Review Article

New Approaches on Self Emulsifying Oil Formulation for the Delivering of Hydrophobic Drugs

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Received: 24-08-2017; **Revised:** 03-04-2019; **Accepted:** 14-05-2019.

ABSTRACT

The oral route is the most preferred route of drug administration in the treatment of many diseases. One of the major challenges in oral drug formulations is low-erratic bioavailability, which is as a result of poor aqueous solubility, and this creates difficulties in drug development. Self-emulsifying oil formulation system is one of the most common techniques for overcoming the formulation difficulties of drugs with poor aqueous solubility. Self-emulsifying drug delivery system is an isotropic mixture of oil, surfactant, co-surfactant and a lipophilic drug with a unique ability to form fine oil-in-water (o/w) or water-in-oil micro or nano-emulsions upon mild agitation in the gastrointestinal tract which presents the drug in a solubilized form. This approach has gained exposure for their ability to increase solubility and bioavailability of poorly aqueous drugs due to the small sizes of the formed droplet that offered large interfacial surface areas for drug absorption. It is a predicting strategy to improve the rate and extent of oral absorption. But upon the advantages of this approach, it still has some limitations such as leakage, GIT irritation and in vivo drug crystallization. These current techniques prevent in vivo precipitation, thereby improving solubility, stability, dissolution, absorption, and bioavailability of poorly aqueous soluble drugs. This review article provides an overview of self-emulsifying oil drug delivery system with emphasis on design, formulation, evaluation and the current techniques.

Keywords: SEOFs, oil, surfactant, co-surfactant, bioavailability, supersaturable SEDDS.

INTRODUCTION

Almost 40 % of new chemical moieties (NCM) are attributed to poor aqueous solubility. This has presented a great challenge in drug development. Solubility is the rate-limiting step for absorption of such drugs. Self-emulsifying oil formulations (SEOFs) is one of the most common techniques for overcoming the formulation difficulties of drugs with poor aqueous solubility. Self-emulsifying oil formulations could be formulated as a self-emulsifying drug delivery system (SEDDS) or self-micro/nano-emulsifying drug delivery system (SM/NEDDS). New chemical moieties are classified into different groups of four based on the solubility and permeability properties of the drugs by Biopharmaceutical classification system (BCS). The class I has no solubility and permeability challenge. Class II has poor solubility with good permeability quality. Class III has high solubility and poor permeability while class IV has both poor solubility and permeability challenges. These challenges of different classes of BCS have attracted the interest of many researchers in drug development. Numerous techniques such as SEOFS, solid dispersion, microparticles, liposomes are in existence to ameliorate the challenges of NCM.[1] Self-emulsifying oil delivery system has gained exposure for their ability to increase solubility and bioavailability of poorly aqueous drugs due to the small sizes of the formed droplet that offered large interfacial surface areas for drug absorption. It is a predicting strategy to improve the rate and extent of oral absorption. Self-emulsifying oil formulation system is an isotropic mixture of oil, surfactant, co-surfactant and a lipophilic drug with a unique ability to form fine oil-in-water (o/w) or water-in-oil micro or nano-emulsions upon mild agitation in the gastrointestinal tract which presents the drug in a solubilized form. The SEOFs readily disperse in the gastrointestinal tract, and the peristaltic movement of the stomach and the intestine provide the agitation necessary for self-emulsification. This provides faster drug release from the emulsion in a reproducible manner, which can be designed further to make the release characteristics independent of the gastrointestinal physiology and the fed/fasted state of the patient.[2, 3] Formation of SEOF as self-emulsifying drug delivery system (SEDDS) or self-micro/nano-emulsifying drug delivery system (SM/NEDDS) has distinct features based on the size of globules of the formed emulsion. The SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant, and drug, while SM/NEDDS formulation requires the incorporation of a co-surfactant to produce a micro/nano-emulsion. The SEOFs are characterized by *in vitro* lipid droplet sizes of 200 nm - 5 mm with a turbid appearance, while SM/NEDDS have a smaller lipid globule sizes (< 100 nm) with an optically clear to translucent appearance. The two systems generate large surface area dispersions that provide optimum conditions for the increased absorption of poorly aqueous soluble drugs. Both systems form fine oil-in-water (O/W) or water-in-oil (W/O) dispersion when in contact with GI fluids. They could be formulated as liquids and semi-solid for capsule or solid dosage forms. They equally require a pseudo-

ternary diagram for optimization. Therefore, SEOF is a general term and could be used to describe both systems unless specificity is required in terms of globules sizes.

