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Orally administered self-emulsifying drug delivery system in disease management: Advancement and patents

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Abstract

Introduction: Oral administration of a drug is the most common, ideal and preferred route of administration. The main problem of oral drug formulations is their low bioavailability arises from poor aqueous solubility of drug. Aqueous solubility of lipophilic drugs can be improved by various techniques like salt formation, complexation, addition of co-solvent etc. but self-emulsifying drug delivery system (SEDDS) is getting more attention for increasing the solubility of such drugs. The SEDDS is an isotropic mixture of drug, lipids, and emulsifiers, usually with one or more hydrophilic co-solvents/co-emulsifiers. This system is having ability to generate oil-in-water (o/w) emulsions or microemulsions upon gentle agitation followed by dilution with aqueous phase. The SEDDSs are relatively newer, lipid-based technological innovations possessing unparalleled potential in improving oral bioavailability of poorly water-soluble drugs.

Areas covered: This review provides updated information regarding the types of SEDDS, their preparation techniques, drug delivery and related recent patents along with marketed formulations.

Expert opinion: The SEDDS has been explored for improving bioavailability, rising intra-subject heterogeneity and increasing solubility. SEDDS offers the benefit of a protective effect against the hostile environment in the gut. The unique fabrication techniques provide specific strategy to overcome the low bioavailability and poor solubility problems.

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Article highlights

- Conceptually self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipids, and emulsifiers, usually with one or more hydrophilic co-solvents/co-emulsifiers.
- The SEDDS possess a great potential in oral bioavailability enhancement of poorly water-soluble drugs.
- 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.
- Drug solubility plays a pivotal role in the selection of excipients in SEDDS formulation.
- SEDDS are proving themselves as promising nanocarriers for the efficient drug delivery.

1. Introduction

Around 50% of the novel drug entity has low aqueous solubility and is facing a drug delivery obstacle. Dissolution is the rate-limiting step for less soluble drugs, hence a small increase in dissolution rate sometimes leads to increase in the bioavailability. Formulation performance depends on the rate and extent of the drugs belonging to the Biopharmaceutical Classification System (BCS) Class II [1]. Self-emulsifying drug delivery system (SEDDS) is a lipid-based formulation and an isotropic mixture of surfactants, oil phase, co-solvents and drug that form a milky emulsion with a submicrometric droplet size following mild agitation in water or gastrointestinal fluid [2]. The small globules produced increase the interfacial area allowing for a quicker release of drugs, which can increase the intestinal permeability of a number of drugs by stimulating lymphatic transport and bypassing the metabolism of the first step, thus improving drug bioavailability [2]. The SEDDS typically produces emulsion with a droplet size above 300 nm, however it may be vary from coarse to micron size while self-microemulsifying drug delivery system (SMEDDS) forms transparent microemulsions with a droplet size of 100-250 nm. The self-nanoemulsifying drug delivery system (SNEDDS) contains nanoemulsion with low quantity of surfactants with droplet size below 100 nm. These are physically

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stable formulations as compared to the emulsions, which are sensitive and metastable dispersed forms. Thus, for lipophilic drug exhibiting dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles [3-8]. The prime distinguished features of SEDDS, SMEDDS and SNEDDS are enlisted in **Table 1**.

Different fabrication techniques, types, characterization process and biomedical applications of SEDDS are depicted in Ishikawa fishbone diagram [Figure 1]. The SEDDS shows some merits and demerits over the conventional drug delivery system, which are elaborated in Figure 2 [9-11].

The SEDDSs are relatively newer, lipid-based technological innovations possessing unparalleled potential in improving oral bioavailability of poorly water-soluble drugs. These formulations have been shown to reduce the slow and incomplete dissolution of a drug, facilitate the formation of its solubilized phase, increase the extent of its transportation via the intestinal lymphatic system, and bypass the P-gp efflux, thereby augmenting drug absorption from the GI tract. The SEDDSs is one of the commercially feasible techniques and several products have been filed as new drug application (NDA) and abbreviated new drug application (ANDA). The commercially available SEDDS formulations include Sandimmune®, Neora® (Novartis Pharmaceuticals Corporation); Gengraf®, Norvir®, Depakene® (AbbVie Inc.); Fortovase®, Rocaltrol®, Vesanoid®, Accutane® (Roche Laboratories Inc.); Agenerase® (GlaxoSmithKline); Targretin® (Ligand Pharmaceuticals/ Eisai Ltd.); and Aptivus® (Boehringer Ingelheim Pharmaceuticals, Inc.). In totality, the present review furnishes an updated compilation of wide-ranging information on various requisite vistas of the self-emulsifying formulations, thus paving the way for accelerated progress into the SEDDS application in pharmaceutical research.

2. Composition of SEDDS

2.1. Surfactants

It is one of the essential components in the formulation, as they promote the emulsification properties. Surfactants, being amphiphilic in nature, can dissolve (or solubilize) relatively high amounts of hydrophobic drug compounds. The type and concentration of the surfactant showing effect on droplet size of micro- or nano-emulsions. Therefore, two important factors are hydrophilic-lipophilic balance (HLB) value and concentration of the surfactants [12]. The frequently utilized emulsifiers

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include Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), Sorbitan mono oleate (Span 80), Polyoxy-40-hydrogenated castor oil (Cremophor RH40), and Polyoxyethylated glycerides (Labrafil M 2125 Cs). In selection of a surfactant, safety is an important factor. Synthetic surfactants are considered to be less safe than the emulsifiers, which are obtained from natural origin. Moreover, these surfactants have a limited capacity for self-emulsification. Emulsifiers from natural sources are seldom employed for the formulation of SEDDS. Ionic surfactants are shown to be more harmful than non-ionic surfactants but may induce reversible improvements in intestinal lumen permeability. Normally, to form stable formulations, the surfactant concentration varies from 30-60% w/w [13].

2.2. Oils

The oil serves as among the most essential excipients in SEDDS formulation, as it not only solubilizes the required amount of lipophilic material or promotes self-emulsification, but also improves the fraction of lipophilic drug transferred through the intestinal lymph system. It also improves secretion from the gastrointestinal tract (GIT) based on the molecular properties of the triglyceride [14]. Medium and long and chain triglyceride (MCT and LCT) oils of varying degrees of saturation have been used for the fabrication of self-emulsifying preparations [15]. Mostly the unmodified and raw forms of edible oils provide base as lipid vehicles, but the significant challenges are faced when it fails to dissolve large amounts of lipophilic drugs. Hydrolyzed or modified vegetable oils have made a significant contribution to the application of the systems. In the existence of a significant amount of non-ionic surfactants, such excipients produce good emulsification systems that are approved for oral administration [16, 17].

Most of the mono-, di-, and triglycerides and their mixtures in varying proportions, with or without the fatty acid esters of propylene glycol, are available commercially in the purified form. Both unsaturated and saturated fatty acids have been widely employed in the formulation of lipidic systems. However, the SEDDS in particular are comprised of saturated fatty acids such as caproic, caprylic, capric, lauric, and myristic acid. One can make the appropriate choice of these by examining their composition, potential utilities, physical state, and hydrophilic-lipophilic balance (HLB) [13].

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2.3. Co-solvents

Relatively high concentrations (usually greater than 30% w/w) of surfactants are required for the development of optimum SEDDS, therefore the concentration of the surfactant may be decreased by the addition of the co-surfactant. This reduces the surface tension and creates a mixed micelle along with a surfactant, which gives more surface area. Also, it keeps the spontaneity of self-emulsification process. Ethanol, propylene glycol (PG) and polyethylene glycol (PEG) are few such examples [18].

Various studies on different kind of SEDDS along with their compositional account and outcome have been summarized in **Table 2**. The inclusion criteria of these studies are similarity in type of surfactant, co-surfactant used and dissimilarity in the type of developed formulations and in their applications. Katla and Veerabrahma developed losartan containing solid self-emulsifying drug delivery system (S-SEDDS) and altered it into liquid self-emulsifying drug delivery system (L-SEDDS). It was observed that L-SEDDS exhibited better self-emulsification efficiency and thermodynamic stability. The *in vivo* study has confirmed the enhancement of oral bioavailability by 2.82 folds. The SEDDS showed stability for three months at room temperature [19].

Zupancic et al. prepared various SEDDS formulations including no lipids (NL-SEDDS), short chain lipids (SC-SEDDS), medium chain lipids (MC-SEDDS), long chain lipids (LC-SEDDS) containing enoxaperin, a low molecular weight heperin (LMWH). The formulations were evaluated for drug release and mucous permeability. The MC-SEDDS and NL-SEDDS revealed good mucous permeability. The MC-SEDDS degraded in presence of pancreatic lipase whereas NL-SEDDS within 90 min showed good stability. The bioavailability of enoxaparin was found to be enhanced by 2-fold [20].

In another study, Zupancic et al. developed daptomycin (lipopeptide) containing SEDDS and performed in vitro digestion, permeability and enzyme degradation studies. The optimal formulation was found to be hydrolyzed within 90 min by lipase and showed better mucous permeation along with protection by α-chymotrypsin. The formulation demonstrated sustained drug release for not less than six hours. The study revealed that the payload of daptomycin has been enhanced by 5-folds. Moreover, the result showed that SEDDS comprising 8% drug complex might be tested as a potential oral drug delivery device [21].

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Sandhu et al. developed tamoxifen (TMX) and neringenin (NG) containing SNEDDS formulation (TMX-NG-SNEDDS) for the treatment of breast cancer. Different combination of SNEDDS were prepared and evaluated by cell line study, drug release, pharmacokinetic study, and *in vivo* antitumor activity. The authors reported that the formulation showed good micelle forming capacity, drug release within 30 min and reduced percent of tumor burden [22].

