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Applications of Self Emulsifying Drug Delivery Systems in Novel Drug Delivery- A Review

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Abstract: Self-emulsifying drug delivery systems are isotropic mixtures of oils, surfactants and co-surfactants. Sometimes co-solvents are also incorporated to increase the solubility. That is why SEDDS are also becoming important tool in novel drug delivery since last couple of years. The problems of low bioavailability issues associated with poorly water soluble drugs can be easily solved by SEDDS. The bioavailability of BCS class -II and class-IV can be enhanced by these systems. These systems form fine emulsions (micro-/nano-emulsion) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility. The increased surface area and amphoteric nature of SEDDS lead to increase in bioavailability. SEDDS also minimizes the gastric irritation. The hepatic first-pass effect can be bypassed by these systems because the drugs can subsequently be absorbed by lymphatic pathways. In this review we present a report on the formulation, evaluation and dosage forms and applications of self-emulsifying formulations, with examples of currently marketed preparations.

Key words: Self-emulsifying drug delivery systems · Bioavailability · Oils · Surfactants · Co-surfactants · Co-solvents · Poor solubility

INTRODUCTION

Drugs are most often administered by the oral route. Almost 50% of the new drug compounds exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery [1, 2]. Different formulation strategies such as the use of surfactants, lipids, permeation enhancers, micronization, salt formulation, cyclodextrins, nanoparticles and solid dispersions are now being used to overcome these problems. The absorption and availability of the drug can be enhanced by solubilising the drug within a colloidal dispersion [3]. Physically stable formulations such as lipid solutions, emulsions and emulsion pre-concentrates are more popular and suitable for encapsulation of poorly soluble drugs [4]. Much attention has been focused on self emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly aqueous soluble drugs. SEDDS are isotropic mixtures containing drug, lipids and surfactants and one or more co-surfactants [5]. Drugs are most often administered by the oral route. However, more than 40% of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Much attention has been focused on self emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly aqueous soluble drugs. SEDDSs emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation [6, 7]. SEDDS can be orally administered in soft or hard gelatin capsules and form fine, relatively stable oil-in-water emulsions upon aqueous dilution. 'Self-nano-emulsifying drug delivery systems' are recent term having the globule size range less than 100 nm [8]. In oral absorption of drug from SEEDS many parameters like surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge plays a important role. The bioavailability of the drug is increased due to increase in the solubility of drug from this formulation. The gastric irritation is also minimizes in this formulation by using proper oil, surfactant and co-surfactants [9].

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Advantages of Self-emulsifying Drug Delivery Systems:

- Drug loading capacity is higher in SEDDS, than other lipid/oil based formulation.
- Peptides that are prone to enzymatic hydrolysis in GIT can be delivered in this formulation.
- Lipid digestion process has no influence on SEDDS.
- The oral bioavailability of the drug is improved in SEDDS.
- These formulations reduce the dose of the drug by increasing solubility and bioavailability of the drug.
- The SEDDS offer ease in manufacture & scale-up.
- Onset of action of SEDDS is quick.

Disadvantages of Self-emulsifying Drug Delivery Systems:

- Since these formulations depend on digestion prior to release of the drug, traditional in vitro dissolution methods do not work, for SEDDS.
- Before evaluating the strength of SEDDS *in vitro* model, development and validation are needed.
- *In vitro* - *in vivo* correlations are responsible for further development, therefore development of different prototype lipid based formulations and there *in vivo* testing in a suitable animal model are necessary.
- This system has different drawbacks such as chemical instabilities of drugs, high concentration of surfactants in formulation (approximately 30-60%) which causes irritation in GIT.

Drug Candidates Suitable for SEDDS: The self emulsifying drug delivery systems can be used for all four categories of biopharmaceutical classification system (BCS) class drugs but the BCS class-II and class-IV categories of drugs are more needful as well suitable for the SEDDS formulations. Figure 1 gives a representative diagram showing drug candidates eligible for SEDDS delivery.