There is a fact that oral bioavailability of some hydrophobic drugs is enhanced when co-administered with a meal rich in fat.[4, 5] This has led to much increase in developed interest in the formulation of lipophilic drugs in lipids. Lipid-based drug delivery has gained considerable interest after the commercial success of Sandimmune Neoral (Cyclosporin A), Fortovase (Saquinavir), and Norvir (Ritonavir) SEOFs.[6]

Biopharmaceutical classification system

Drugs are classified into four groups according to the Biopharmaceutical classification system (BCS) based aqueous solubility and permeability as shown in Table 1. If a maximum daily dose of a drug is soluble in 250 ml of aqueous medium over the pH range of 1-7.5, the drug substance is considered highly soluble, while a drug substance is considered highly permeable when more than 85 % of the administered dose is absorbed.[7] Lipinski's rule of five states that a drug molecule with more than 5 H-bond donors, more than 10 H-bond acceptors, a molecular weight greater than 500 and log P greater than 5 are considered poorly permeable.[8] Bioavailability of an active pharmaceutical principle is greatly dependent upon its solubility in gastrointestinal tract fluids, where dissolution is the rate-limiting step in the absorption of poorly aqueous soluble drugs. And because of this issue, the dose of poorly aqueous soluble drugs is increased to attain effective therapeutic drug concentration in the system.[9] Based on the fact that the hydrophobic nature is in-built for a molecule and cannot be altered; various approaches have been made to overcome this drawback. The approaches include the following particle size reduction, formation of salts, cocrystals, amorphous formulations, pH modification, lipid-based formulation, and prodrug approach.[10] Each of these approaches is associated with some merits as well as limitations and hence the choice for selection of each approach is an important step in the enhancement of the bioavailability. For example, in salt formation which is either neutral, weak acid or weak base of a poorly soluble drug may not always be feasible. Also, a decrease in the particle size of a drug makes it difficult for handling due to the development of static charges.[11] And, the process of a mechanical size reduction may cause deterioration of crystal structure and/or partial or complete amorphization of the drug with a resultant decrease in the stability as discovered with candesartan cilexetil.[12] On the reverse, the micronization technique has been excellently used to produce smaller fenofibrate particles (Tricor®) which are dispersed in hydrophilic polyvinylpyrrolidone to decrease its dose. [13] Currently, attention has been directed towards the development of lipid-based formulations for the delivery of poorly aqueous soluble drugs with a goal to improve the dissolution and then the bioavailability. This has been observed when hydrophobic drugs were administered along with food, an especially fatty meal with increased bioavailability. This is true because of the fact that fat rich food may contribute to one or more of the following such as it stimulates bile flow and pancreatic secretions, delays gastric emptying, change in gastrointestinal pH, enhances lymphatic transport, enhances mesenteric and liver blood flow increases intestinal wall permeability and reduces efflux activity. Due to these facts, United States Food and Drug Administration (US FDA) established new guidelines entitled "food-effect bioavailability and fed bioequivalence studies" with recommendations for the determination of the impact of food in the enhancement of bioavailability (IND) and fed bioequivalence (ANDA) studies.[5]

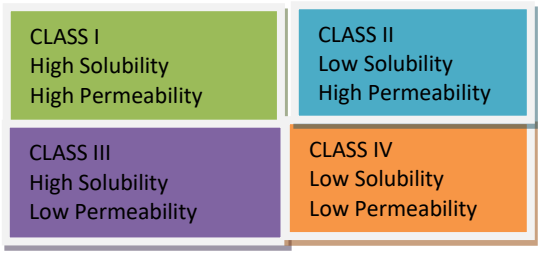

Figure 1: Biopharmaceutical Classification System

Table 1: Properties of Self-Emulsifying Oil Formulations (SEOFs)

SEDDS	SM/NEDDS
Simple binary formulations with the drug and lipid excipients able to self emulsify when in contact with GI fluid or comprises of oil, surfactant and drug.	Consists of oil, surfactant, co-surfactant and drug.
Droplet sizes ranges from 200 nm to 5 mm	Droplet sizes is < 200 nm
Dispersion has a turbid appearance	Has an optically clear to translucent appearance
The system is not thermodynamically stable in aqueous or physiological medium	The system is thermodynamically stable in aqueous or physiological medium

Composition of SEOFs

Self-emulsifying oil formulation constitutes three major vehicles such as oil, surfactant, and co-surfactant. Different vehicles of SEOFs are presented in Table 2. The self-emulsifying depends on [14]

i. The nature of the oil-surfactant pair.

ii. The surfactant concentration.

iii. The temperature at which self-emulsification occur.