Lee et al developed thirteen formulations of 5α-reductase inhibitor, dutasteride (DTS) loaded supersaturable-SEDDS (SS-SEDDS) for improving the oral absorption of DTS. A polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, Soluplus® (precipitation inhibitor) was employed to develop SS-SEDDS by selecting DTS: SEDDS vehicle:Soluplus® in 1:67.6:10 w/v/w proportion. Under *in vivo* study, the SS-SEDDS preparation displayed 3.9- and 1.3-folds higher area under the curve (AUC) values in comparison to the drug suspension and SEDDS, respectively. The maximum plasma concentration of SS-SEDDS was found to be 2.0- and 5.6-fold greater than SEDDS and drug suspension, respectively. High absorption of drug, pH dependent dissolution of formulation and 3.9-fold enhancement of bioavailability as compared to drug suspension was observed. The outcome suggested that the SS-SEDDS might be an effective tool to enhance the physicochemical property and oral absorption of 5α-reductase inhibitor [23]

3. Method of preparation of SEDDS

3.1. High pressure homogenizer

Nano-formulation is prepared under high pressure. The formation of fine emulsion depends upon the high shear stress applied. The droplet size can be explained by two theories i.e., cavitation and turbulence. This method can produce nanoemulsion of droplet size smaller than 100 nm. The droplet size of nanoemulsions produced by high pressure homogenizers depend on sample composition, homogenizer type, and homogenizer operating conditions such as energy intensity, time, and temperature. High-pressure homogenization is widely used to form food, pharmaceutical, and biotechnological ingredient nanoemulsions [24, 25].

3.2. High energy approach

The high energy approach requires high mechanical energy by which mixture of components like oil, surfactants and co- solvent are mixed to form nanoemulsion.

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High energy methods are extensively used to formulate nanoemulsion [26]. High mechanical energy is used that provide strong disruptive forces, which break up large droplets to nano-sized droplets and produce nanoemulsions with high kinetic energy [27]. However, SNEDDS are based on the self-emulsification phenomenon and require low energy [28].

3.3. Micro-fluidization

The micro-fluidization method requires a device called Micro-Fluidizer. The positive displacement pump pushes the product to the interaction chamber. This system contains a small droplet channel known as micro channel. The obtained product was sent through the micro channels to the impingements area, which produces very fine droplets of nanoemulsion. The mixture of oil phase and aqueous phase gets into the homogenizer, which yield course emulsion. It is further processed and forms homogeneous, stable, transparent nanoemulsion.

3.4. Sonication method

The sonication method is the very useful method for the preparation of the SNEDDS. Ultrasonication is better than other high energy methods in terms of operation and cleaning. In ultrasonic emulsifications, ultrasonic waves provide cavitation forces that break the macroemulsion to nanoemulsion [29]. By using this method, the droplet size of the emulsion decreases and a nano-sized emulsion is obtained. The droplet size is reduced by the sonication mechanism [30].

4. Evaluation techniques of SEDDS

4.1. Droplet size analysis

The surfactant nature and concentration determine the size of the droplet [31]. Droplet size is critical and possesses key importance for self-emulsification as it determines the rate and extent of drug release followed by absorption. Low dilutions are preferred for accurate droplet size evaluation. However, Photon correlation spectroscopy is helpful for determining the droplet size of the emulsion, especially, when the properties of the emulsion do not change upon infinite aqueous dilution [32, 33].

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4.2. Emulsification time and Dispersibility test

The rate of self-emulsification is usually determined by keeping self-emulsifying formulations (pre-concentrate) in a capsule and it to a sufficient amount of water or bio-relevant media. The rate of dispersion is determined by visually. Light microscopy is used to observe the process of self-emulsification. The USP XXII dissolution apparatus can be used for determining the efficiency of oral nanoemulsion or microemulsion. In this case, sample formulation (1 mL) is mixed with water (500 mL) at temperature of 37±1°C. For continuous agitation stainless steel dissolution paddle has been utilized with the stirring speed 100 rpm and the time is noted for the emulsion formation. The precipitation and the phase separation of resultant mixture are checked at different time intervals (2, 4, 6, 8, 12, 24 hrs). Grading system, used for evaluating the *in vitro* performance [34] is given below:

Grade A: Rapidly forming nanoemulsion, which takes time less than 1 min and gives bluish colored clear solution.

Grade B: Rapidly develop a nanoemulsion with a bluish-white color.

Grade C: Develop fine milky nanoemulsion within 2 min.

Grade D: Formation of dull, grayish colored emulsion with oily appearance that emulsifies gradually and requires more than 2 min.

Grade E: Weak emulsification resulting in large oil globules on the surface.

The time for emulsification at room temperature is indicated as self-emulsification time for the formulation. Pouton et al. analyzed the emulsification capacity of the different compositions of the Tween 85 and MCT systems via a rotating paddle to facilitate emulsification in a crude nephelometer. It assisted in the measurement of the time taken for emulsification. Once the emulsification was complete, photon correlation spectroscopy (also known as quasi-elastic light scattering or dynamic light scattering) technique was used for particle sizing. The self-emulsified systems were compared with that of homogenized systems. Light microscopy technique was used to observe the self-emulsification process [35].

4.3. Test for transmittance/turbidity measurement

Turbidimeters are used to establish, whether the dispersion attains equilibrium quickly and in a reliable time frame [36]. Orbeco-Helle turbidity meter and Hach turbidity meter have been used frequently [37, 38]. A dissolution apparatus is connected to the turbidity meter. At every 15 sec, optical clarity is observed to

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determine clarity of micro or nanoemulsion formed. Turbidity can also be measured in terms of spectroscopic characterization of optical clarity by taking the absorbance of suitably diluted aqueous dispersion at 400 nm [39].

4.4. Transmission electron microscopy

The SNEDDS sample was introduced inside TEM for visual observation [40]. A drop of SNEDDS sample was kept on the copper grid and 1% w/v phosphotungistic acid solution was added on the grid and kept in room temperature for 5 min. The image was observed with the help of TEM at an accelerated voltage of 100 kV [41].

4.5. Liquefaction time

This study is performed to calculate time needed by solid SEDDS formulation to melt in vivo without agitation in simulated gastric fluid (SGF) [42]. The formulation is wrapped in a transparent polyethylene film and attached to a thermometer bulb, which is dipped in a round bottom flask filled with SGF without pepsin maintained at 37±1^{o}C.

4.6. Dynamic dispersion study

This study is used to determine if drug was precipitated during dispersion, and if so, what proportion of the dose was precipitated and at what rate [43]. Mohsin et al. performed a dispersion study by dissolving fenofibrate in each SEDDS/SNEDDS at 80% saturation level based on its equilibrium solubility studies in the relevant anhydrous formulation. One gram of each formulation was dropped into 100 mL of water in a glass jar and kept in a dry heat incubator at 37°C for 24 h. During this 24 h period, 1 mL of the dispersed sample from each container was withdrawn periodically (0-24 h) and centrifuged at 2,500× g. A 100 µL aliquot of the resulting clear supernatant was assayed by the UHPLC method. The dispersion studies confirmed that the mixed glycerides can retain a high percentage of drugs in solution for 24 h in the intestinal media [44].

4.7. Lipolysis test

In vitro lipolysis model for lipid digestion have been increasingly used as tools to assist in the design of self-emulsifying lipid-based formulations to enhance the oral bioavailability of poorly water-soluble drugs. During *in vitro* lipolysis studies, the data

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generated from the pH-stat can be used to quantify the rate and extent of lipolysis, and more importantly, the products of lipolysis can be examined after completion of the reaction, to determine the fate of the drug; whether it is solubilized or precipitated [45].

5. Types of SEDDS in drug delivery

5.1. Self-emulsifying capsules

The basic form of SEDDS is liquid and can be encapsulated in soft/hard gelatin capsules. After the administration of capsules containing conventional liquid self-emulsifying (SE) preparations, the droplets of microemulsion have been formed and dispersed in the GIT and reached to the site of absorption. If microemulsion shows irreversible phase separation, then there will be no improvement in drug absorption. For managing this problem, sodium dodecyl sulfate has been added to the SE formulation. This helped in creating and sustaining the supersaturated form under *in vivo* condition. Such formulations contain less surfactant; hence reduce any side effects on GIT [46].

5.2. Solid SEDDS

The SEDDS are generally designed in the liquid state, so it has to be administered by soft gelatin capsules, which leads to greater manufacturing costs, lesser portability, lower drug loading and poor stability. For overcoming these problems solid SEDDS(S-SEDDS) has been developed, which shows greater advantages over conventional SEDDS *i.e.* enhancement of solubility, bioavailability, reduced production cost, improved stability and patient complains. For the fabrication of S-SEDDS, liquid or semisolid ingredients are incorporated into powders by various solidification methods like melt extrusion, melt granulation, nanoparticle technology and spray drying. Other techniques can also be employed for the development of S-SEDDS such as adsorption of liquid formulation onto the solid carriers like colloidal silica, hydroxypropyl methyl cellulose (HPMC) and microcrystalline cellulose (MCC) [47-52].

5.3. Self-emulsifying controlled/sustained-release pellets

Pellets are more advantageous then other conventional solid dosage forms. These are easy to fabricate, lower GI irritations, intra- and inter-subject variability in plasma

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profile. Glyceryl benzoate and glyceryl palmito stearate are mostly preferred for the development of sustained release pellets e.g. SE nitrendipine pellets and progesterone pellets [53].

5.4. Dry emulsion

It is mostly oil in a water emulsion converted into solid by various methods like carrier adsorption, spray drying and freeze drying. Before use, dry emulsions are dispersed in water. Emulsification of these powders occurs when it gets exposed to an aqueous media. The use of toxic organic solvents can be avoided by this technology and it also removes the stability issues related to contamination by microbes, phase separation and creaming. For developing these types of formulations, MCTs are mostly used as non-aqueous phase [54, 55].

5.5. Self-emulsifying suppositories

The SE-Suppositories not only increase the GI adsorption but also improve the vaginal and rectal absorption e.g. the indomethacin given orally does not achieve the therapeutic plasma concentration but by vaginal or rectal route it achieves satisfactory therapeutic level [56].

