution rate, rate of absorption and bioavailability. Tabular information is given in Table 2.

CONCLUSION

SEDDS offer an enhanced absorption and dissolution rate for lipophilic drug compounds wherein absorption is limited

by the rate of dissolution. The ease of manufacturing and the superior physical stability offered by the SEDDS has captivated the interests of the formulation scientist, which is evident from the commercial success of the multiple NDA's and ANDA's filed in the recent years.

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