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Recent Progress in Self-Emulsifying Drug Delivery Systems: A Systematic Patent Review (2011–2020)

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ABSTRACT: Self-emulsifying drug delivery systems (SEDDS) are lipid-based isotropic mixtures that enhance the bioavailability of poorly water-soluble drugs and reduce the possible side effects, offering a wide variety of treatments for several pathologies. The aim of this review is to discuss the state of the art of patents for this drug delivery system by studying recent patent applications (2011 to 2020). We performed a thorough screening using the European Patent Office's Espacenet database, from which 37 inventions were selected and fully studied. China had more patent applications, and the articles published about SEDDS exceeds both in number and technological advance the submitted inventions. Nevertheless, the patents presented herein are innovative to address known issues to traditional SEDDS, including storage and formulation stability, solid formulations, acute gastrointestinal toxicity from surfactants, and drug delivery through alternative routes of administration. This study also revealed that release behavior for SEDDS and associated pharmacokinetics were not completely disclosed by the inventors of the patents and that further studies are required.

KEY WORDS: surfactants, lipids, co-surfactant, oil carrier

I. INTRODUCTION

New drug delivery systems are important in drug development as they may solve current formulation challenges. This challenges arise due to the physicochemical nature of the drug and the biological barriers of the body, and are conceived generally as poor drug solubility and permeability, delivery of biological and biotechnological drugs, drug irregular distribution in the body, and lack of targeting properties, among others.[1]

Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of drug, lipid, surfactant, and co-surfactant (Fig. 1) that are able to form an oil-in-water emulsion in the gastrointestinal tract under minimum agitation.[2] They are classified as lipid-based drug delivery systems (LBDDSs), and they depend on the droplet size, emulsification properties, dispersion rate, and drug solubilizing properties.[3] These systems work by producing a large interfacial area that allows efficient partitioning of the drug between

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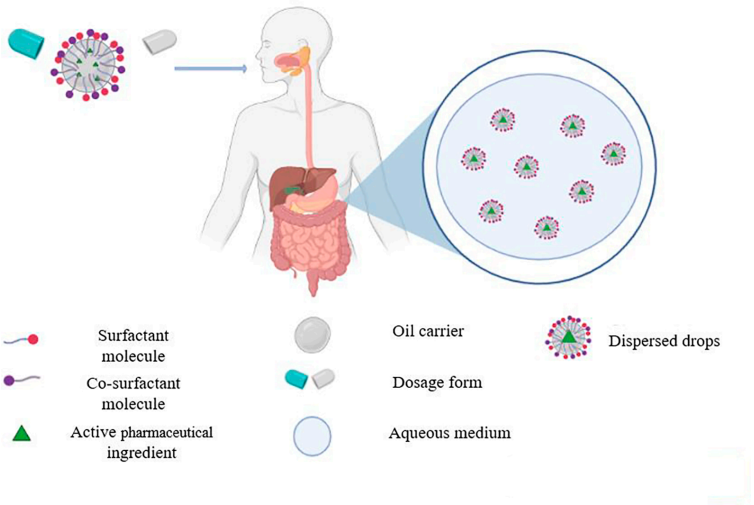


FIG. 1: Representation of a self-emulsifying drug delivery system. The pharmaceutical dosage form could be a soft or hard capsule depending on the patent, a liquid, or may include solid materials as absorbents to develop tablets. Created by Biorender.com.

the oil droplets and the aqueous medium where absorption takes place.[4] Thus, the dissolution step natural to conventional solid forms is absent. As a result, SEDDSs increase bioavailability of poorly soluble drugs.

This type of system is not regarded as new, but interest in developing them for clinical applications has been increasing in recent years.[5] The growing interest in SEDDSs development is due to its capability of increasing the dissolution rate of drugs in Classes II and IV of the Biopharmaceutics Classification System (BCS), and the ease for developing an oral formulation for improved patient treatment and compliance. Moreover, ongoing research is exploring the delivery of therapeutic peptides[6] and genes[7] as SEDDS is able to protect macromolecules from the biological environment. Hence, the applications of this system for several pathologies is not limited.

Once a new drug delivery system is developed, it needs to reach the market and become available as a medical product. This can be done through a technology transfer process from laboratory research to industrial production. Once this is achieved, the company or inventor may apply for a patent. Patents are legal acts issued by a country to protect intellectual property and profit since they also emerge from the increasing need of external funding to perform high-tech and trending research. Furthermore, the patent publication has to sufficiently describe the product for evaluation of its novelty by the readers, since innovation is the principal requirement to obtain a patent. This process promotes advances in research and technology, and may ultimately contribute to improve society.[8]

The aim of this study is to critically evaluate the current state of patents of self-emulsifying drug delivery systems. For this, a systematic review was carried out using

the European Patent Office official database Espacenet. The innovations disclosed focus on surpassing SEDDS limitations regarding their drug solubilizing power, stability, compatibility, metabolism, and toxicity.

II. METHODOLOGY

The Espacenet database was used to conduct our review. The patent selection was based in several inclusion criteria; the first was to include recent patents available in English with the keywords *self-emulsifying*, *delivery*, and *systems* present in the title, abstract, or full description.

A total of 176 patents were identified from Espacenet for primary examination and filtering using the keywords, as shown in Fig. 2. The next step was to identify patents published in 2011 to 2020. Patents published in previous years (n = 120) were not included, because they were considered too old. For further revision, duplicated documents (n = 11) and patents whose description was not readable in English (n = 22) were sorted out. In this stage, 43 patents were selected, but 6 were excluded because they did not relate to a therapeutic drug delivery system and were considered out of the scope intended for this review. The final selection was narrowed to 37 patents, which is a representative sample and offers a suitable perspective about the technology currently employed in SEDDSs.