5.6. Self-emulsifying beads

In the development of this system, the number of excipients used was very less. Solvent evaporation method was mostly used for depositing the SE system onto the microporous polystyrene beads, which consist of complex internal void structures and prepared by copolymerization of divinyl benzene and monomer, styrene. These were found to be chemically inert, biocompatible and stable over a broad range of temperature, pH and humidity [57].

5.7. Self-emulsifying nanoparticles

Nanoparticles (NPs) can be prepared by various methods including sonication method and solvent injection method. In later technique [58], the molten lipid, drug and surfactant are injected drop wise to the non-solvent system. After this, larger particles were separated by filtration and the remaining filtrate is dried up to obtain the NPs [59].

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6. Biomedical applications of SEDDS

Since the earth evolution, naturally occurring compounds are a great source of medicinal principles. These plant constituents are facing many hurdles in their delivery in the body like low bioavailability, low solubility, and fast release. The SEDDS has attracted more consideration due to better oral bioavailability of drug allowing dose reduction and enhancing their physio-chemical features [60]. Some of the SEDDS mediated drugs with improved oral solubility and bioavailability discussed below and summarized in **Table 3**. The inclusion criteria of the mentioned studies are the drugs showing poor solubility, less bioavailability and used for different applications.

6.1. Anti-coagulant activity

Mundada and Sawant developed SMEDDS using P-glycoprotein (P-gp) modulator excipient to elevate the systemic availability of dabigatran etexilate (DE). Researchers have taken Transcutol HP as co-surfactant, Cremophor EL as surfactant and Capmul MCM C8 as oil phase for the fabrication of SMEDDS. On the basis of MTT assay on Coco-2 cells, the DE-SMEDDS was found to be non-cytotoxic and safe. In addition, the $AUC_{0\rightarrow t}$ of DE from DE-SMEDDS formulation showed 2.5 times higher and relative bioavailability was improved by 3.36 times more than that from drug suspension on oral administration to rats. The DE-SMEDDS demonstrated higher anticoagulant activity than product suspension [61].

6.2. Antimicrobial activity

Jalil et al. fabricated a SEDDS system containing monododecylamide-EDTA (alkyl-EDTA) and chlorhexidine (CX), which shows enhancement of antimicrobial properties. SEDDS comprising of Tween 80 (17%), Captex 300 (20%), DMSO (18%), and Cremophor EL (45%) were incorporated with alkyl-EDTA (F_A) (3% m/v). Further, formulations have been developed by selecting 1% m/v CX (F_A-CX1%) and 1.5% m/v alkyl-EDTA (F_A-ED1.5%) individually and in combination (F_A-CX1% andF_A-ED1.5%). The biocompatibility of SEDDS was evaluated by Resazurin assay. More than 85% cells were found to be viable after 4 hr. Antimicrobial properties were analyzed by *Escherichia coli* model. The outcomes of this study revealed that combination of (F_A-CX1% and F_A-ED1.5%) demonstrated 34.3- and 12.9-fold improved antimicrobial effect as compared to the 1% of F_A-CX and 1.5% of F_A-ED,

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respectively. The researchers concluded that combination of F_A-CX1% and F_A-ED1.5% in SEDDS system improved the antimicrobial activity [62].

Zaichik et al formulated vancomycin loaded SMEDDS with enhanced intestinal mucosa permeating properties and increased absorption of orally administered drug by enhancing the drug lipophilicity via HIP with cetyltrimethylammonium bromide. The formulation exhibited better (4-8-fold) ability to permeate porcine intestinal mucosal barrier. HIP with SEDDS is found to be promising for oral antibiotic delivery [63].

Zaichik et al developed ciprofloxacin, a fluoroquinolone antibiotic loaded SEDDS for revealing antimicrobial activity and extremely mucus permeating properties through *in vitro* models. Furthermore, the antimicrobial activity of formulation (F11-ciprofloxacin)containing 10% oleic acid as lipid phase, 20% Labrasol, 30% Labrafil M1944 CS, 25%Cremophore EL as surfactants, and 15% Transcutol as co-surfactant against *S. aureus* was found to be higher in contrast of free drug. The outcome of the study suggested that SEDDS formulations might be considered as an effective delivery system for treating pulmonary infections convoyed by mucus dysfunction [64].

6.3. Antihyperlipidemic activity

Ahsan et al. fabricated S-SNEDDS of rosuvastatin for increasing the in vitro drug release and analyzed its anti-hyperlipidemic activity. After 14thday of treatment the results of antihyperlipidemic study showed that cholesterol level was found to be decreased to 33.47% followed by atherogenic index 81.28% and triglycerides 40.77%, however high-density lipoprotein (HDL) was increased to 118.43% [65].

6.4. Antioxidant activity

The SS-SMEDDS were developed by Zheng et al to increase the solubility of ellagic acid. The *in vivo* and *in vitro* antioxidant activity of SS-SMEDDS loaded with ellagic acid have been found considerably higher than that of pure ellagic acid at the same concentration [66].

Balakrishnan et al composed SEDDS for oral administration of a lipophilic drug, Coenzyme Q_{10} (CoQ_{10}) to improve its bioavailability and solubility. The optimized SEDDS formulation consisting of 25% v/v Labrafil M 1944 CS, 65% v/v Labrasol and 10% v/v Capryol 90 and exhibited least mean droplet size of 240 nm.

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The SEDDS formulation has significantly improved the C_{max} and AUC of CoQ_{10} than powder form ($P < 0.05$). Thus, SEDDS can be a potential oral dosage form for increasing the bioavailability of CoQ_{10} [67].

Mamadou et al formulated and studied the capability of SEDDS to increase permeation of resveratrol across the intestine of rat and control its pre-systemic metabolism. Jejunal absorptive transepithelial fluxes (J_{ms}) and pre-systemic metabolization of resveratrol released from semisolid and L-SEDDS formulations were analyzed. The absorptive fluxes from the semisolid nanoemulsions and liquid nanoemulsion were found to be 20.5±3.1 and 28.9±2.9 μg $h^{-1}cm^{-2}$, respectively. These fluxes were found to be improved as compared to an ethanolic control solution (J_{ms} = 3.4±0.3 μg h^{-1} cm^{-2}; $p<0.05$). The results revealed that o/w nanoemulsion with medium-chain lipids could be a possible preparation for improved oral delivery of resveratrol [68].

6.5. Anticancer activity

The SEDDS have been broadly employed for chemotherapeutic agents to improve their oral bioavailability. **Table 4** enlists the different types of anticancer drugs/active constituents and their pharmacokinetic effects [69-76].

Cadete et al. used a self-emulsification process for formulating docetaxel (DTX)-loaded nanocapsules of hyaluronic acid (HA) without the use of heat and organic solvent. Researchers used A549 lung cancer cells for *in vitro* studies and found effective intracellular delivery of DTX, whereas the blank nanocapsules showed a very low cytotoxicity [77].

Timur and co-workers fabricated doxorubicin (DOX) and LyP-1 peptide containing SMEDDS for evaluating their efficacy in breast cancer. The result showed significantly enhanced in vitro cytotoxicity in p32-expressing breast cancer cells (MDA-MB-231 and 4T1), however, metastasis and tumor growth were significantly reduced on intraperitoneal administration of DOX-LyP-1 SMEDDS [78].

6.6. Chronic heart failure

Jiang et al prepared and analyzed SEDDS to determine the improved preventive activity of curcuminoids on chronic heart failure in rats. Different pathological changes were analyzed in model (coronary artery ligation) group comparative to sham group. After treatment using curcuminoids SEDDS or

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suspension, these changes were inverted related to model group. In the meantime, the SEDDS (ameliorative effect) based curcuminoids was evidently well in its activity than curcuminoids suspension as witnessed by pharmacodynamic studies [79].

6.7. Antifungal activity

Kontogiannidou et al fabricated Amphotericin B (AmB) containing N-trimethyl chitosan chloride (TMC) based SNEDDS and analyzed its transportation ability through GIT. Application of this developed formulation in intestinal epithelium (Caco-2 monolayer) demonstrated its ability to promote the temporary opening of tight junction, duly assisted by TMC. The outcomes of this study suggested that combination of SNEEDS and TMC enhanced the permeation ability to enable oral delivery of AmB [80].

Alhakamy et al formulated Bifonazole (BF)-loaded SNEDDS (BF-SNEDDS) using the mixture design and analyzed the antifungal activity against *Candida albicans*. Researchers found 26±3 mm of zone of inhibition, which indicated enhanced the antifungal activity. So SNEDDS can be used as a promising system for transdermal delivery of BF [81].

Elbahwy et al developed mucoadhesive SEDDS with extended ocular residence time of poorly water-soluble drug, Econazole. The droplet size of SEDDS was found to be<100 nm with polydispersity index <0.3. The SEDDS formulation revealed 2.5-fold greater mucoadhesive activity than plain SEDDS and sustained drug release for 8 hr without noticeable corneal adverse effect in 0.5% m/v concentration. Thus, the formulated mucoadhesive SEDDS was suggested as an effective ocular delivery system for lipophilic drug [82].

6.8. Antidiabetic activity

Agarwal and co-workers developed SMEDDS using extract of *Lagerstroemia speciose* (SEL) leaves (SEL-SMEDDS) and evaluated its pharmacodynamic performance as antidiabetic activity. At 50 mg/kg dose, the SEL-SMEDDS formulation demonstrated a higher reduction in blood glucose level (BGL) as compared to the plain SEL formulation, however, this reduction was found to be more significant at dose of 100 mg/kg on 15th day of study [83].

El-Bagory and co-workers prepared dapagliflozin loaded SNEDDS and converted it into S-SNEDDS using Avicel pH-101as a biocompatible adsorbent. In

diabetic albino rats, the researchers found higher hypoglycemic activity of dapagliflozin containing S-SNEDDS and SNEDDS as compared to the plain drug. This study proposed that S-SNEDDS could serve as an efficient nanovehicle for the oral delivery of dapagliflozin for improved diabetes mellitus management [84].