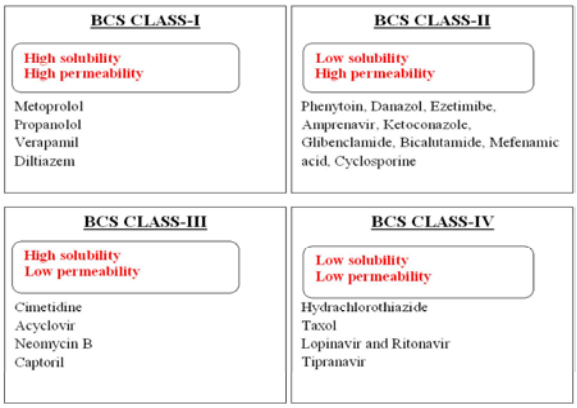

Fig. 1: Drug candidates suitable for SEDDS delivery

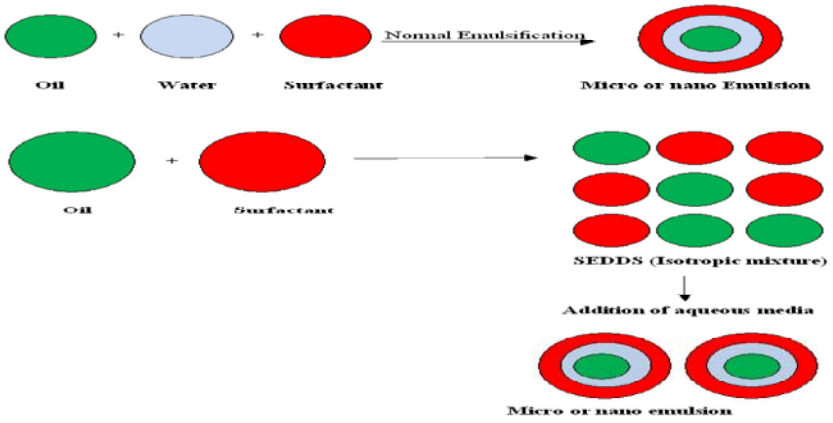

Fig. 2: Self-emulsification mechanism

SEDDS form fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation following dilution by an aqueous phase. A clear dispersion is formed rapidly from SEDDS and it should remain stable on dilution. The difference between normal emulsion and the emulsion formed from SEDDS after appropriate dilution is shown in Figure 2.

Dosage Forms of SEDDS: Different dosage forms of SEDDS can be formulated. For oral delivery of SEDDS, self-emulsifying capsule, sustained/controlled release tablets, sustained/controlled release pellets, solid dispersions are available. And topical delivery, oculars and pulmonary delivery, parenteral delivery are also available for SEDDS.

Composition of Self Emulsifying Drug Delivery Systems: The process of self-emulsification depends on:

- The nature of the oil-surfactant pair.
- The surfactant concentration.
- The temperature at which self-emulsification occurs.

The excipients used in the formulation of SEDDS are given below-

Oils: Oils can solubilize the lipophilic drug that is why oil is the most important excipient in SEDDS formulation [10-12]. It also facilitates self-emulsification. The fraction of lipophilic drug transportation via the intestinal lymphatic system is increased and also absorption from the GIT is increased depending on the molecular nature of the triglyceride [13-15]. The oils that are used in formulation of SEDDS are generally long and medium chain triglyceride (LCT and MCT). The LCT and MCT are used with different degrees of saturation.

Surfactants: Surfactants are having amphiphilic character. They help in solubilisation of lipophilic drug compounds. In GI lumen, this prevents precipitation of drug. So the drug exists in GI lumen for prolonged time. Many compounds which are having surfactant properties may be used for the formulation of self-emulsifying systems, but only those surfactants which are orally acceptable are used [16-17]. The non-ionic surfactants are mostly recommended because they have relatively high hydrophilic-lipophilic balance (HLB). Safety is a major issue in selection of surfactants. There are four types of surfactants available. Such as cationic surfactants. eg: quaternary ammonium halide, anionic surfactants. e.g.: potassium laureate, sodium lauryl sulphate, ampholytic surfactants. e.g.: sulfobetaines and nonionic surfactants. eg: sorbitan esters (spans), poly -sorbates (tweens). It is reported that a cationic emulsion show greater absorption than an anionic emulsion. To form a stable SEDDS, 30-60% concentration of surfactant is used [18].

Co-Solvents: Various organic solvents are used as cosolvents such as ethanol, propylene glycol and polyethylene glycol, which may help to dissolve large amounts of drug in liquid base. The optimum SEDDS formulation requires generally high concentrations (generally more than 30-50% w/w) of surfactants; therefore the incorporation of co-surfactant is done to reduce the concentration of surfactant [19]. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value [20]. At this value the fine dispersed droplets are formed due to expansion of the interface, resulting into more absorption of surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. For many non-ionic surfactants, the use of co-surfactant in self-emulsifying systems is not necessary. The proper selection of surfactant and co-surfactant is very important for the formation of SEDDS and also for solubilisation of the drug in the SEDDS.