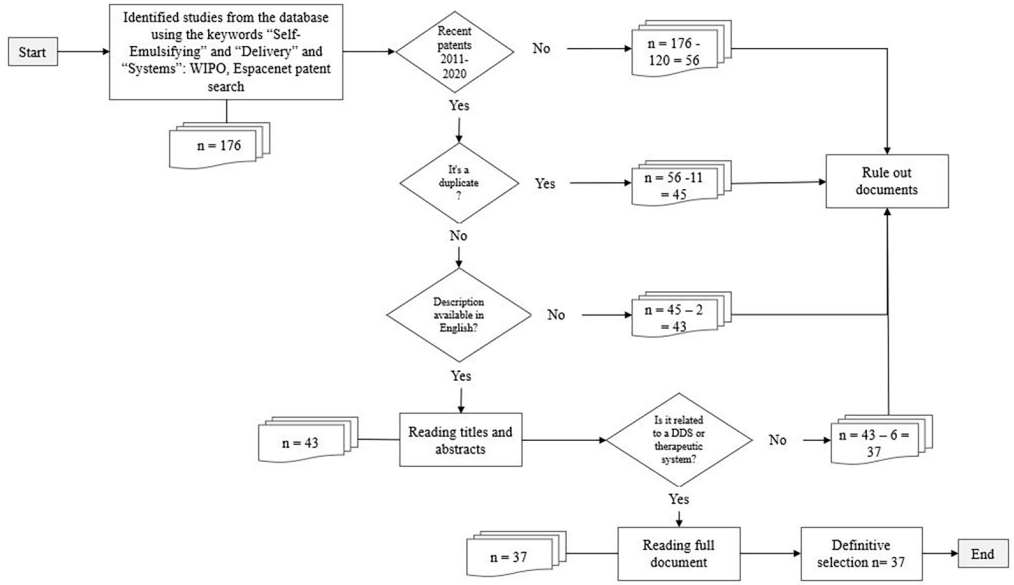


FIG. 2: Flowchart of patent searching filtering and selection. DDS, drug delivery system.

III. RESULTS AND DISCUSSION

A. SEDDS Patents and Publications

The country of origin of the 37 SEDDS patents was identified (Fig. 3). China has the greater number of inventions published, surpassing other countries, such as South Korea, India, and the United States.

Additionally, the number of patents published by year was also considered, along with the number of articles published in PubMed for the same period (2011–2018), found with the same search criteria. As shown in Fig. 4a and 4b, it is possible to say that the research done outnumbers the inventions output for SEDDS, and, in general, the research of SEDDS is experiencing an increase in the number of publications per year.

Of the 37 patents reviewed, the vast majority belong to class A61 of the international patent classification system, established in the Strasbourg Agreement in 1971 and available from the World Intellectual Property Organization (WIPO). Class A61 accounts for inventions in the section entitled Medical or Veterinary Science; Hygiene

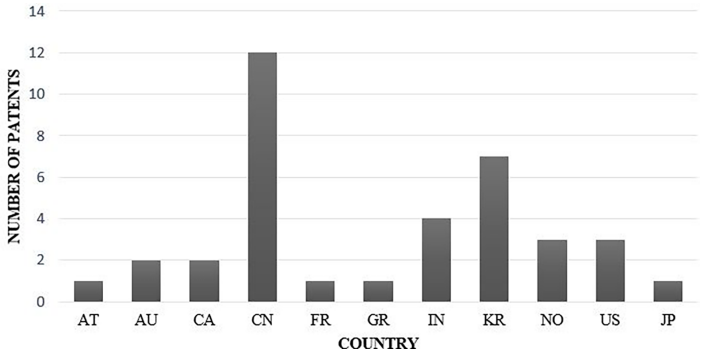


FIG. 3: Number of SEDDs patents published by country between 2011 and 2020. AT, Austria; AU, Australia; CA, Canada; CN, China; FR, France; GR, Greece; IN, India; KR, Korea (south); NO, Norway; US, United States of America; JP, Japan.

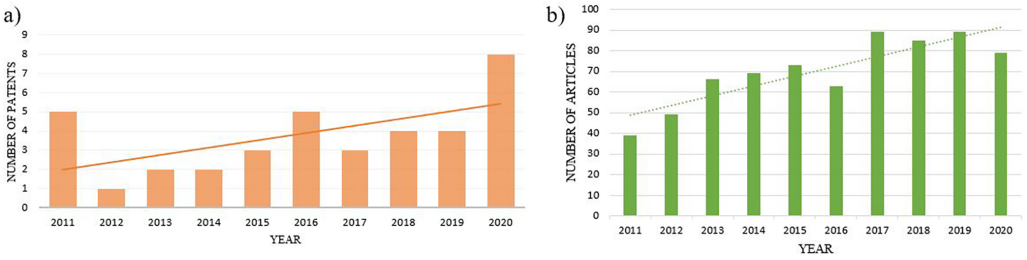


FIG. 4: (a) Number of SEDDS patents published by year between 2011 and 2020. (b) Number of articles published in PubMed between 2011 and 2020 concerning SEDDS.

Field. Almost all patents in this class were also part of subclass A61K: Preparation for Medical, Dental, or Toilet Purposes. Only one document belongs to A61J subclass: Devices or Methods Specially Adapted for Bringing Pharmaceutical Products into Particular Physical or Administering Forms; and only one document was categorized as class A23: Food or Foodstuff; Their Treatment; subclass A23L: Foods, Foodstuff and Nonalcoholic Beverages Not Covered by Subclasses A21D or A23B-A23J; Their Preparation and Treatment.