In another study Agrawal et al developed L-SEDDS of glipizide and converted into S-SEDDS with adsorbent, Syloid® 244 FP. The optimized formulation of L-SEDDS comprised of phosphatidylcholine, Transcutol P and Tween 80. The BGL has been effectively regulated using S-SEDDS as compared to the pure drug *in vivo* [85].

6.9. Hepatoprotective activity

Ogino et al employed SS-SEDDSto increase the nutraceutical characteristics of ginger extract (GE). The SEDDS of GE comprised of glycerin, lysolecithin and MCT. The formulations enhanced the dissolution property of GE by creating fine micelles of 110 nm size. On oral administration of GE, the relative bioavailability of 8-gingerol and 6-gingerol in SS-SEDDS/GE-treated rat group was found to be 3-fold greater than GE-treated group. The frequent oral administration of SS-SEDDS/GE in dose of 100 mgGE/kg showed hepatoprotective action in carbon tetrachloride-induced hepatotoxicity in rat [86].

6.10. Benign prostatic hyperplasia

Alhakamy et al. formulated SNEDDS formulation by taking tadalafil (TDL) as drug andpumpkin seed oil (PSO). The zeta potential and average globule size of TDL-PSO were found to be7.86 ± 1.21 mV and 204.8 ± 18.76 nm, respectively. TDL-PSO showed reduced prostate index (36.71%) and prostate weight (35.51%) as compared to that of the testosterone. As per pharmacodynamic study the concentration of TDL increased 2.3-fold in TDL-PSO system in contrast to the plain TDL. The outcomes of this study concluded that TDL-PSO SNEDDS could enhance the effectiveness of TDL in benign prostatic hyperplasia management [87].

6.11. Hypertension

Prajapat et al fabricated SMEDDS for a BCS class II drug, nimodipine. Firstly, L-SMEDDS was fabricated by employing simplex lattice matrix design then the optimized formulation was converted into S-SMEDDS using different adsorbents.

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The pharmacodynamic study revealed that optimized S-SMEDDS decreased the blood pressure (BP) in rats [88].

6.12. Cardiovascular activity

Yadava et al developed a stabilized hydrogel system comprising of SEDDS to enhance the bioavailability of HMG CoA reductase inhibitor, lovastatin. The AUC_{0-5} of formulated hydrogel was found as 2.27-fold greater than free drug. Furthermore, the maximum concentration (C_{max}) was increased around 1.42-fold [89].

7. Marketed approaches of SEDDS

Figure 3 presents some of the SEDDS products available in the market. It is obvious that the SEDDS is a commercially viable system for BCS Class II and IV drugs [90].

8. Patent perspective of SEDDS: Recent updates

Various methods have been developed or patented for the fabrication of drug or therapeutics containing SEDDS. A description of the SEDDS related patents has been presented in **Table 5** especially for the period of 1999-2020 [91-130].

Wang et al 2020 invented a fabrication method for self-microemulsionof β-elemene. Proposed fabrication method has utilized3-12 parts of β-elemene, 6 parts of ethyl oleate, 6-10 parts of a co-surfactant (PEG400 and/or 1, 2-propylene glycol), and 10-15 parts of a surfactant (polyoxyethylene 40 hydrogenated castor oil and/or Tween 80). Results have shown that ethyl oleate, polyoxyethylene 40 hydrogenated castor oil and 1, 2-propylene glycol have better compatibility and can be excellently dissolved as well as rapidly emulsified in different proportions. The emulsifying potential of Tween 80 is low, so polyoxyethylene 40 hydrogenated castor oil is used as a surfactant and PEG400 is selected as a co-surfactant [91].

Zhang et al 2020 developed a solid self-microencapsulated microcapsule, which uses combination of astaxanthin and quercetin so that the conventional single-carrying astaxanthin mechanism can be disrupted and quercetin can inhibit the external discharge effect of P-glycoprotein (P-gp) to the drug. This action of drug metabolizedCYP3A4 enzyme, inhibited P-gp and improved bioavailability. The findings of this invention concluded that proposed system can improve the stability, dissolution rate and bioavailability of the drug [92].

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Xue et al 2020 invented a self-emulsification system by using water-based epoxy resin as curing agent. Mentioned system contains amino silicone oil (1-10 parts), epoxy resin (20-30 parts),reaction auxiliary agent (0.01-5 parts), solvent (120-250 parts) and end-capping agent (1-10) parts. This system can provide outstanding curing efficiency on various water-based epoxy resins. Further, the epoxy resin film has reasonable durability including heat and chemical resistance, electrical insulation, and hydrophobicity [93].

Chen et al 2019 developed a type of injectable self-emulsifying drug emulsion and disclosed its fabrication process along with application. Mentioned system uses surfactants with high emulsibility and low dose so that it becomes less irritant to body tissue. The outcomes have revealed that if the pre-mixing liquor of emulsion is less than 40%, then the corresponding dosage type is oil-in-water (o/w) emulsion, however, if it is more than 65%, then the subsequent dosage form is water-in-oil (w/o) emulsion. The inventors have been claimed that drugs accounting 40-60% (ideally 50%) are appropriate for slow release and can help to attain higher stability [94].

Liu et al 2019 patented an invention of chlorogenic acid self-emulsifying composition and its application. Inventors prepared the composition by taking chlorogenic acid, a matrix material compound, emulsifier and oily phase and disclosed that for avoiding lamination or solidification, formulation should be placed at room temperature. Above composition could be administered as orally, percutaneously, nebulized inhalation system and mucosal delivery. The formulation was found effective for antiviral, antitumor and anti-inflammatory treatment [95].

Jung et al 2019 developed SMEDDS containing ticagrelor for enhancing the bioavailability by alleviating poor solubility and low intestinal permeability of ticagrelor. Furthermore, the composition of ticagrelor enhanced the efficacy of active components and reduced their amount [97].

Christopher et al 2019 disclosed SEDDs for oral administration of water-insoluble cannabinoids. This mentioned cannabinoid-loaded SEDDS preparation permitted the oral administration of cannabinoids to achieve their higher oral bioavailability to control or prevent a disease, condition or symptom of the disease [100].

Xiong et al 2018 patented a research of sanguisorbin containing SEDDS. Inventors prepared the formulation by taking large amount of sanguisorbin along with

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0.05-0.25% of oil phase, 0.45-0.65% of surfactant and 0.1-0.3% of co-surfactant. The goal of the discovery was to resolve the prior art deficiency in order to provide a kind of SE sanguisorbin drug. The inventors found significantly improved solubility and dissolution rate of sanguisorbin loaded SEDDS [104].

Zhang et al 2018 fabricated a kind of osthole SEDDS by taking 0.1-10% of osthole (an active ingredient isolated from extract of fruit cnidii, along with 5-45% of surfactant, 25-55% of oil phase and co-surfactant as an auxiliary material. The inventors found that osthole SMEDDS can attain 90% or more dissolution in 45 min as compared to osthole bulk pharmaceutical chemicals (less than 40% in 180min). The dissolubility of the product enhanced osthole infiltration and increased bio-use of ostholes in the human body [103].

Jianget al 2018 patented an invention of asarone encapsulated SEDDS. This system was made up of asarone, oil phase (10-70%), surfactant (30-80%) and co-surfactant (0-30%). The inventors claimed that above prepared system significantly enhanced the drug bioavailability, increased the stability and improved the drug-eluting rate [106].

Hustvedt et al 2017 patented a formulation containing fatty acid like eicosapentaenoic, docosahexaenoic acid etc., free fatty acid, antioxidants, and various surfactants. The pre-concentrates are able to form SEDDS, SNEDDS or SMEDDS in aqueous solution. It can be given in the form of tablet or capsule for the treatment of any health-related problem like visual function, cardiovascular function, insulin action, immune function etc [108].

Chow et al 2016 disclosed about the formulation containing mebendazole, a benzimidazole derivative, oil, surfactant, dipolar aprotic solvent and co-solvent prepared by micro-emulsion and co-solvency method. The formulation increased the bioavailability by improving the solubility and drug release by 130-fold as compared to unformulated suspension. The developed formulations demonstrated high efficacy in the treatment of hyper-proliferative diseases and cancer [110].

Nahat et al 2015 disclosed the pharmaceutical composition incorporating rhein or diacerein and other excipients. The invention claimed that 50 mg of diacerein was found to be bioequivalent to marketed product, Art 50®and reduced the side effect i.e. soft stool. The SS-SEDDS was prepared, which lowered the side effects of surfactant and resulted in reduction in gastrointestinal side effects [112].

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Liu et al 2014 developed SEDDS based novel delivery system, which composed of 1-65% butylphthalide and 10-65% other essential ingredients. Inventors claimed that with the increase in surfactant concentration, microemulsion was formed inside GIT. The SEDDS was first emulsified than dispersed throughout the GIT and resulted in lowering of mucosal irritation. Thus, the nano-or micro-sized particles crossed the membrane and oil droplets moved into the blood circulation leading to increase in bioavailability and stability of drug [115].

Khan et al 2014 disclosed about the eutectic SNEDDS formulation containing CoQ_{10}, essential oil, copolymers and co-surfactants. The semisolid formulation was developed and introduced inside the soft gelatin or hard gelatin capsule. It melted down at body temperature losing consistency from semisolid to liquid and dispersed to form nanosized droplets [116].

Legen et al 2013 developed SMEDDS with the help of polysorbate 80 to improve the solubility of poorly soluble substance. Further, it has overcome the problem related to the liquid or semisolid administration by delivering the substance in hard or soft gelatin capsule [117].

Lin et al 2012 prepared SMEDDS, which comprised of CoQ_{10},poorly soluble excipients like hydrophilic surfactant with HLB value more than 12, hydrophobic co-surfactant having HLB less than 8 and hydrophobic solvent with co-surfactant and surfactant. The ratio of hydrophilic surfactant to lipophilic co-surfactant was selected in the range from 30:1 to 3:1.Inventors demonstrated increased loading capacity, with improved stability up to 80 days and enhanced dissolution near to 100% [118].

Kohli et al 2011 fabricated SNEDDS containing curcumin. Precipitation of curcumin by surfactant is a common problem in curcumin-based formulations, however, this problem was not observed in case of developed SNEDDS. The formulation showed good loading capacity, enhanced bioavailability and better stability [119].