Evaluation of SEDDS

Droplet Size Analysis: The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle. It is very important factor in self-emulsification performance. The rate and extent of drug release, as well as the stability of the emulsion is determined by droplet size [21, 22].

Visual Evaluation of SEDDS: SEDDS formulations were visually examined for clarity, homogeneity and color. To observe the color of the formulations, normal visual examination was performed. SEDDS formulations were kept standing against light to examine the clarity. Presence or absence of precipitation was noticed to assess the homogeneity of the prepared formulations.

The SEDDS formulations were than kept in optimum room temperature for 1 month. After 1 month, those properties of the SEDDS formulations were again examined to determine the stability of the formulation SEDDS [23].

Self-Emulsification Time: Self-emulsification time was determined for all the developed formulations. SEDDS formulations was added to aqueous media under continuous stirring (50 rpm) using a USP type II (paddle type) at 37 ± 0.5°C. The time required to disperse the system completely and uniformly was recorded as the self-emulsification time [24].

Thermodynamic Stability Studies: The performance of a lipid based formulation is very important and it depends upon its physical stability and it can be affected by precipitation of the drug in the excipients matrix. The physical stability can cause separation of the phase of excipients, affecting formulation performance and visual appearance resulting in poor formulation. The incompatibilities between the gelatin capsules shell and the formulation cause deformation or brittleness and also lead to delayed disintegration, or incomplete release of drug.

Heating Cooling Cycle: Six cycles is performed for studying heating cooling cycle by storing each formulation at refrigerator temperature (40°C) and 45°C respectively for not less than 48 hr. The formulations which are stable at these temperatures are subjected to centrifugation test.

Centrifugation: The centrifugation test between 21°C and 25°C is performed for those formulations which passed the heating cooling cycle with storage at temperature for not less than 48 hr. This is done for 30 min at 3500 rpm. The formulations which does not show any phase separation are subjected to freeze thaw stress test.

Freeze Thaw Cycle: Three freeze thaw cycle are performed for the formulations. Those formulations passed this test show good stability with no creaming, cracking or phase separation.

Measurement of Zeta Potential: This is used to identify the charge of the droplets. In conventional SNEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids. The charge of the droplets is determined by zeta potential measurement. The charge on an oil droplet is negative in conventional SEDDS, because of the presence of free fatty acids. Cationic lipid, such as oleylamine(at a concentration range 1-3%) incorporation will yield cationic SEDDS. Zeta potential helps in predicting the flocculation effect and stability in emulsion systems. Colloid will aggregate due to attractive forces if the zeta potential falls below a certain level [25].

Refractive Index and Percentage Transmittance: Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333). The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature.

Viscosity Determination: Soft gelatin or hard gelatin capsules are generally used for the administration of the SEDDS system. Therefore the SEDDS can be easily pourable into capsules and such system should not too thick to create a problem. Viscometer is used for the evaluation of the rheological properties of the micro emulsion. The nature of the system i.e. w/o or o/w is confirmed by the viscosities determination.

Applications

Protection Against Biodegradation: The self-emulsifying drug delivery system is able to reduce degradation as well as improve absorption may be especially useful for drugs which have both low solubility and degradation in the GI tract and low oral bioavailability. Because of acidic pH, enzymatic degradation or hydrolyte in stomach, many drugs are degraded in physiological system. These degradation processes can be well protected when drug is presented in the form of SEDDS, as liquid crystalline phase in SEDDS might act as barrier between degradation environment and the drug. For example Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because in an acid environment, it is readily hydrolysed to salicylic acid. By the Galacticles Oral Lipid Matrix, the oral bioavailability of un- degraded acetylsalicylic acid is improved by 73%.

Improvement in Solubility and Bioavailability: If SEDDS is used to incorporate the drug, the solubility increases because it circumvents the dissolution step in of BCS Class-II drug (Low solubility/high permeability). Ketoprofen, a non steroidal anti-inflammatory drug (NSAID) is moderately hydrophobic (log P 0.979). For sustained release formulation it is a drug of choice and during chronic therapy it has high potential for gastric irritation. Ketoprofen shows incomplete release from sustained release formulations because of its low solubility. The SEDDS formulation of this drug enhanced bioavailability due to increase in the solubility and it also minimizes the gastric irritation. The release of Ketoprofen in SEDDS is sustained due to incorporation of gelling agent. The lipid matrix interacts readily with water in SEDDS, leading to the formation of a fine particulate oil in-water (o/w) emulsion. The drug is delivered to the gastrointestinal mucosa by the emulsion droplets, in the dissolved state readily accessible for absorption. Therefore SEDDS shows increase in AUC i.e. bioavailability and C max of many drugs.