As shown in Fig. 3, 28% of the inventions come from China, 19% from South Korea, and 22% from both India and the USA. Normally, it is not expected for the USA to have so few inventions, considering its strong pharmaceutical market and regulatory status. However, this can be explained by the investment made by the country. As reported in 2016, the USA primary inversion goes to the research and development of new drugs and biologics, and the budgetary contribution for drug delivery technology for the former and the latter is minimal.[9] Additionally, when searching the scientific literature for SEDDSs, recent research seems to be concentrated in Europe, Asia, and the Middle East, as if this kind of drug delivery system currently had no relevance in the USA. On the other hand, China, as the country with a greater number of published patents, arises no suspicion since both the government and the private institutions have provided a strong investment in biopharmaceutical research and development (R&D). This may be linked to the fact that most Chinese patents in this study consist of a naturally derived compound or mixture whose bioavailability is enhanced by the used of SEDDSs. China supports the development and integration of its traditional medicine within its pharmaceutical industry.[10]

The number of patents published by year has significantly increased recently. This is also supported by the increasing trend on research published (see Fig. 4b) as the number of inventions concerning SEDDSs have increased since 2016 (see Fig. 4a). However, there are far more scientific publications than patent filings. This misalignment may be due to the sources of patent filings and published articles. Although most of the articles are published by universities, the patent filings are submitted by formal companies. The goal of the universities and research institutes is the production and dissemination of new findings, and conversely to what one may expect, this does not always translate into financially exploitable inventions. Quick publication of articles may provide renown to the authors, giving them access to productivity grants and funding. Meanwhile, patent filing can be considered a time-consuming process with long-term financial gratification.[11] This should not be the case, as there are studies showing that universities are institutions capable of accelerating technical progress by prompting established firms to commercialize an invention.[12] This means that universities have the upper hand as they introduce new knowledge into the market. While industry adopts this knowledge, nevertheless, patenting of academic research is still a challenge because many universities and companies in developing countries receive little to no investment in R&D.[11] Hence, there are no meaningful incentives to seek patents for these processes.

B. SEDDS Types

All the SEDDSs published in the patents are presented in Table 1, which reveals that the oral administration route is still the most targeted, since it offers a higher patient compliance and fewer problems associated with microbiological quality of the formulation. Many of the inventions aimed for a SEDDS formulation in semisolid or solid state to be packaged in soft capsules or to be granulated for delivery in hard capsules. There were many patents where the SEDDS could be adsorbed in a solid, then granulated and compressed to form a tablet, or even coated to develop a modified release system. However, administration of SEDDSs through ophthalmic, topic, enteral, and inhalation routes have also been reported in several of the documents.

Up-to-date research on SEDDSs, as reviewed by Mahmood and Bernkop-Schnürch,[13] explores the delivery of hydrophilic macromolecular active substances, such as peptides, proteins, polysaccharides, and DNA, by implementing hydrophobic ion pairing (HIP). The research also introduces new forms of SEDDSs that are resistant to enzymatic degradation, having mucoadhesive and mucus-permeating properties, and cell-penetrating properties.

HIP works by the association of a hydrophobic counter ion to the drug, improving its lipophilicity as a result.[14] This way, a formulation may contain a water-soluble drug in a completely lipophilic drug carrier. Although none of the aforementioned macromolecular substances is among the active pharmaceutical ingredient (API) chosen in any of the reviewed inventions and none may be considered as using HIP, there is an interesting association in patent number 9 and number 27 (see Table 1). The former presents a chlorogenic acid SEDDS, in which the molecule has to be associated with phospholipids in order to be added into the formulation, and the latter presents a complex between cyclosporin A and cyclodextrins to form a solid powdered SEDDS with little to no need for surfactant. The SEDDS presented in patent 9 for the oral delivery of chlorogenic acid can be considered innovative, because it could be used to deliver an API through an administration route not possible before for a specific substance. Since it is highly metabolized through the oral route, it is therefore possible to predict this will be true for other drugs. It also opens the possibility of loading hydrophilic compounds into a SEDDS, which often concerns itself only with the loading of hydrophobic compounds. The principle is the same as that for HIP, although in this case, chlorogenic acid is considered a small molecule, not a large one.

Regarding enzymatic resistance, Leonaviciute et al.[15] reported that a SEDDS formulation may be inert against lipases by containing an oil carrier without ester linkages, since it offers no cleavage site for the enzyme to act on. Resistance against proteases is given by the inherent hydrophobic nature of the SEDDS, which prevents the proteolytic enzymes from entering the oil droplets. The resistance against nucleases could be achieved by coupling the genetic material to cationic surfactants for delivery, because positive charges may protect the negatively charged DNA chain. Enzymatic resistance was evidenced as a recurring claim in each patent, and this is part of the reason why drugs that are highly metabolized through the oral route can be taken orally if formulated in a SEDDS. Patent 11 (see Table 1) discloses a SEDDS for the oral delivery of a

TABLE 1: Self-emulsifying drug delivery patents published in the EPO from 2011 to December 2020

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
1	WO2020253689 (A1)	CN/2020	Oral, transdermal, enteral	Chlorogenic acid	Cancer treatment	Assay on ICR mice with induced tumors; Self-emulsifying preparation demonstrated an enhanced therapeutic response compared to the raw materials	Not available	The surfactant is selected from polyethylene glycol glyceride derivatives such as caprylic acid, capric acid, polyethylene glycol glycerides, oleic acid, polyethylene glycol glycerides, or linoleic acid polyethylene glycol glycerides	The oil carrier may be one or a mixture of the following: Labrafil 1944cs, Maisine 35-1, Gelucire, and Capryol 90. A complexation between the chlorogenic acid and phospholipids is needed to solubilize the drug
2	CN111700882 (A)	CN/2020	Sublingual	Asarone (2,4,5-trimethoxy-1-propenylbenzene)	Effective as a sedative, antispasmodic, anticonvulsant, anti-Alzheimer's disease, anti-Parkinson, anti-inflammatory, anti-tumor, choleretic, and hypolipidemic agent	Not available	Not available	The surfactant may be selected from polyoxyethylene castor oil, polyoxyethylene ethylene hydrogenated castor oil, polysorbate 80, caprylic acid-capric acid polyethylene glycol glyceride, or 15-hydroxystearic acid polyethylene glycol ester. The co-surfactant is selected from diethylene glycol monoethyl ether or polyethylene	Oil carrier can be chosen from oleic acid, isopropyl myristate, medium-chain triglycerides, linoleic acid glyceride or oleic acid polyethylene glycol glyceride