Oils

In designing of SEOFs, both long and medium-chain triglyceride oils with different degrees of saturation have been employed. Unmodified edible oils provide the most `natural basis for lipid vehicles, but they have poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduces their use in SEOFs. However, modified or hydrolyzed vegetable oils have imparted widely to the success of SEOFs.[2, 15, 16] Oils form good emulsification systems in the presence of a good concentration of non-ionic surfactants, i.e. non-toxic substance with their degradation products resembling the end products of intestinal digestion. In the recent time, medium chain triglyceride oils and non-ionic surfactants have been used in the formulation of SEOFs.[7, 17, 18] Medium chain triglycerides were desired in the earlier SEOFs.[19, 20] This was due to higher fluidity, better solubility properties, and self-emulsification property. Although, they are considered to be less attractive when compared to the novel semi-synthetic medium chain derivatives which are known as amphiphilic compounds with surfactant properties.[21] This means that the lipophilic surfactant may equally play the role of the hydrophilic oil in the formulation.[22, 16] Moreover, the solvent capacity for less hydrophobic drugs can be improved by blending triglycerides with mono- and diglycerides.[23]

Surfactants

Surfactants with a relatively high hydrophilic-lipophilic balance (HLB) are recommended for the design of self-dispersing systems. The non-ionic surfactants are most preferred as they are non-toxic when taken orally and compared to ionic surfactant agents as they may cause moderate reversible changes in intestinal wall permeability. [24, 25] Some examples of surfactants used in preparation SEOFs include where the various liquid or solid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80), etc. Surfactants or emulsifiers from natural sources are anticipated to be safer than synthetic ones and are advocated for self-dispersed lipid formulation notwithstanding their limited ability to self-emulsify. [25, 26, 27]

The use of minimal surfactant content of 3 % has been proposed to avoid the potential toxicological problems associated with the amount of surfactant.[21] The required amount of surfactant in self-emulsifying formulations to form and maintain an emulsion state in the GI tract ranged from 30 to 60 % w/w of the formulation. A high concentration of surfactant may irritate the GI tract. There is a need for selection of a surfactant with high HLB and subsequent hydrophilicity for the immediate formation of o/w droplets and/or rapid dispersion of the formulation in the aqueous environment, in order to exhibit good dispersing/self-emulsifying activity. The surfactants play important role in emulsification as they are amphiphilic in nature, and therefore, they easily dissolve and even solubilize relatively high quantities of the hydrophobic drug. This role is of high importance for the prevention of precipitation within the GI lumen and for the prolonged existence of the drug molecules in soluble form, which is critical for effective absorption.[22] The lipid mixtures with the appropriate amount of surfactant and co-surfactant/oil ratios lead to the formation of self-micro emulsifying formulations.

Co-surfactant/Co-solvents

Relatively high surfactant concentrations (usually more than 30 % w/w) are needed in order to produce an effective self-emulsifying system. Some organic solvents or vehicles in preparation for oral administration such as ethanol, propylene glycol, and polyethylene glycol can be employed in synergism to dissolve large amounts of either the hydrophilic surfactant or the drug in lipid formulation. These solvents could confer the role of the co-surfactant in the microemulsion systems. However, alcohol-free self-emulsifying microemulsions have also been reported in the literature.[24] These alcohol-free self-emulsifying microemulsions had some advantages over the former formulations. This is because when the preparation is incorporated in capsule dosage forms, since alcohol and other volatile cosolvents are known to migrate into the shells of soft gelatin, or hard, sealed gelatin capsules, resulting in the precipitation of the lipophilic drug. Also, the hydrophobic drug dissolution ability of the alcohol-free formulation may be limited. Drug release from the formulation increased with increasing amount of cosurfactant.

Table 2: Excipients of SEOFs

Oils	Surfactants	Co-Surfactant /Co-solvent
Triacetin	Labrasol	Labrafil PGMC
Cotton seed oil	Polysorbate 20 (Tween 20)	Span 20
Soyabean oil	Polysorbate 80 (Tween 80)	Span 80
Corn oil	D-alpha Tocopheryl polyethylene Glycol	Caproyl 90
Sun flower oil	Succinate (TPGS)	Lauroglycol 90
Castor oil	Polyoxy-35-castor-oil (Cremophor RH 40)	Transcutol P
Sesame oil	Polyoxy-40-hydrogenated castor oil (Cremorphor RH 40)	Capmul
Peanut oil	Labrasol	Polyethylene glycol
Labrafil		Ethanol