Holmerg et al 2010 prepared a formulation having nitrogen oxide (NO) releasing non-steroidal anti-inflammatory drug (NSAID), phospholipids, surfactants, semisolid fat or oil and short chain alcohol. The formulation was in pre-concentrate form, which could be enclosed in capsules, lozenges or chewable pills at the time of administration. On contact with gastric fluid pre-concentrate converted into o/w emulsion and it could be a better solution for preventing problems related to stomach [120].

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Simonnet et al 2001 developed a nanoemulsion containing anionic surfactant, aqueous phase and oily phase belonging to oxyethylenated derivative and phosphoric acid fatty ester. The globule of oil having molecular weight more than 400 dalton showed the size less than 100nm. The weight ratio of the oil phase to the aqueous phase varies from 2 to 10. This invention explained about the method of preparation, its good transparency and uses of nanoemulsionin dermatological, ophthalmic, cosmetics and topical pharmaceuticals [128].

Mulye et al 2000 developed a formulation, which contained cyclosporine, non-ionic surfactant with HLB value more than 10 and fatty acid with carbon chain C6 to C22. This system was found to overcome the problems related to solubility and dissolution with advantages of high drug load and patient compliance because of reduction in size of the dosage form. Leakage and brittleness could also be prevented by administrating it in soft or hard gelatin capsule [129].

In another study Bhalani et al 1999 prepared a formulation possessing cyclosporine, a water insoluble drug having problem related to taste and instability. For controlling such problems polar lipid SEDDS (PLSEDDS) was developed by adding cyclosporine with polar lipid and surfactant, which in presence of aqueous medium formed emulsion with globule size less than 50 nm. The PLSEDDS demonstrated the advantage of self-stability of formulation, no need of hydrophilic co-solvent or aluminum blister packaging [130].

9. Conclusion

Based on the various published studies, it can be concluded that SEDDS can be an appropriate carrier for the delivery of lipophilic substances with a minimum concentration of surfactant, a high drug loading potential and the necessary dilution can be obtained without drug precipitation. The SEDDS can be used for the development of the formulations of drug/bioactive with poor aqueous stability. Further, this technique can be explored for the development of a formulation with prolonged drug release by introducing appropriate polymer in composition. The advancement of this technology would give rise to a new application in the area of drug delivery. SEDDS has been shown to be essentially effective in enhancing oral bioavailability of lipophilic products.

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10. Expert opinion

Conventionally, drugs which are clinically magnificent and significant have always been difficult to handle, owing to its poor aqueous solubility or permeability which leads to lower therapeutic response (causing multiple dose regimen; also may lead to toxicity) and poor bioavailability has automatically reduced the chance of any drug to come to the market claiming it to be therapeutically safe and efficacious. Therefore, converting a drug in such a formulation which would not only reduce the dosing frequency, but also ensure to reduce the dose with maximized efficacy is an art and a challenge for formulation scientists. Approximately 40% of active pharmaceuticals are poorly water soluble. Lipid-based drug delivery systems in general and SEDDS in particular has great potential for enhancing solubilityand bioavailability of poorly water-soluble drugs. Since this ability has been recognized for almost two decades, the full impact of SNEDDS and its elements on the handling of these issues has been acknowledged in recent years.

Research articles and patents in various countries report many of the application and fabrication techniques of SEDDS. We have incorporated the latest patents focusing on the composition, classification and systemic optimization techniques of SEDDS. This will open the way for rapid advancement in pharmaceutical research as well as patents on SEDDS technology. The great interest in fabrication of SEDDS is to be a specific viable strategy for solving the problem with low oral bioavailability of hydrophobic drugs. Currently, oral SEDDS has received a lot of attention as a remedy to solve issues related to intra-and inter-subject heterogeneity, shortage of dose proportionality of hydrophobic drugs, and poor oral bioavailability. Some significant *in vitro* features like zeta potential, oil/surfactant ratio, droplet size, emulsion polarity and surfactant concentration play key roles in the oral absorption of SEDDS containing drug. It can be administered orally as a hard-gel capsule (HGC) or soft-gel capsule (SGC) and also boosts the bioavailability of drug to maximize solubility and reduces gastric discomfort. After the administration of formulation, drug remains trapped in the oily droplets (within the droplet or in the film of the surfactant at the interface) of the emulsion formed during the self-emulsification process in the GIT. It is also a bit troubling to claim that the medication is being extracted from SMEDDS, it is more correct to say that it diffuses into the GIT media from oily droplets and in reality the mixture is established

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between the substance absorbed in oily droplets and the outer distributed media (e.g. GIT fluids).

In addition to enhancing the solubility of poorly soluble drugs, SEDDS also improves the bioavailability of drugs through a number of other possible pathways, such as inhibiting P-gp efflux, resistance to metabolism by cytochrome P450 family enzymes in GIT and liver, as well as bypassing the hepatic first-pass effect.

A significant growth in both published research papers and patents in the area of SEDDS clearly demonstrates that it is an innovative delivery method for safe and selective distribution of drugs and other bioactives. The SEDDS can be developed by high pressure homogenization, high energy approach, sonication and micro-fluidization techniques. However, these approaches yield SEDDS of different size and distribution. One needs to be careful when choosing a technique. In general, SEDDS are composed of oil, surfactant, co-surfactant and water. However, the choice of ingredients can influence various features including size, shape, solubility of drug, polydispersity, in vitro and in vivo drug release from SEDDS. Such specifications should also be carefully optimized for maximum efficacy of the fabricated formulations.

The SEDDS as a drug carrier has been tested for a wide range of applications including enhancement of oral bioavailability and solubility of drugs with low aqueous solubility. From the literature review, it is very obvious that patents are coming from every corner of the world in almost all directions of drug delivery utilizing SEDDS as one of the choices among drug carrier options. Hence more modified version of SEDDS or simplified and industry-friendly fabrication techniques are warranted in near future.

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Figure Legends

Figure 1. Ishikawa fishbone diagram depicting different fabrication techniques, types, characterization process and biomedical applications of SEDDS

Figure 2. Merits and demerits of SEDDS

Figure 3. Some marketed products of SEDDS

Table Legends

Table 1. Comparative features of SEDDS, SMEDDS and SNEDDS

Table 2. Tabular presentation of different kind of SEDDS along with their compositional account and outcome

Table 3. SEDDS mediated drugs with improved oral solubility and bioavailability

Table 4. Different anticancer drug containing SEDDS and its pharmacokinetic action

Table 5. Description of SEDDS related patents especially for the period of 1999-2020 [91-130]

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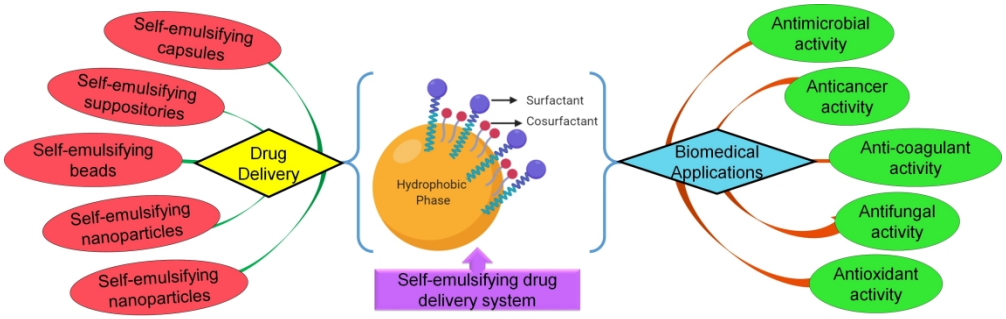

Graphical Abstract

988x315mm (96 x 96 DPI)

Table 1. Comparative features of SEDDS, SMEDDS and SNEDDS

Features	**SEDDS**	**SMEDDS**	**SNEDDS**
Appearance	Turbid	Optically clear	Optically clear
Size	>300 nm	100-250 nm	<100 nm
Concentration of surfactant	30–40%	40–80%	40–80%
Concentration of oil	40–80%	>20%	>20%
HLB value of surfactant	<12	>12	>12
Category as per Lipid formulation classification system	Type II	Type IIIB	Type IIIB

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Table 2. Tabular presentation of different kind of SEDDS along with their compositional account and outcome

Type of SEDDS	Composition	Features	Cell line study/in vivo study	Outcome	Reference
Solid-SEDDS	Losartan, Labrasol, Labrafil M1944 CS, Lauroglycol 90, Labrafaclipophile WL1349, Transcutol P, Labrafil M2125, Cremophore, Campul, Tween 80, Oleic acid, Mannitol, Neusilinsylysia, Stearyl amine, Neusilin, Sylysia 350	Globule size-142.51±3.46 nm; PDI - 0.254±0.01; Zeta potential (ZP)-+16.66±0.47	The study was performed in male wister rat. Losartan suspension was taken as control and S-SMED-N (Neusilin) as test. Pharmacokinetic parameters like C_{max}, T_{max}, AUC_{total}etc were determined using Kinetica software.	The C_{max} and AUC_{total} were found to be 7.79±0.54 µg/mL and 39.57±5.31 µg/ml/hr, respectively. These values were statistically evaluated. The values were observed to be much higher than the losartan suspension levels. It showed 2.82-fold increase in bioavailability as compared to losartan suspension.	[19]
SEDDS	Enoxaparin, Float-a-lyse, Captex 8000, CapmulPG-8 EP/NF, Peceol, Labrafil M 1944 CS, Maisine, Labrasol, Transcutol HP, Mygliol 840, Cremophore, Triacetin, Propylene glycol, Sesame oil, Cetrimonium bromide, Dodecylamine hydrochloride, Olive oil, Benzalkonium chloride, Fluorescein daiacetate, Lipase, Bile salts Azure hydrochloride, Sodium deoxycholate and Sodium cholate in 1:1 ratio	The droplet sizes of LC (Long chain lipids) 10, MC (Medium chain lipids) 10 and NL (No lipids) 9 were found to be 60.20±37.7, 38.2±6.2 and 44.7±12.46 nm, respectively. The PDI value of all was found in between 0.31-0.52.	In vivo research was conducted in 6 male Sprague- dawley rat groups, One group was treated with enoxaparin injection and others with oral administration. The enoxaparin sample was analyzed using Biophen®heparin anti-Xa kit.	There is an increase in 2-fold of anti-Xa activity of oral enoxaparin as compared to enoxaparin aqueous solution Hence, the absolute bioavailability was found to be 2.25% and 2.02%, respectively.	[20]