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
3	KR20200077676 (A)	KR/2020	Oral	Sildenafil	Treatment of erectile dysfunction	Assay in SD rats, the maximum blood concentration was increased by 7 times and the AUC by 13 times compared to the sildenafil free base	Evaluation of dissolution rate of several formulations prepared by conventional method and high-pressure homogenization, using HPLC for the detection	Carilocaproyl polyoxyglyceride as the surfactant (Labrasol), and diethylene glycol monoethyl ether as the co-surfactant (Transcutol®)	Coconut oil and other medium chain triglycerides (Captex 300) as the oil carrier
4	CN111317718 (A)	CN/2020	Oral	Cordycepin	Described as an anti-aging, anti-tumoral and antibacterial compound	Not available	Not available	Polyoxyethylene sorbitan monooleate (Tween 80) as an emulsifier and glycerin alcohol as a co-surfactant	Caprylic acid glyceride, polyglycerol castor oil, and glyceryl monostearate as oil carriers
5	JP2020090538 (A)	JP/2020	Oral	Lipophilic drug with a LogP value of 5. Typically, a prodrug is selected, such as paclitaxel docosahexaenoate, paclitaxel undecanoate, paclitaxel oleate, and paclitaxel stearate	Treatment of hormone associated cancer, such as prostate, ovarian, and breast cancer	Single-dose pharmacokinetic study of fasted and fed beagle dogs: the composition presented enhanced bioavailability and reduced dietary effect, variations in absorption are reduced during the fasting state	Not available	A hydrophilic surfactant is selected from hydrogenated castor oil ethoxylates, polysorbates and any combination thereof, having a HLB value of 10 or greater	Oil carriers: linoleic acid, oleic acid, palmitic acid, stearic acid, soybean oil, olive oil, sesame oil, safflower oil, peanut oil, rapeseed oil, sunflower oil, coconut oil, corn oil, sunflower seed oil, cotton seed oil, palm oil, and lacquer oil. Or a combination of any of them. Silicon dioxide as solid absorbent

TABLE 1: (*continued*)

6	WO2020118415 (A1)	CA/2020	Oral	Tetrahydrocannabinol, cannabidiol, tetrahydrocannabivarin, cannabigerol, cannabidiolic acid, tetrahydrocannabinolic acid, cannabinol	Inflammation, loss of appetite, nausea, vomiting, pain, chronic pain, muscle spasms, multiple sclerosis, glaucoma, AIDS, a neuropathic condition, cancer, acne, malnutrition, arthritis, chemotherapy induced nausea and vomiting, and/or a spinal cord injury	Not available	Not available	PEG-32 stearate, Gelucire 50/13, Kolliphor HS 15, Labrafil M 2130 CS, Labrasol. Polysorbate 80 or 60 as a further surfactant/ emulsifier	PEG 400, 300, 200 as co-surfactants. MCT and LCT oils are used as carriers

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
7	CN110833527 (A)	CN/2020	Oral	Ulipristal acetate	Emergency contraception, treatment of severe uterine fibroids	Not available	Not available	Polysorbate 80, liquid lecithin, polyoxymethylene oleate, polyethylene glycol glyceride, polyoxymethylene (25) glycerol trioleate, Cremophor EL. The co-emulsifier is one or more of the following: ethanol, propylene glycol, polyethylene glycol, isopropanol, glycerin, and ethylene glycol monoethyl ether, Transcutol HP	The invention presents an S-SEDDS (super saturable) formulation, it contains crystal growth inhibitors, such as HPMC and other polymers. There is a solid phase consisting of mesoporous silica SBA-15. The oil phase may be glyceryl monocaprylate, *n*-butyl oleate, ethyl linoleate, isopropyl laurate, isopropyl myristate, medium-chain fatty acid triacylglycerol, or more fatty acid triglycerides

TABLE 1: (*continued*)

8	CN110742861 (A)	CN/2020	Oral	Cannabidiol	Adjuvant in the treatment of depressive, anxiety, and epileptic disorders; adjuvant in cancertreatment; adjuvant in analgesic, anti-inflammatory, and sedative treatments	The rats were randomly divided into 7 groups with 3 rats in each group. The drugs of the experimental group were the cannabidiol solid self-emulsifying tablets, capsule contents, and granules. The maximum plasma concentration (C_{max}), peak time (T_{max}), the area under the drug concentration-time curve (AUC), and terminal elimination half-life ($T_{1/2}$) are determined	Measured in accordance with the relevant pulp method regulations in the appendix of the Chinese Pharmacopoeia. Use of the standard curve method to calculate the cumulative dissolution percentage	Poloxamer 407, Tween 85, 80, 60, phospholipids and lauric acid monoglycerides	The co-emulsifier of the present invention may be 2 or more of propylene glycol, PEG400, *n*-butanol, ethanol, glycerine, and polyglycerol ester. The oil phase may be hemp seed oil, medium chain triglycerides (MCT), soybean oil, coconut oil, olive oil, and polyoxyethylene hydrogenated castor oil (RH40). Dextrin as a solid carrier