Controlling the Release of Drug: Sustained release, bioavailability enhancement and decreased gastric irritation of Ketoprofen achieved by different formulation approaches which include preparation of matrix pellets of nano-crystalline Ketoprofen, sustained release Ketoprofen micro particles and floating oral Ketoprofen systems and transdermal systems of Ketoprofen. Processing, stability and economic problems are the drawbacks of preparation and stabilization of nano-crystalline or improved solubility forms of drug. When Ketoprofen is presented in SEDDS formulation, this problem can be successfully overcome. The SEDDS formulation of this drug enhanced bioavailability due to increase in the solubility and it also minimizes the gastric irritation. The release of Ketoprofen in SEDDS is sustained due to incorporation of gelling agent. The lipid matrix interacts readily with water in SEDDS, leading to the formation of a fine particulate Oil in-water (o/w) emulsion.

Marketed Formulations of SEDDS: Many pharmaceutical companies are formulating SEDDS formulations. These are also available in market. The SEDDS formulations available in market are listed in Table 1.

Table 1: A brief account of SEDDS available in market

Brand/name	Drugs/API	Excipients	Indication	References
Neoral	Cyclosporine	Corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil NF, DL-á-tocopherol USP, gelatin NF, glycerol, iron oxide black, propylene glycol USP, titanium dioxide USP, carmine	Soft gelatin capsule	http://www.rxlist.com/neoral-drug.htm
Norvir	Ritonavir	Butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil and titanium dioxide.	Soft gelatin capsule	http://www.rxlist.com/norvir-drug.htm
Invirase/ Fortovase	Saquinavir mesylate	lactose, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc and magnesium stearate.	Soft gelatin capsule	www.rxlist.com/invirase-drug.htm
Agenerase	Amprenavir	d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400) 246.7 mg and propylene glycol 19 mg. d-sorbitol and sorbitans solution, gelatin, glycerin and titanium dioxide.	Soft gelatin capsule	http://www.rxlist.com/agenerase-drug.htm
Targretin	Bexarotene	Polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP and butylated hydroxyanisole, NF. Gelatin, NF, sorbitol special-glycerin blend and titanium dioxide.	Soft gelatin capsule	http://www.rxlist.com/targretin-drug.htm
Rocaltrol	Calcitriol	butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), fractionated triglyceride of coconut oil, fractionated triglyceride of palm seed oil. Gelatin capsule shells contain glycerin, parabens (methyl and propyl) and sorbitol	Soft gelatin capsule	http://www.rxlist.com/rocaltrol-drug.htm

Table 1: Continue

Brand/name	Drugs/API	Excipients	Indication	References
Cipro	ciprofloxacin	Cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hypromellose, titanium dioxide and polyethylene glycol.	Soft gelatin capsule	http://www.rxlist.com/cipro-drug.htm
Coreg CR	Carvedilol phosphate	Crospovidone, hydrogenated castor oil, hydrogenated vegetable oil, magnesium stearate, methacrylic acid copolymers, microcrystalline cellulose and povidone.	CR Hard Gelatin Capsule	http://www.rxlist.com/coreg-cr-drug.htm
Sandimmune	Cyclosporine	Corn oil, gelatin, iron oxide red, linoleoyl macrogolglycerides, sorbitol and titanium dioxide.	Soft gelatin capsule	http://www.rxlist.com/ sandimmune-drug.htm
Marinol	Dronabinol	2.5 mg capsule contains gelatin, glycerin, sesame oil and titanium dioxide; 5 mg capsule contains iron oxide red and iron oxide black, gelatin, glycerin, sesame oil and titanium dioxide; 10 mg capsule contains iron oxide red and iron oxide yellow, gelatin, glycerin, sesame oil and titanium dioxide.	Soft gelatin capsule	http://www.rxlist.com/marinol-drug.htm
Avodart	Dutasteride	mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene. capsule shell contains ferric oxide (yellow), gelatin (from certified BSE-free bovine sources), glycerin and titanium dioxide.	Soft Gelatin Capsules	http://www.rxlist.com/avodart-drug.htm
Lipofen	Fenofibrate	Gelucire 44/14 (lauroyl macrogol glyceride type 1500), polyethylene glycol 20,000, polyethylene glycol 8000, hydroxypropylcellulose, sodium starch glycolate, gelatin, titanium dioxide, shellac, propylene glycol, may also contain black iron oxide, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, D&C Yellow #10.	hard gelatin capsules	http://www.rxlist.com/lipofen-drug.htm
Accutane	Isotretinoin	beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl)	soft gelatin capsules	http://www.rxlist.com/accutane-drug.htm
Kaletra	lopinavir/ritonavir	The yellow, 200 mg lopinavir/50 mg ritonavir, tablets contain the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, colloidal silicon dioxide, polyethylene glycol 3350, yellow ferric oxide E172 and polysorbate 80. The pale yellow, 100 mg lopinavir/ 25 mg ritonavir, tablets contain the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide and sodium stearyl fumarate. The following are the ingredients in the film coating: polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol 3350 and yellow ferric oxide E172.	Tablets	http://www.rxlist.com/ kaletra-tablets-drug.htm