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SEDDS	Daptomycin, Capmul MCM EP, Dermofeel MCT, Cremophore RH 40, Cremophore EL, Benzalkonium chloride, Cetrimonium bromide, Dodecyl amine hydrochloride, Lipase, Bile salts, α-chymotrypsin, Float-a-lyser.	Droplet size 36±5 - 274±151 nm, PDI- ≤0.3.	-	-	[21]
SNEDDS	Tamoxifen (TMX), naringenin (NG), Labrafil 1944 CS, Caproyl-90, Labrasol, Transcutol P, Corn oil acconon C6, Soyabean oil, Sunflower oil, Sesame oil, PEG 400, Acrysol EC-35, Tween 80, Acconon CC-6, Transcutol HP.	Globule size 53 and 73 nm; Emulsification time 1-3 min.	**Cell line study:** By PBS (pH 7.4) MCF-7 cells were washed and 100 µL of TMX (5 mg/mL in PBS), incubated for 4 hrs. Formazon crystals were formed and it was thawed in DMSO (100 µL), absorbance was checked by microplate reader at 570 nm. **In vivo antitumor activity:** Breast cancer was induced in female wister rats using 7, 12-dimethyl benz-anthracene (DMBA) with dose of 45 mg/kg for three weeks consecutively. Animals were separated and divided into different groups. After 10 weeks of DMBA dosing, drug was	Cell line study showed that after 24 hrs of incubation, TMX-SNEDDS and TMX-NG–SNEDDS showed 6.5 and 22-fold increased cytotoxicity, respectively. **In vivo study** The tumor size was estimated to be 15% for TMX-NG-SNEDDS, which was smaller than from other formulations. The Kaplan-Meier scenario indicated species reproduction in the case of TMX-NG-SNEDDS. The TMX-NG suspension and TMX-SNEDDS displayed 80% and 40% mortality, respectively.	[11]

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			administered once in 3 days to one group and positive control as saline given to another group orally. For 30 days tumor growth was observed and survival rate was monitored for 60 days. Percent tumor burden was determined by Kaplan-Meier curve.		
Super saturable-SEDDS	Dutasteride (DTS), Transcutol HP, Capryol, Cremophore EL, Soluplus, Kollicoat MAE 30 DP (Methacrylic acid ethylacrylate copolymer), Hypromellose 2910, Kollidon 90F, Acetonitrile, Finasteride and Methanol.	The particle sizes of F1-F3 and F4-F13 formulation were found to be 130 nm and 90-110 nm, respectively. The PDI was less than 0.3 and the drug content was 97.6-105.7%.	Male Sprague-Dawley rats were taken and segregated in three different groups and fasted for 16 hrs. 1 mL (0.2%) of methylcellulose (MC) suspension, which contains DTS was given to the first group, conventional SEDDS is given to the second group and S-SEDDS is administered to the third group with dose of 2 mg/kg.	SEDDS and SS-SEDDS showed significant increase in plasma level (within 3 hrs) as compared to drug suspension (12 hrs). AUC $_{(0\text{-}24hrs)}$ of S-SEDDS was 3.9-fold more than the drug suspension and 1.3-fold higher than SEDDS. The C_{max} of SS-SEDDS was found to be 2.0 and 5.6 folds higher than SEDDS and drug suspension, respectively.	[23]

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Table 2. SEDDS mediated drugs with improved oral solubility and bioavailability

Indication	Bioactives/ Drugs	References
Anti-coagulant	Enoxaparin	[57]
Antibiotic	Daptomycin, Vancomycin, Ciprofloxacin	[38-60]
Anti-hyperlipidemic	Atorvastatin calcium	[61]
Antioxidant	Alpha-mangostin, Coenzyme $Q_{10,}$ Resveratrol	[63-65]
Anticancer	Enoxaparin, Diindolylmethane-14 (DIM-14),1, 1-bis (3′-indolyl)-1-(p-substituted phenyl) methanes (DIM-P), Erlotinib, Paclitaxel, E804, Lycopene	[66-73]
Chronic heart failure	Curcuminoids	[76]
Antifungal	Econazole	[79]
Anti-diabetic	Glipizide	[82]
Hepatoprotective	Gingerol	[83]
Benign prostatic hyperplasia	Dutasteride	[84]
Hypertension	Nimodipine	[85]
Cardiovascular activity	Lovastatin	[86]

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Table 3. Different anticancer drug containing SEDDS and its pharmacokinetic action

Drug/Active constituent	Use	Excipients	Size (nm)	Dose (mg/kg)	Species/ Cell lines	Pharmacokinetic effect	Reference
Enoxaparin	Tumor targeting ligands		91-102 nm	-	Human epithelial colorectal adenocarcinoma and human breast adenocarcinoma cell lines	• High stability in albumin and serum plasma • Insignificant hemolytic activity • Higher uptake on both cell lines then uncoated SEDDS	[69]
DIM-P	Nonsmall-cell lung cancer	Labrafil 1944, TPGS, Enova oil, Eudragit, Cremophor EUL, Mannitol, L30 D55	64-292	20 and 3.33	Labrador retriever dogs and Sprague dawley rats	• C_{max} and AUC_{0-t} increased to 2.49 and 3 times, respectively in rats as compared to the native approach • C_{max} and AUC_{0-t} increased 2 and 2.92 times, respectively, in dogs as opposed to native treatment	[70]
DIM-14	Nonsmall-cell lung cancer	TPGS, Labrafil, Enova oil,	230–246	3.33	Labrador retriever dogs	• C_{max} and AUC_{0-t} increased to 1.8 and 2.4 times, respectively, as compared to native approach	[71]
E804	Chronic myelocytic leukemia	Solutol HS 15, PEG 400, Capmul MCM	16.8–140	50	Beagle dogs	• In contrast to the E804 aqueous suspension, C_{max} and AUC_{0-t} improved to 6.3 and 9.8 times, respectively	[72]
Paclitaxel	Breast, prostate, and lung cancer	Labrasol, Sesame oil, sodium deoxycholate	<100	10	Rabbits	• Compared to PTX-suspension, C_{max} and AUC_{0-t} increased to 3.99 and 2.7 times, respectively	[73]

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Erlotinib	Nonsmall-cell lung cancer	Transcutol HP, Aerosil200, Labrafil M2125CS, Labrasol, Dextran 40	150-250	20	SD rats	• In comparison to erlotinib, dextran-based S-SEDDS showed C_{max} and AUC_{0-t} increased to 2.4 and 2.1 times, respectively • In comparison to erlotinib, Aerosil-based S-SEDDS showed C_{max} and AUC_{0-t} increased to 4.2 and 3.5 times, respectively	[74]
Lycopene	Prostate cancer	Gelucire, Cremophor RH, Tween 85, LCT	37	50	Female landrace pigs	• In comparison to Lycovit, C_{max} and AUC_{0-t} have increased to 2.85 and 2.3 times, respectively	[75]

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Table 4. Description of SEDDS related patents especially for the period of 1999-2020 [91-130]

Inventors/ Assignee	Patent number	Year of patent	Composition	Reference
Wang Yancai, Guo Juan, Yan Beibei, et al.	CN111135143A	2020	Ethyl oleate, surfactant, co-surfactant, β-elemene	[91]
Zhang Chaoyan, Zhou Ying, Li Xueyan et al.	CN111264860A	2020	Astaxanthin,Quercetin,Cinnamon oil or Castor oil,Tween 80, Polyoxyethylene hydrogenated castor oil 40,Polyethylene glycol 400	[92]
XueRuizhi	CN111234178A	2020	Amino silicone oil,Epoxy resin,Reaction auxiliary agent,Solvent,End-capping agent	[93]
Chen Dexiang, Dong Lichun	CN109528652A	2019	Oil phase (30-50%), Emulsi¦er (5-10%) and Pharmaceutical aqueous solution (40-60%)	[94]
Liu Yuling, Chen Xiaoguang, Zhang Jie et al.	CN110179750A	2019	Chlorogenic Acid, Oil phase, Emulsi¦er	[95]
Anavi-Goffer S	US20190060300A1	2019	One CB2 receptor modulator,Self-emulsifying vehicle,Active agents (one antipsychotic agent,one GPR55 modulator, one anti-inflammatory agent)	[96]
Jung-Won Cho, Na-Guk, Lee Hong-ki, et al.	KR102007731B1	2019	Ticagrelor, Oil phase (Caprylic acid glycerides), Surfactant (Polyoxyethylenesorbitan fatty acid), Co-surfactant (Diethylene glycol monoethyl ether and Tetraglycol)	[97]
Chang-Shan, HsuWei-Hua Hao, Jong-Jing Wang et al./Innopharmax Inc	US20190275006A1	2019	Hydrophilic drug,Solvents Surfactants,hydrophilic carriers.	[98]
Mandip Sachdeva, Ketankumar Patel, Arun Rishi/Florida Agricultural and Mechanical University	US10172838B1	2019	Cell cycle and apoptosis regulatory protein-1,Lipidic excipient,Surfactant,Organic solvent (Dimethyl acetamide)	[99]