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
9	CN110179750 (A)	CN/2019	Oral, topical, enteral, and inhalation	Chlorogenic acid	Used for antitumor, anti-inflammatory and antiviral therapy	C57BL/6 mice subcutaneously inoculated with Lewis lung carcinoma were used to evaluate the tumor suppressive effect of the chlorogenic acid self-emulsifying composition	Not available	Caprylic acid–capric acid polyethylene glycol glyceride (Labrasol), oleic acid polyethylene glycol glyceride or linoleic acid polyethylene glycol glyceride. The co-emulsifier is Transcutol HP, propylene carbonate, ethylene glycol monoethyl ether, glycerol furfural, dimethyl isosorbide, diethylene glycol monoethyl ether, PEG400, glycerol, benzyl alcohol	Labrasol is the best emulsifier, and Transcutol HP is the best co-emulsifier. Tocopherol and BHT are added as antioxidants for the formulation. The API must be associated to phospholipids to be incorporated into the oil phase, which may be constituted by several available pharmaceutical oils

TABLE 1: (*continued*)

10	GR1009542 (B)	GR/2019	Oral	Ospemifene	Indicated for the treatment of insomnia associated with vulvar and vaginal atrophy in postmenopausal women	Not available	The release of ospemifene from the soft gel capsules was assessed using a peripheral II device (method II). USP 2 on a dissolution test machine	Tween 20 and 80, Cremophor, sesame oil, Tyloxapol, Miglyol 812, and PEG as surfactants, and diethylene glycol monoethyl ether, Transcutol HP, and PG as co-surfactants	HPMC is added to the formulation to prevent the precipitation of the drug. Tween 20 as surfactant and Transcutol HP as co-surfactant showed the best solubility. The oil phase may be caprylic acid, capric acid, lauric acid, and/or myristic acid
11	CN109589305 (A)	CN/2019	Oral	Docetaxel, cyclosporin A	Indicated for the second-line treatment of anthracycline-resistant breast cancer, advanced breast cancer, ovarian cancer, non-small cell lung cancer, head and neck cancer, and small cell lung cancer	42 rats were randomly divided into 7 groups (n = 6), corresponding to prescriptions 1–7; each group was administered by gavage. The bioavailability of docetaxel is increased from 1% to 20% when associated with cyclosporin A, and to 50% when incorporated in SEDDS	Not available	Polyoxyethylene 35, castor oil, caprylic acid–capric acid monoglycerides and diglycerides	MCT is recommended for the oil phase. Dexamethasone pretreatment is required if Tween 80 is part of the formulation

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
12	US20190153346 (A1)	US/2019	Oral	Tetrahydrocannabinol, cannabidiol, tetrahydrocannabivarin, cannabigerol, cannabidiolic acid, tetrahydrocannabinolic acid, and cannabinol	Treatment of glaucoma, AIDS wasting, neuropathic pain, spasticity associated with multiple sclerosis, fibromyalgia, chemotherapy-induced nausea, allergies, inflammation, infection, epilepsy, depression, migraine, bipolar disorders, anxiety disorders, drug dependency, and drug withdrawal syndromes	*Oral bioavailability I:* Subjects are selected for the *in vivo* oral bioavailability study. Three SEDDS formulations are administered to 3 groups of subjects (n = 10). Orally as solid, orally as an oil solution, and intravenously. Serial blood samples are analyzed using an HPLC or LC/MS/MS assay specific for the CNS administered to each subject. *Oral bioavailability II:* The plasma pharmacokinetics of a cannabinoid SEDDS formulation and a commercially available THC tablet were measured in a study utilizing non-naïve male beagle dogs (n = 4 for each test compound).	Not available	Caprylic/capric triglycerides and ascorbic palmitate	Antioxidants for both the oil and aqueous phases are incorporated in the formulation. The oil phase is composed of lauroyl polyoxyl-32 glycerides and Gelucire 44/14

TABLE 1: (*continued*)

13	CN108703949 (A)	CN/2018	Oral	Indirubin	Not available	18 healthy SD rats (200 ± 20g), half male and half female, are randomly divided into 3 groups. After single-dose intragastric administration of indirubin SMEDDS and indirubin raw material drug gavage solution to rats, the average blood concentration-time curve *in vivo* was used to calculate the pharmacokinetic parameters by statistical moment method with DAS 2.0 pharmacokinetic software	Measure of emulsification time of the formulation in water and in simulated gastric juice, no pharmacopeial method referenced	EL is the emulsifier and Transcutol P is a co-emulsifier	The oil phase is Labrafil M 1944 CS

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
14	KR20180036638 (A)	KR/2018	Oral	Dutasteride and tadalafil	Prostate hyperplasia treatment	Not available	Procedure according to the dissolution test method 2 of 10 revisions of the *Korean Pharmacopoeia*. The eluent was 1% aqueous sodium lauryl sulfate, and the rotational speed was 50 rpm. A comparison between the SEDDs formulation and the commercially available dosage form for both APIs was carried out	Polysorbate-based oxysorbitan fatty acid esters, namely polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polyoxylglyceride-based PEG 6 glyceryl caprylate/ caprate, Labrasol	The oil carrier is determined as glycerol caprylate/ caprate and propylene glycol monocaprylate or any other fatty acid ester derivative of 8 or 10 carbon atoms. Labrasol is the preferred emulsifier. PEG can be used as a dissolution aid.