Formulation of SEOFs

A pre-formulation study is a necessary test in the formulation of SEOFs. Solubility study is one of the pre-formulation tests. The solubility of the hydrophobic drug as a component of SEOFs is the primary pre-formulation test which helps in the selection of suitable excipients for initial optimization of formula. The vehicles such as oil, surfactant, and co-surfactant in which drug show maximum solubility are selected to achieve optimum drug loading and to minimize the final volume.[18, 28, 29]

Pseudo-ternary phase diagrams are another pre-formulation test. These are constructed with the selected optimized vehicles using titration method and by keeping the ratio of any two of the four components (oil, surfactant, co-surfactant, and water) as constant (usually surfactant and co-surfactant). The surfactant/co-surfactant ratio is mixed with a required volume of the third phase (usually oil) in different ratios. The mixture is titrated with the fourth component usually water in incremental amounts drop wisely and tested for the clarity, flowability, time for self-emulsification and dispersibility.[18, 30, 31] The compositions which form clear solutions are selected and assigned suitable symbols in a ternary diagram, joined and the larger area indicates the microemulsion area as shown in Fig. 2. The wider area indicated the good self-emulsification capacity and the ratios that formed that part is selected as optimized ratios for the SEOFs.[18, 32] In the pseudo-ternary phase diagram, the formulation is optimized mainly based on globule size and self-emulsification time. Self-emulsifying oil formulations can then be easily prepared in a single step by dissolving the drug in the selected optimized components ratio of the vehicles by simple mixing with no critical steps. Different active pharmaceutical ingredients with various pharmacological activities have been delivery through SEOFs. Some of the reports are shown in Table 3.

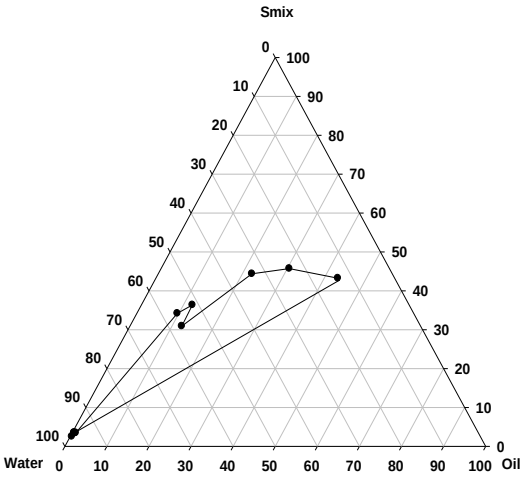

Figure 2: The pseudoternary diagram of the Smix ratio 1:0.5.[18]

Table 3: Self Emulsifying Oil Formulations of Different API

API	Pharmacological activity	Author	Research
Artemether	Antimalaria	**Ugwu *et al.*, 2016a**[18]	Prepared the SMEDDS for improvement of dissolution and oral absorption of artemether
Ibuprofen	Analgesic/anti-inflammatory	**Obitte *et al.*, 2009** [33]	Designed and optimized SEDDS with landolphia oweriensis latex as a release modulator of a poorly water soluble drug Ibuprofen.
Vinpocetine	Vasodilator	**Cui et al., 2008** [34]	Designed and optimized self micremulsifying drug delivery system of a poorly water soluble drug Vinpocetin
Oridonin	Anti-inflammatory	**Liu *et al.*., 2008** [35]	Released rate of oridonin is enhanced by SMEED formulation
Carvedilol	β-adrenergic blocker/antihypertensive	**Enas *et al.*, 2009** [36]	Prepared self emulsifying drug delivery system of carvedilol tablet
Fenofibrate	Hypolipidimic drug	**Patel *et al.*, 2007** [37]	SMEDDS formulation significantly reduced serum level in Triton test as compared with lain fenofibrate
Acyclovir	Antiviral	**Patel *et al.*, 2007** [38]	BA enhanced to 3.5 fold
Paclitaxel	Anticancer	**Kang *et al.*, 2004** [39]	Control release of paclitaxel

Carvedilol	β-adrenergic blocker	**Wei *et al*., 2005** [40]	BA enhanced to 415%
Repaglinide	NSAID	**Shivabindu et al., 2014** [41]	Designed and characterized SEDDS of Repaglinide
Simvastatin	Hypolipidimic drug	**Sunitha and Sowjanya, 2015** [42]	The release rate of Simvastatin as well as bioavailability was higher than conventional
fenofibrate	antilipidimic	**Wei *et al*., 2010** [43]	Enhances the bioavailabiliy
Metronidazole	Anti-fungal/bacterial drug	**Obitte *et al*., 2008** [44]	To enhance the dissolution and oral absorption of poorly water-soluble metronidazole, self-emulsifying drug delivery system (SEDDS

Mechanism of Self Emulsification

In the emulsification process of SEOFs, the free energy (ΔG) associated is given by the equation 1:[16]

$\Delta G = \Sigma N_i \pi r_i^2 \sigma$ ..... Eqn 1

Where "N" is the number of droplets with radius "r" and "σ" is interfacial energy. It is apparent from the equation that the spontaneous formation of the interface between the oil and water phase is energetically not favored. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. The process of self-emulsification was observed using light microscopy. The emulsification process may be associated with the ease with water penetrates the oil-water interface with the formation of liquid crystalline phases resulting in swelling at the interface thereby resulting in greater ease of emulsification.