Table 1: Continue

Brand/name	Drugs/API	Excipients	Indication	References
Kaletra	lopinavir/ ritonavir	FD&C Yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide and water.	Capsules	http://www.rxlist. com/kaletra-capsules-drug.htm
Pentasa	Mesalamine	Acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc and white wax.	Controlled-Release Capsules 250 mg and 500 mg	http://www.rxlist.com/pentasa-drug.htm
Lovaza	Omega-3-acid ethyl esters	4 mg a-tocopherol (in a carrier of soybean oil) and gelatin, glycerol and purified water (components of the capsule shell).	Hard gelatine capsules	http://www.rxlist.com/lovaza-drug.htm
Zemplar	Paricalcitol	Medium chain triglycerides, alcohol and butylated hydroxytoluene. The medium chain triglycerides are fractionated from coconut oil or palm kernel oil.	SG Capsules	http://www.rxlist. com/zemplar-capsules-drug.htm
Rapamune	Sirolimus	Phosal 50 PG® (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids and ascorbyl palmitate) and polysorbate 80. Tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, dl-alpha tocopherol and other ingredients. The 0.5 mg and 2 mg dosage strengths also contain yellow iron (ferric) oxide and brown iron (ferric) oxide.	Oral solution/ Tablets	http://www.rxlist.com/rapamune-drug.htm
Aptivus	Tipranavir	Ingredients in the capsule are dehydrated alcohol (7% w/w or 0.1 g per capsule), polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin. Ingredients in the oral solution are polyethylene glycol 400, vitamin E polyethylene glycol succinate (TPGS), purified water and propylene glycol.	Capsules / oral Solution	http://www.rxlist.com/aptivus-drug.htm
Detrol® LA	Tolterodine tartrate	Sucrose, starch, hypromellose, ethylcellulose, medium chain triglycerides, oleic acid, gelatin, yellow iron oxide and FD&C Blue #2.	Extended Release Capsules	http://www.rxlist.com/detrol-la-drug.htm
Vesanoid	Tretinoin	Beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils and soybean oil.	Soft gelatin Capsules	http://www.rxlist.com/vesanoid-drug.htm
Depakene	Valproic acid	250 mg capsules: corn oil, FD&C Yellow No. 6, gelatin, glycerin, iron oxide, methylparaben, propylparaben and titanium dioxide. Oral Solution: FD&C Red No. 40, glycerin, methylparaben, propylparaben, sorbitol, sucrose, water and natural and artificial flavors.	Soft gelatin capsules/ Oral Solution	http://www.rxlist.com/depakene-drug.htm

CONCLUSION

Self-emulsifying drug delivery system can be use for the formulations of drugs compounds with poor aqueous stability. Oral bioavailability of poorly water-soluble compounds is increased by using this formulation. In general, the liquid/semi-solid SEDDS formulations are now being converted into powders and granules which can then be further processed into conventional 'powder-fill' capsules or even compressed into tablets by using different techniques such as hot melt granulation. The inert adsorbents, such as the Neusilin products for converting liquids into powders are also used and then it is processed into powder fill capsules or tablet. So in future the SEDDS may be used as a vital tool in reducing the dose size in the formulation. Also SEDDS will be a promising approach for the formulation of lipophilic drugs.

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