TABLE 1: (*continued*)

15	US2018036233 (A1)	US/2018	Ophthalmic	Cyclosporine, prednisolone, loteprednol, dexamethasone, testosterone, declomethasone, rimexolone, fluorometholone, betaxolol, levobetaxolol, cephalosporin, amphotericin, fluconazole, tetracycline, brimonidine, brinzolamide, nepafenac, besifloxacin, natamycin, neomycin, and levocabastine	Not available	The ocular tolerability of the various pharmaceutical grade excipients used in the formulations was evaluated *in vivo* using New Zealand White female rabbits. The maximum tolerated doses and the reason for a "not tolerated" observation was listed	Compatibility with simulated tear fluid was confirmed with all formulations to ensure that the composition of the tear fluid would not negatively impact the ability of the SEDDS formulations to spontaneously disperse	Cremophor ELP, Cremophor RH-40, or polysorbate 80 were used as surfactants; and PEG 400, PEG 300, or propylene glycol were used as co-surfactants	The addition of viscosity enhancers or use of polymers with thermal, pH, or ion-sensitive gelling properties have been used to increase ocular residence time. The oil component may be a natural oil such as castor oil or a synthetic oil such as Captex 355 or Capmul MCM. The Captex oil component may also be a combination of these oils
16	CN107661287 (A)	CN/2018	Oral	Ziyuglicosides present in Sanguisorba officinalis	Treatment of bone marrow suppression resulting from the radiotherapy and chemotherapy of cancer	Not available	The dissolution was determined in accordance with the provisions of the slurry method under Appendix XC of the 2015 edition of the *Chinese Pharmacopoeia*	Tween 20 is the emulsifier and Transcutol P is the co-emulsifier	The oil phase is Labrafil M 1944CS

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
17	NZ731986 (A)	AU/2017	Oral	Tocotrienols present in Vitamin E	Antioxidant activity having powerful neuroprotective, tumor suppressive effects and cholesterol lowering properties	A group of rats were administered orally with several formulations constituted by a different emulsifier blend and different oil phases. Plasma was extracted from blood samples and analyzed. The area under the curve (AUC) is measured for each formulation	Not available	Polyoxylated castor oil (Cremophor), polyoxylated glycerides of fatty acid, polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid esters (Span 20, 40, 60, 80), sucrose fatty acid esters, lecithin, saponins, or mixtures thereof	There is addition of fatty acids to improve the solubility of the formulation (e.g., oleic acid, palmitic acid, stearic acid, or mixtures thereof). The oil carrier is glycerol trioleate (GTO) oil

TABLE 1: (*continued*)

18	KR20170116892 (A)	KR/2017	Oral	Coenzyme Q	Treatment of periodontal disease, memory loss, fatigue, coronary artery disease, irregular heartbeat, high blood pressure, and immune system regulation. Treatment and prevention of Alzheimer disease, Parkinson disease, dementia, Lou Gehrig disease, cortical basal degeneration, multi-system lateral gastrointestinal disease, progressive nuclear paralysis, and Huntington disease	Sprague Dawley male rats 6 weeks old (180–200 g) were raised and acclimatized under laboratory conditions for more than 3 days by supplying water and feed. Then apparently healthy rats were selected and used for the experiment. On the day of blood collection, coenzyme Q10 is administered once, and then blood and brain tissue were collected	Not available	Gelucire 34/14 and Lauroglycol 90	The oil carrier can be a derivative of a natural oil, an animal oil or a synthetic oil; it can be chosen from a wide variety and incorporated in the formulation in, preferably 25% to 35% by weight, based on the total composition

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
19	GB2541387 (A)	AT/2017	The SEDDS of the invention may be administered orally, parenterally, topically, intranasally and/or ocularly	Cyclosporin A and other lipophilic drugs	Not available	Not available	Not available	The emulsifier can be selected from the sorbitan esters group (Span), the polyoxyethylene sorbitan fatty acid esters (Tween), poloxamers and polyethylene glycols	The invention is a combination of SEDDS and nanoparticles to improve drug loading, in which the API may be incorporated in the organic phase of the SEDDS, the nanoparticles, or both. The nanoparticles are functionalized and designed to have imaging and target properties. The lipid acting as the oil phase for SEDDS is selected from a group consisting of triglycerides, diglycerides, monoglycerides, and mixtures thereof. For example: caprylic/capric triglyceride (Captex 300)

TABLE 1: (*continued*)

20	TW201622705 (A)	KR/2016	Oral	Dutasteride	Treatment of benign prostatic hyperplasia, prostate cancer, and androgenetic alopecia	Not available	The dissolution test was carried out according to the test methods (second method) in the *Korean Pharmacopoeia*, 8th ed.	PEG-40 hydrogenated castor oil (HCO-40)	Using HCO-40, the initial dissolution rate of dutasteride can be maintained even when stored for a long time under any condition. The oil phase may consist of monoglycerides or diglycerides of caprylic/capric acid, coconut oil, oleic acid, or linoleic acid

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
21	CN105708797 (A)	CN/2016	Oral	Cinnamic amide derivatives	Treatment of depression	Twelve male Wistar rats were randomly divided into 2 groups; 1 group was given SEDDS aqueous dispersion emulsion; the 2 groups were given drug-loaded solid dispersion aqueous dispersion. The drug content in plasma was determined to calculate the AUC, mean residence time (MRT), clearance rate (CL), and biological half-life ($T_{1/2}$) of the substituted cinnamide derivative preparation	Not available	The emulsifier is one or a mixture of the following: caprylic/capric acid polyethylene glycol glyceride, polyoxyethylene 35 castor oil, polyoxyethylene hydrogenated castor oil, lauric acid polyethylene glycol glyceride, stearic acid polyethylene glycol glycerides, glycerol polyethylene glycol-75-stearate, polyethylene glycol-7-stearate, Span 20, Span 40, Span 60, Span 80, Tween 80, Tween 60. One or a mixture of PEG 400	The oil phase may be soybean oil, castor oil, medium-chain triglycerides, polyglycerol oleate, polyethylene glycol oleate, glyceryl monooleate, glyceryl monolinoleate, and glycerine