There are other mechanisms by which lipid-based drug delivery systems enhance the absorption of lipophilic drugs such as

i. Enhanced dissolution/Solubilization: The presence of lipids in the GI tract stimulates gallbladder contractions and biliary and pancreatic secretions, including bile salts (BS), phospholipids (PL) and cholesterol. These products, along with the gastric shear movement, form a crude emulsion that promotes the solubilization of the co-administered lipophilic drug.[45]

ii. Affecting intestinal permeability: Different kinds of lipids have been indicated to change the physical barrier function of the gut wall, and hence permeability.

iii. Reduced metabolism and efflux activity: Currently, some lipids and surfactants have been observed to decrease the activities of efflux transporters in the gastrointestinal wall. Thereby increasing the fraction of the absorbed drug, because of the interplay between P-gp and CYP3A4 activity as this mechanism might have reduced the intra-enterocyte metabolism.

iv. Prolongation of gastric residence time: Lipids in the GI tract elicit delay in gastric emptying. Consequently, the residence time of the co-administered lipophilic drug in the small intestine is equally increased which enables better dissolution of the drug at the absorptive site and then improved absorption.

v. Stimulation of lymphatic transport: The bioavailability of lipophilic drugs may also be enhanced by the stimulation of the intestinal lymphatic transport pathway.

Potential advantages of SEOFs:

The potential advantages of SEOFs include

- High drug payloads.
- Liquid or solid dosage forms.
- Selective targeting of drug(s) toward specific absorption window in GIT
- Enhanced oral bioavailability enabling a reduction in dose.
- More consistent temporal profiles of drug absorption.
- Reduced variability including food effects.
- Protection of drug(s) from the hostile environment in the gut.
- Control of delivery profiles.
- Protection of sensitive drug substances.

Disadvantages of SEOFs:

- Chemical instabilities of drugs and high surfactant concentrations.[46]
- The large quantity of surfactant in self-emulsifying formulations (30 - 60 %) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered.
- Migration of volatile co-solvents in the conventional self-emulsifying formulations into the shells of soft or hard gelatin capsules, leading to precipitation of the lipophilic drugs.
- Lack of *in vitro* model for the assessment of the formulations.

Biopharmaceutical aspects

The possibility of lipids and/or food to enhance the bioavailability of poorly aqueous soluble drugs has been studied. Although not yet clearly understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms which include the following: [47]

- A decrease in gastric transit time which slows the delivery of the drug to the absorption site thereby increasing the time available for dissolution.[48]
- Increases in effective luminal drug solubility: Due to the presence of lipids in the GI tract there is an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), contributing to the formation of BS/PL/CH intestinal mixed micelles with an enhancement in the solubilization capacity of the GIT. However, embolism of administered (exogenous) lipids into these BS structures, either directly (if sufficiently polar) or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity.[49]
- Stimulation of intestinal lymphatic transport: Lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly through a reduction in the first-pass effect for highly lipophilic drugs.
- Changes in the biochemical barrier function of the GIT: Some certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism.
- Changes in the physical barrier function of the GIT: Some lipids, lipid digestion products, and surfactants have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs.[2]

Packaging of SEOFs

The commonest method of packaging liquid SEOFs is a measurement of an appropriate dose of the drug into a soft of the hard capsule shell. Therefore, for oral route capsule filling technique is the simplest and most common technology for encapsulation of liquid or semisolid SEOFs formulation. The steps are given below:

· Heating of semisolid excipients at least 20 °C above its melting point,

· Incorporation of active substances with stirring,

· Capsule filling with the molten mixture and cooling to room temperature.

While for liquid SEOFs as presented in Fig. 3, it requires a two-step process:

· Filing of formulation into capsule and

· Sealing of body and cap of the capsule, either by banding or by micro-spray sealing.

This technique is associated with some advantages such as simplicity of manufacturing; suitable for low dose highly active drug and high drug loading potential up to 50 % W/W.