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Christopher Diorio/ Pharmacannis Labs LLC	US20190015346A1	2019	Cannabinoid, Lipophilic carrier with surfactant and solubilizing properties,Oil-soluble antioxidant,Water-soluble antioxidant, Carrier	[100]
Michael A. ZeligsIrwin C. Jacobs/BioResponse LLC	US10441569B2	2019	Diindolylmethane,Essential oil,Lauroyl polyoxyl-32 glyceride,Propylene glycol caprylate, Polysorbate 80 or Tocopherol PEG 1000 succinate, Lecithin	[101]
Michael A, Zeligs Irwin C, Jacobs/ BioResponse LLC	US9918965B2	2018	Diindolylmethane,Caprylocaproyl polyoxyl-8 glyceride, Lauroyl polyoxyl-32 glyceride,Phosphatidyl choline or lysophosphatidyl choline,Oleoyl polyoxyl-6 glyceride,Poloxamer	[102]
Zhang Xiaofei Guo, Qiuting Shi Yajun, Zou Junbo et al.	CN108553417A	2018	Osthole,Oil phase,Surfactant and Co-surfactant	[103]
XiongYongai, Zeng Yan	CN107661287A	2018	Sanguisorbin, Oil phase (0.05-0.25%), Surfactant (0.45-0.65%), Co-surfactant (0.1-0.3%)	[104]
YumnaShabaik, Jim Jiao, Chetan Pujara/Allergan Inc	US20180036233A1	2018	Oil, A poorly water-soluble drug, and One or more surfactants	[105]
Jiang Shuguang, Xu Xiaochang, Wang Senyi	CN108938566A	2018	Oily phase (10-70%), Surfactant (30-80%), Co-surfactant (0-30%)	[106]
Doron Friedman	WO2018011808A1	2018	Cannabinoid or a mixture of cannabinoids, Terpene,Emulsifier	[107]
S.O. Hustvedt, P.H. Olesen, G. Berge, et al./ PronovaBiopharma Norge AS	US9532963B2	2017	Eicosapentaenoic acid (EPA) 25%, Docosahexaenoic acid (DHA) 75%, Antioxidant, Super-disintegrant, Nonionic surfactant (Polysorbate 20, Polysorbate 40), Cationic surfactant (Quaternary ammonium compounds), Zwetterionic (dodecyl betaines) and solvent.	[108]
Guy Derrieu, Disma Giovanni Mazzola, Giancarlo Mazzola	WO2017211909A1	2017	Hydrophilic phase,Oily phase,Ionic polymer,Anionic surfactants,Cationic surfactants	[109]
D.S. Chow, Gupta P, Qi Y, et al./ The University of Houston System	US20100310611A1	2016	Benzimidazole derivative (Methyl 5-benzoyl benzimidazole-2-carbamate), Oil (Propylene glycol dicaprylocaprate or caprylic triglyceride or capric triglyceride (19-56.5%), Dipolar aprotic solvent (dimethylsulfoxide, 5-10%) and Surfactant.	[110]

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Emadeldin Hassan/ Pharmaceutics International Inc	US20150320864A1	2015	Poorly water-soluble drug,One surfactant,One polar lipid	[111]
P. Nahat, P. Mandaogade, G.K. Jain, et al./ Wockhardt Ltd.	US20150164851A1	2015	Diacerein (10-90%), Labrafil (1-70%), polyoxyethylene glycerol esters of fatty acid (10-90%), Methylcellulose (2-50%), PEG 40 hydrogenated castor oil (5-70%).	[112]
Mohamed Skiba	WO2015022454A1	2015	Cyclodextrins,Oily or oleaginous substance,Antioxidant	[113]
H. Yesim karasulu, Sebnemapaydin, Evrengundogdu et al.	WO2015142307A1	2015	Rosuvastatin,Surfactants, Co-surfactants	[114]
Z. Liu, L. Yang, H. Yang, Y et al./ CSPC Zhong Qi Pharmaceutical Technology (Shijiazhuang) Co., Ltd	US20080319056A1	2014	Butylphthalide, Ethoxypolyoxyethylene glyceride, Polyoxyethyleneoleate, Liquid lecithin, Polyoxyethylene castor oil, Coconut oil, Polyethyleneglycol glyceride, Almond oil oleate, Polyethyleneglycol glycerin ester, Polyoxyethylene glycerin trioleate, Polyoxyethylenesorbitanoleate, Polyethyleneglycodl-8 glycerin caprylate	[115]
M.A. Khan, S. Nazzal/Jarrow Formulas, Inc	US20120269792A1	2014	Coenzyme Q10 (CoQ10) (70%), Volatile essential oil (peppermint oil, peppermint oil, menthol, anise oil and lemon oil), Surfactant and co-solvent, co-polymer of vinyl acetate and vinylpyrrolidone, Microcrystalline cellulose (MCC), Maltodextrin.	[116]
I. Legen, J. Kerc, P. Jurkovic/ LEK PharmaceuticalsD	US20100331356A1	2013	Polyoxyethylenesorbitan fatty acid ester emulsifier, Co-emulsifier (glyceryl mono- or di-fatty acid esters) (2.5:1) (3.5:1), Oil (caprylic or capric triglyceride oil).	[117]
J. Lin/ Catalent Australia Pvt Ltd	US20060275358A1	2012	Coenzyme Q10, Lipophilic co-surfactant, Hydrophilic surfactant, Lipophilic solvent (one or more than one).	[118]

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C. Kohli, S. Chopra, S. Arora, R, et al./ ArbroPharmaceuticals Ltd., Jamia Hamdard (Hamdard University)	US20110294900A1	2011	Curcuminoid (1-10%), Propyleneglycol monocaprylate (25-33%), Polyoxyethylene or Polyethoxyl derivative of a vegetable oil (35-45%), one or more co-surfactant (8-16%)	[119]
C. Holemberg, B. Siekmann/Nicox S.A	US7736666 B2	2010	No-NSAIDS, Short chain alcohol (ethanol, propylene glycol or glycerol, Phospholipid (egg lecithin), Semi-solid fat or oil.	[120]
Arvind Kumar Bansal, Bhushan Munjal, Sarsvat Babulal Patel	WO2010010431A1	2010	Curcuminoids,Lipid carrier system,Fatty acid, Surfactants	[121]
Sara Abelaira, Mariela Paula Becher, Juan Francisco Gel et al.	WO2008142090A1	2008	Tipranavir,Vitamin E TPGS,One or more pharmaceutically acceptable solvents	[122]
Jody Firmin Voorspoels	US20070104740A1	2007	(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl(1S,2R)-3-[[(4-aminophenyl)sulfonyl](isobutyl) amino]-1-benzyl-2-hydroxypropylcarbamate, Salts, Esters, Polymorphic and pseudopolymorphic forms	[123]
Zhentao Liu, Liying Yang, Hanyu Yang/Shijiazhuang Pharma Group Zhongqi Pharmaceutical Technology (Shijianzhuang) Co Ltd	EP1787638A1	2007	Butylphthalide,Emulsifying agent,Excipient	[124]
Gregory Lambert, Alain Razafindratsita, Jean-Sébastien garrigue et al./Novagali SA Yissum Research Development Company of Hebrew University of Jerusalem	EP1480636B1	2007	One or more taxoid(s), Vitamin E TPGS, One co-solvent selected from propyleneglycol and ethanol, One or more bile salts, Tyloxapol.	[125]
Sophie Cote, Gilbert Gaudel, Maria-Teresa	EP1498143A1	2005	Taxoid and at least one amphiphilic surfactant, Labrasol®	[126]