TABLE 1: (*continued*)

22	AU2016203127 (A1)	AU/2016	Oral	Delta-9-tetrahydrocannabinol and other cannabinoids, or standardized extracts of *Cannabis sativa*	Treatment of nausea associated with cancer chemotherapy and brain damage associated with stroke, heat trauma, and cardiac arrest	Not available	The formulation is evaluated in different dissolution media. The percentage release obtained in each of the tested dissolution mediums is observed. No pharmacopeial method directly referenced	The emulsifier may be chosen from a group consisting of polyglycolized glycerides, polyoxyethylene glycerides, polyoxyethylene castor oil derivatives, polyethylene glycol-fatty acid esters, polyethylene glycol glycerol fatty acid esters, and transesterification products of oils and alcohols	This formulation was found to promote targeted chylomicron/ lipoprotein delivery, and optimal bioavailability. The dosage form may include cytochrome P450 metabolic inhibitors, P-GP efflux inhibitors, and amphiphilic/ nonamphiphilic solutes to induce semisolid formation for targeted release rates. The oil phase may be triglycerides and/or mixed glycerides and free fatty acids
23	CN105535979 (A)	CA/2016	Not specified	Poorly water-soluble drugs categorized in Class II of BCS. Danazol, indomethacin, and haloperidol are used as model drugs	Not available	Not available	The research method adopts US Pharmacopoeia method II (pulp method). The dispersibility and release of the formulation is observed	Cremophor RH40, Cremorphor EL, Brij 97, Tween 80. The PEG group compounds may act as a co-emulsifier	The oil phase is composed of Capmul MCM, capric, caprylic, or caproic acid

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
24	KR101608178 (B1)	KR/2016	Oral	Atorvastatin calcium	Treatment of hyperlipidemia	A suspension of atorvastatin calcium as a nano-microemulsified drug delivery system and a control were administered to male Sprague Dawley rats. The blood concentration curve (AUC), the highest blood concentration (C_{max}), and the time to reach the highest blood concentration (T_{max}) were calculated using BA Calc 2007 provided by the Korea Food and Drug Administration	The dissolution test was performed according to the USP apparatus II (paddle) method	Tween 20, Tetraglycol and Transcutol P	The oil phase or carrier is Capmul MCM

TABLE 1: (*continued*)

25	IN3370MU2013 (A)	IN/2015	Oral	Efavirenz	Treatment of AIDS and VIH	Not available	Not available	The oil carrier in this invention may be chosen from hydrogenated castor oil, caprylic/ capric glycerides, and medium chain triacylglycerols. The self-emulsifying drug delivery system of efavirenz may further contain additional active ingredients, such as protease inhibitors, nucleoside reverse transcriptase inhibitors, nucleotide reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors, and integrase inhibitors
							The emulsifier may be one or a combination of the following: D-α-tocopherol PEG 1000 succinate, polyoxyl castor oils, hydrogenated polyoxylcastor oils, lauroyl macrogolglycerides, caprylocaproyl macrogol glycerides, diethylene glycol monoethyl ether, polyoxyl 40 hydrogenated castor oil, and polyoxyl 35 castor oil. Cremophor ELP	

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
26	US2015164851 (A1)	IN/2015	Oral	Diacerein	Treatment of osteoarthritis	Not available	For determination of drug release rate, USP type 2 apparatus (75 rpm) was used wherein 1,000 mL of pH 5.7 phosphate buffer at 37°C ± 0.5°C, was used as the medium	The following compounds and their mixtures act like an emulsifier: surfactants from the Tween, Labrafil, Labrafac, and Labrasol groups	The oil phase for this invention may be composed of Miglyol derivatives (fractionated coconut oil), soy oil, almond oil, olive oil, peanut oil, other fatty acid esters of glycerols, and medium chain triglycerides. This formulation includes a polymer that prevents precipitation of the drug. The polymer may be one or more of the cellulosic polymers group or their derivatives

TABLE 1: (*continued*)

27	WO2015022454 (A1)	FR/2015	Oral	Ketoprofen, nimesulide, AMP, nalbuphine, cyclosporin A, cholecalciferol, fenofibrate	Not specified	The oral passage was evaluated in 6 rats (Charles River) of mean weight 250 g. The plasma cyclosporine level was determined with HPLC	Not available	No emulsifier used	This invention discloses a spontaneous powder self-emulsifying drug delivery system associated with cyclodextrins. This new system may undergo direct compression to form tablets. The aim is to present an innovative system that is compressible and dispersible in water or in biological media, without surfactants and without organic solvents based on cyclodextrins to prevent recrystallization and precipitation of insoluble active ingredients

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
28	WO2014140695 (A1)	IN/2014	Oral	(+) trans-2-(2-chloro-phenyl)-57-dihydroxy-8-(2-hydroxymethyl-1-methyl-pyrrolidin-3-yl) -chromen-4-one (pyrrolidine substituted flavone)	Treatment of cancer, polycystic kidney disease, nephrological disorder, psoriasis, immunological disorder involving unwanted proliferation of leukocytes, restenosis, proliferative smooth muscle disorder, radiation induced mucositis, viral infection, mycotic infection, or cardiovascular abnormality	The pharmacokinetic parameters of compound A were determined in 3 male beagle dogs by a single bolus intravenous (IV) and oral capsule (PO) administration. The noncompartmental module of WinNonlin Professional 5.2 was used to calculate parameters	Not available	The emulsifier for this invention may be one or a mixture of the following: Cremophor EL, Cremophor RH, D-α- tocopherol polyethylene glycol 1000 succinate (vitamin E TPGS or TPGS), polysorbate 20, polysorbate 80, Solutol HS 15, sorbitan monooleate, poloxamers, Labrafils, Labrasol, Gellucire 44/14, Softigen 767, mono- and di-fatty acid esters of polyethylene glycol	In this invention de emulsifier and the solubilizer act as the oil phase, there is no additional oil incorporated. The solubilizer for the formulation may be one or a mixture of the following: the group comprising polyethylene glycol (having molecular weight between 300–6000), propylene glycol derivatives, glycerine, Cremophor, polysorbates, Lutrol, Carbitol