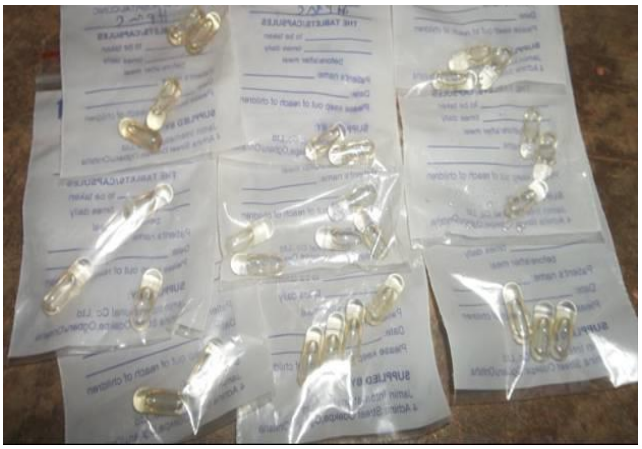

Figure 3: Capsules of artemether (ART) loaded-SMEDDS.[18]

Factors affecting SEOFs formulation

- Highly dosed drugs are not suitable for SEOFs unless they exhibit extremely good solubility in at least one of the components of SEOFs, preferably lipophilic phase. The drugs exhibit limited solubility in water and lipids are most difficult to deliver by SEOFs.[15, 50]
- The polarity of the lipid phase is one of the factors that regulate the release of drugs from the microemulsion. The HLB, chain length degree or unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets. In fact, polarity shows the type of forces involved. High polarity promotes a rapid rate of release of the drug into the aqueous phase. It has been reported that the rate of release of idebenone from SMEDDS is dependent upon the polarity of the oil phase used.[15] The result showed the highest release was obtained with the formulation that had an oily phase with the highest polarity.[16]
- The ability of SEOFs to maintain the drug in a solubilized form in the oily phase is necessary. When the surfactant or co-surfactant is contributing to a greater extent for drug solubilization, there could be a risk of precipitation, as dilution of SEOFs will lead to lowering of the solvent capacity of surfactant or co-surfactant.[19]

Current Techniques in Self Emulsifying Oil formulations

Supersaturable SEOFs

The presence of high surfactant level in a typically SEOFs can lead to GI side effects and drug precipitation. These led to the development of a new class of supersaturable formulations such as supersaturable SEDDS/ SEOFs. The S-SEDDS formulations have been designed and developed to reduce the surfactant side effect and inhibit crystal development thereby achieve rapid absorption of poorly soluble drugs. The S-SEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Supersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and therefore, to result in an increased driving force for transit into and across the biological barrier.[51, 52] Research has reported an improved antimalaria activity of artemether by the formulation of supersaturable SEDDS of artemether as a potential for prevention of *in vivo* drug crystallization.[53] This research found out that hydroxypropyl methylcellulose has the potential to inhibit an *in vivo* crystallization of drug.

Solid SEOFs

The SEOFs are normally formulated as liquid dosage form that can be administered in soft gelatin capsules, which have some disadvantages such as leakages, especially in the manufacturing process. An alternative technique is adsorption of liquid self-emulsify ingredients into a powder in order to create a solid dosage form.[54]

The techniques for solidification of the Liquid/ Semisolid SEOFs to solid- SEOFs include the following:

- **Adsorption onto solid carriers:** The adsorption process is simple and just involves the addition of the liquid SEOFs into the solid carriers by mixing in a blender.[55] The resultant powder may then be filled directly into a capsule or alternatively, mixed with suitable excipient before compression into tablets. The major advantage of using this technique is good content uniformity. Up to 70 % of SEOFs can be absorbed at a higher level into suitable carriers.[56] The solid carrier can be microporous substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymer or nanoparticles adsorbent such as silica, silicates, magnesium trisilicate, talcum, crospovidone. Cross-linked polymers create a suitable environment to sustain drug dissolution. Nanoparticle adsorbents include porous silicon dioxide, carbon nanotubes, and carbon nanohorns.[57]
- **Melt granulation:** Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperature. It is a one-step operation, which offers several advantages compared with conventional wet granulation since the liquid addition and the subsequent drying phase is omitted. A wide range of solid and semi-solid lipids can be applied as meltable binders.[47] Examples of the binders include Gelucire, PEG, lecithin polysorbates.[58]
- **Melt extrusion/spheronization:** Melt extrusion is a solvent-free process. It allows high drug loading approximately 60 %. Extrusion is a procedure for converting a raw material with plastic properties into a product of uniform shape and density, by forcing through a die under controlled temperature, product flow, and pressure conditions. The extruder aperture size will determine the approximate size of resolution spheroids.[48] This technique is commonly applied in the Pharma industry for preparation of uniformly sized pellets. The preparation of Self-emulsifying (SE) pellets of diazepam and bi-layered cohesive SE pellets have been prepared.[59]
- **Spray drying:** Spray drying technique involves the preparation of a formulation by mixing lipids, surfactant, drug, solid carrier and solubilization of the mixture before spray drying. The formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase evaporates and forming dry particles under controlled temperature and airflow condition. The product particles can be further prepared into tablets or capsules dosage forms.[60] This technique has some advantage which includes very rapid spray drying process such that it has high precision control over particle sizes, bulk density, crystallinity, organic volatile impurities, and residual solvents; and quality of the powder remains constant during the entire processes of drying with the production of uniformly sized-spherical particles. In contrast, it uses very bulky equipment with high cost and the overall thermal efficiency is low.[61]
- **Supercritical fluid based method:** In supercritical fluid-based methods, lipids may be used either for coating of drug particles or for producing solid dispersions. The coating process is later on enhanced by a gradual reduction in pressure and temperature leading to reduced solubility of the coating material in the supercritical fluid allowing gradual deposition onto the drug particles, to form coating layers. The supercritical carbon dioxide is the supercritical fluid of choice. The process for obtaining solid particles, the dissolving drug and lipid-based excipients in an organic solvent such as methanol and then in supercritical fluid followed by lowering the temperature requires skillfulness. The solubility of the formulation components in the supercritical fluids and integrity or stability of the active substance under the process conditions are two important considerations with the formulation technique.[62]

Dosage forms of SEOFs

Different dosage forms of commercial products of SEOFs are in existence. These are marketed by different Pharmaceutical Companies with different brand names as shown in Table 4.

- **Sustained-release microspheres with self-emulsifying:** The formulation containing zedoary turmeric oil (ZTO) was prepared by the quasi-emulsion-solvent-diffusion method. This formulation possesses many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing the intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. The bioavailability improved to up to 135.6 % as compared to the conventional drug.[63]
- **Novel gelled sustained release self-emulsifying oil formulation system:** This was formulated by the preparation of ketoprofen using Captex 200, Tween 80 and Capmul MCM. Silicon dioxide as a gelling agent, which may aid in solidification and retardation of drug release. A Prepared formulation of SE controlled release formulation has been reported to enhance the rate of drug release.[64]
- **Novel self-emulsifying controlled floating drug delivery system:** This has been formulated with tetrahydro curcumin (THC) using silicon as an adsorbent. The release rate and extent of release of THC liquid SEOFs was 80 % within 2 h and self-emulsifying floating pellet formulation released 80 % within 8 h which was significantly higher than that of unformulated THC only 30 % within 8 h.[48]
- **Self-emulsifying solid dispersions:** Solid dispersions enhances dissolution rate and bioavailability of poorly water-soluble drugs but still have some stability limitations which could be solved by SE of the formulation.
- **Oculars and pulmonary delivery:** In the treatment of ocular diseases, drugs are essentially delivered topically. Oil in water (o/w) microemulsions has been investigated for ocular administration, to dissolve poorly soluble drugs with increase absorption and prolong release profile through SEOFs.
- **Parenteral delivery:** With conventional parenteral administration of drugs, limited solubility is a major problem in formulation industry because of the extremely low amount of drug actually delivered to the target site can be delivered by SEOFs.[65]
- **Topical delivery:** In the **t**opical administration of drugs by SEOFs there are some advantages over other methods for several reasons which include avoidance of hepatic first-pass metabolism of the drugs and related systemic side effects.

Table 4: Pharmaceutical product formulated as SEOFs.[45]

Brand Name	API	Dosage form	Company	Therapeutic activity
Neoral®	Cyclosporine A/I	Soft gelatin capsule	Novartis	Immune suppressant
Norvir®	Ritonavir	Soft gelatin capsule	Abbott Laboratories	HIV antiviral
Fortovase®	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche inc.	HIV antiviral
Agenerase®	Amprenavir	Soft gelatin capsule	Glaxo Smithkline	HIV antiviral
Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Lipirex®	Fenofibrate	Hard gelatin capsule	Genus	Antihyper-lipoproteinemic
Sandimmune®	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immuno suppressant
Targretin®	Bexarotene	Soft gelatin capsule	Ligand	Antineoplastic
Rocaltrol®	Calcitriol	Soft gelatin capsule	Roche	Calcium regulator
Gengraf®	Cyclosporine A/III	Hard gelatin capsule	Abbott Laboratories	Immuno suppressnat

Evaluation and Characterization of SEOFs

The principal means of self-emulsification assessment is a visual evaluation. The efficiency of self-emulsification could be approximated by determining the rate of emulsification, droplet-size distribution, and turbidity measurements.