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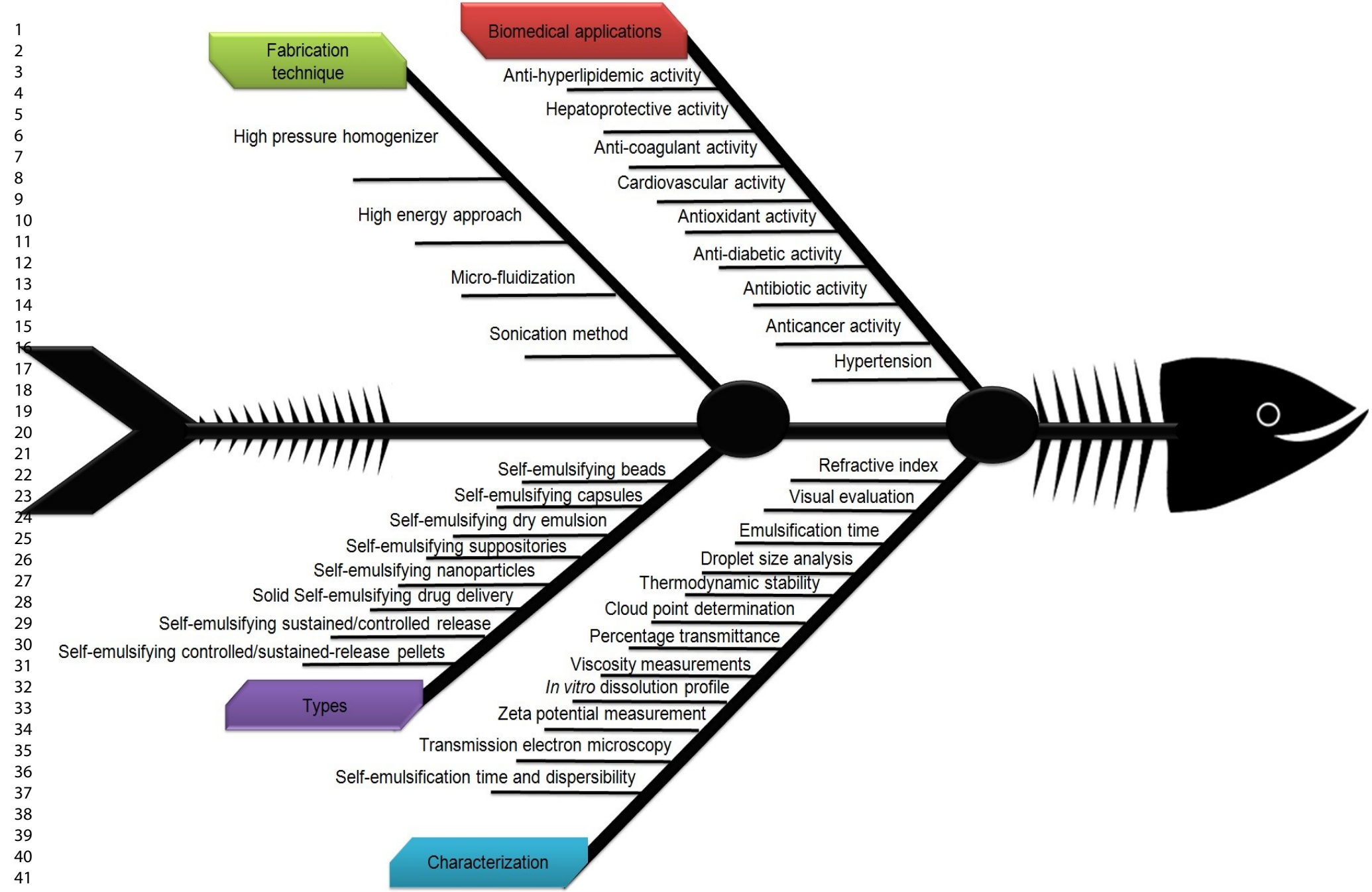
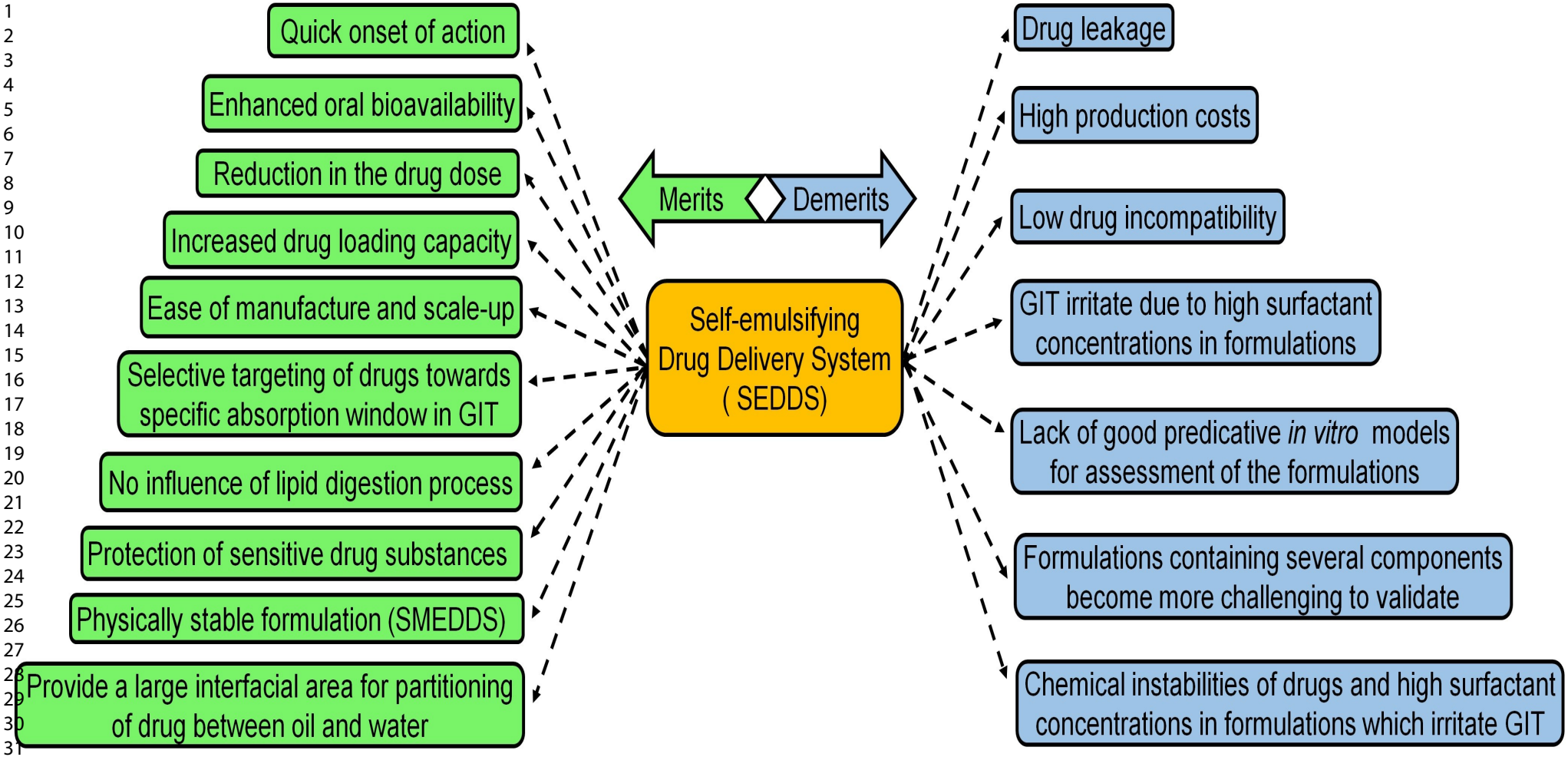
Peracchia/Aventis Pharma SpA				
Simon Benita, Jean-Sébastian Garrigue, NeslihanGursoy et al./Novagali SA Yissum Research Development Company of Hebrew University of Jerusalem	EP1340497A1	2003	One or more therapeutic agents,Vitamin E TPGS, Co-solvent,Bile salts, Surfactant	[127]
J.T. Simonnet, O. Sonneville, S. Legret/L'Oreal (Paris, FR)	US6274150B1	2001	Oily phase (vegetable oil, animal oil, mineral oil, silicon oil, synthetic oil), aqueous phase, anionic surfactant (Oxyethylenated derivatives and phosphoric acid fatty esters), one neutralization agent (organic bases and inorganic bases), one ionic amphiphilic lipid (alkylsulphonic derivatives and anionic amphiphilic lipids) (0.01-5%), transparency improving additives (glycols, lower alcohols and sugar) (5-20%) and active ingredients.	[128]
N. Mulye/Pharmasolutions, Inc.	US6057289A	2000	Cyclosporin, Non-ionic surfactant (HLB greater than 10), Aqueous mediun.	[129]
V.T. Bhalani, S. Patel/ Watson Laboratories, Inc	US5858401	1999	Lipophillic drug (Cyclosporin), Surfactant (polysorbate 80), Glyceryl fatty acid ester, Polyethylene glycol, Polyglycolyzed glycerides (HLB 10 to 16).	[130]

For Peer Review Only

Information Classification: General


Biomedical applications
Anti-hyperlipidemic activity
Hepatoprotective activity
Anti-coagulant activity
Cardiovascular activity
Antioxidant activity
Anti-diabetic activity
Antibiotic activity
Anticancer activity
Hypertension
Fabrication technique
High pressure homogenizer
High energy approach
Micro-fluidization
Sonication method
Types
Self-emulsifying beads
Self-emulsifying capsules
Self-emulsifying dry emulsion
Self-emulsifying suppositories
Self-emulsifying nanoparticles
Solid Self-emulsifying drug delivery
Self-emulsifying sustained/controlled release
Self-emulsifying controlled/sustained-release pellets
Characterization
Refractive index
Visual evaluation
Emulsification time
Droplet size analysis
Thermodynamic stability
Cloud point determination
Percentage transmittance
Viscosity measurements
In vitro dissolution profile
Zeta potential measurement
Transmission electron microscopy
Self-emulsification time and dispersibility


Quick onset of action
Enhanced oral bioavailability
Reduction in the drug dose
Increased drug loading capacity
Ease of manufacture and scale-up
Selective targeting of drugs towards specific absorption window in GIT
No influence of lipid digestion process
Protection of sensitive drug substances
Physically stable formulation (SMEDDS)
Provide a large interfacial area for partitioning of drug between oil and water
Merits
Demerits
Self-emulsifying Drug Delivery System (SEDDS)
Drug leakage
High production costs
Low drug incompatibility
GIT irritate due to high surfactant concentrations in formulations
Lack of good predicative *in vitro* models for assessment of the formulations
Formulations containing several components become more challenging to validate
Chemical instabilities of drugs and high surfactant concentrations in formulations which irritate GIT

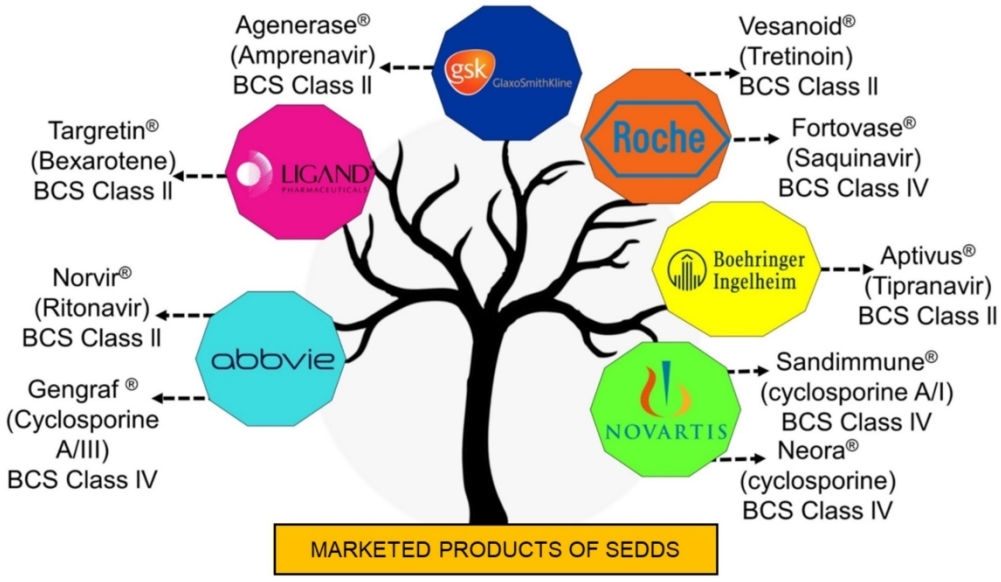


Figure 3. Some marketed products of SEDDS

702x406mm (96 x 96 DPI)