- **Visual assessment:** This may provide necessary information about the self-emulsifying and micro emulsifying property of the mixture and dispersion formed.
- **Turbidity Measurement:** This determines efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.
- **Droplet Size:** This is a crucial factor in self-emulsification performance as it determines the rate and extent of drug release and also the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size. The reduction of the droplet size to values below 50 µm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions.
- **Zeta Potential Measurement:** This test identifies the charges of the droplets. In conventional SEDDSs, the charge on an oil droplet is usually negative due to the presence of free fatty acids.
- **Dispersibility test:** The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP XXII dissolution apparatus II. Where a 1 ml of each formulation was added to 500 ml of water or suitable dispersion medium at 37 ± 5 °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The *in vitro* performance of the formulation is visually assessed using the following grading system.[66]

Grade A: Rapidly forming (within 1 min) Nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish-white appearance.

Grade C: Fine milky emulsion that formed within 2 min

Grade D: Dull, grayish white emulsion having a slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globule present on the surface.

Where grade A and B formulations remain nanoemulsion when dispersed in GIT and grade C could be recommended for SMEDDS formulation as presented in Fig. 4. [18, 67]

- **Drug content**: Appropriate amount of the drug from the SEOFs is measured out and dissolved in a suitable solvent. The drug content in the suitable solvent was analyzed by a suitable analytical method against the standard solvent solution of drug using a spectrophotometric method [18] or HPLC.
- **Electro-conductivity study:** The SEOFs includes an ionic or nonionic surfactant, oil, and water. Therefore, the electroconductivity test is used to measure the electroconductivity using electro conductometer.[68]
- **Thermodynamic stability studies:**

  Refrigeration cycle test: This study six cycles between refrigerator temperature 4 °C and 45 °C with storage at each temperature of not less than 48 h. The formulations, that are stable at these temperatures, are chosen and subjected to centrifugation test.

  Centrifugation test: Those formulations that are stable after refrigeration cycle test are centrifuged thaw cycles between 21 °C and 25 °C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min.

. **Refractive index and percentage transmittance:** Refractive index and percent transmittance confirm the transparency of formulation. A refractometer is used to measure the refractive index of the system by placing a drop of solution on the slide and then comparing with water. The percent transmittance of the system is obtained at a particular wavelength using UV-Spectrophotometer with distilled water as a blank. There is transparency in a formulation if the refractive index of the system is similar to that of water when formulations have percent transmittance > 99 %.

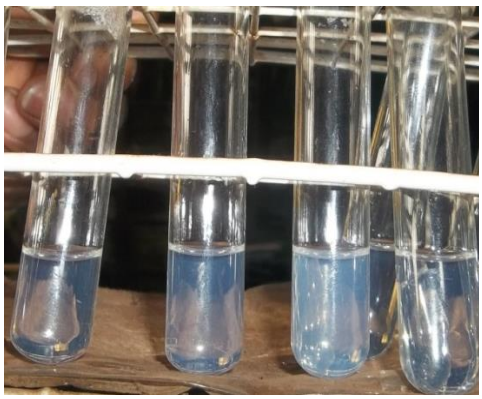

Figure 4: Representation of aqueous SMEDDS.[18]

Characterization of solid SEOFs:

- **Scanning electron microscopy:** The macroscopic structure of solid SEOFs can be observed using scanning electron microscope.
- **Differential scanning calorimetric (DSC)/X-ray diffraction:** Physical state of the drug in solid SEOFs is important to investigate as it may affect drug release and then bioavailability of the drug. The DSC method, as well as X-Ray diffraction, can be used for this purpose.[69]

- **Flow properties of solid SEOFs**: The flow properties can be determined by the angle of repose, Carr's index and Hausner's ratio, Bulk and tapped density.
- ***In vitro* drug release from solid** SEOFs**:** An *in vitro* dissolution determines drug release of solid SEOFs formulations. USP-II type dissolution apparatus containing appropriate dissolution medium is used for carrying out the drug release studies.[69]

CONCLUSION

From the above review, conclusions are drawn that SEOFs is one of the promising techniques for the formulation of poorly aqueous soluble drugs although there are some challenges facing the formulation which has been addressed by the development of newer techniques such as saturable SEOFs and solid SEOFs, etc. These current trends prevent *in vivo* precipitation, thereby improving solubility, stability, dissolution, absorption, and bioavailability of poorly aqueous soluble drugs.

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Source of Support: Nil, **Conflict of Interest:** None.