TABLE 1: (*continued*)

29	US20140177308 (A1)	NO/2014	Oral	Atorvastatin, cerivastatin, fluvastatin, itavastatin, lovastatin, mevastatin, rosuvastatin, simvastatin, pravastatin, and pitavastatin	Treatment of irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, heart failure, and post myocardial infarction (MI)	The study was performed in 8 male Göttingen SPF minipigs. Treatment was performed in a cross-over design. Plasma samples were analyzed within 2 weeks for total lipid content of EPA and DHA by a validated LC-MS/MS method	Not available	Polysorbate 20, polysorbate 80	The oil phase is a mixture of EPA and DHA, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride and are present in the greater proportion. The smaller proportion may be formed by α-linolenic acid (ALA), heneicosapentaenoic acid (HPA), docosapentaenoic acid (DPA), eicosatetraenoic acid (ETA), eicosatrienoic acid (ETE), and stearidonic acid (STA), gamma-linolenic acid (GLA), arachidonic acid (AA), docosapentaenoic acid, and mixtures thereof

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
30	CN103357013 (A)	CN/2013	Oral	Paclitaxel, docetaxel, β-sitosterol, γ-sitosterol, stigmasterol	Treatment of lung squamous cell carcinoma, lung adenocarcinoma, breast cancer, testicular embryonic cancer, ovarian cancer, malignant thymic cancer, gallbladder cancer, and esophageal cancer	NOD/SCID female mice were inoculated with human breast cancer cell MCF-7. Plasma concentration was measured to determine the relative bioavailability of paclitaxel in co-treatment with and without sterol	Not available	Polyoxyethylene castor oil condensate, polyoxyethylene hydrogenated castor oil condensate, polysorbate, egg phospholipids, poloxamers, or a mixture of these	The invention presents an oil phase consisting of a C_{10}-C_{30} terpene solvent containing isoprene structure, such as orange peel oil, lemon peel oil, turpentine oil, eucalyptus oil, squalene, and limonene, or a mixture of these. There is also the inclusion of PEG 200, 300, 400, and glycerol as cosurfactants

TABLE 1: (*continued*)

31	WO2013072767 (A1)	NO/2013	Oral	Acetylsalicylic acid and other salicylates	Treatment of irregular plasma lipid levels, thrombosis, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, heart failure, and post myocardial infarction (MI)	Not available	Not available	Any surfactant selected from the Tween, Pluronic, Brij, Span, Myrj, and Cremophor groups or a mixture of these. Additionally, the emulsifier may be chosen from: ethylene glycol distearate, glyceryl monostearate, propylene glycol monostearate, glyceryl monostearate, diethylene glycol monolaurate, acacia gum, cetrimonium bromide, cetylpyridinium chloride, poloxamer 188, sodium lauryl sulfate	Omega 3-fatty acids (DHA, EPA) are used in this formulation as the oil phase or carrier

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
32	US2012135940 (A1)	US/2012	Oral	Cyclosporins or polypeptide lipophilic drugs	Not specified	Not available	Not available	Polyoxyethylene glyceryl triricinoleate, PEG (35) natural castor oil, PEG (35) hydrogenated castor oil, PEG (40) natural castor oil, and PEG (40) hydrogenated castor oil, Labrasol group, and Tween group	This invention describes a polar lipid self-emulsifying delivery system (PLSEEDS), this means the drug is dissolved in a polar lipid oil carrier such as Capmul MCM and Capmul MCM C8

TABLE 1: (*continued*)

33	JP2017193555 (A)	NO/2011	Oral	Omega-3 fatty acids, EPA, DHA	Therapeutic treatment and/or regulation of irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, heart failure, and post myocardial infarction (MI)	The study was performed in 8 male Gottingen SPF minipigs. Treatment was performed in a crossover design. The dose was 2 g per animal. Plasma samples were analyzed within 2 weeks for total lipid content of EPA and DHA by a validated LC-MS/MS method	Not available	Polysorbate 20, 80, Tween family, and lecithin as surfactants, and ethanol, benzyl alcohol, PEG, PEG 400, tetrahydrofurfuryl PEG ether, *N*-methyl pyrrolidone, 2-pyrrolidone, bile salts, for example sodium deoxycholate, and ethyl oleate as co-surfactants	The EPA and DHA can be in ethyl ester, free fatty acid, or triglyceride form. The oil phase can be constituted by linolenic acid (ALA), heneicosapentaenoic acid (HPA), docosapentaenoic acid (DPA), eicosatetraenoic acid (ETA), eicosatrienoic acid (ETE), and stearidonic acid (STA). The fatty acid oil mixture may be derived from animal oils and/or nonanimal oils

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
34	KR20110136256 (A)	KR/2011	Oral	Flurbiprofen	Treatment of mild and severe pain, rheumatoid arthritis, osteoarthritis, pain after tooth extraction and minor dental surgery	Not available	The experiment used the second test method (paddle method) of the *Korean Pharmacopoeia*	Labrasol and diethylene glycol monoethyl ether (Transcutol HP)	The oil phase in this invention is Labrafil M 1944 CS. A solid carrier to deliver the formulation may be chosen from dioxy silicone, magnesium stearate, dextran, and hydroxyl propyl-beta-cyclodextrin
35	KR101055412 (B1)	KR/2011	Oral	Dutasteride	Treatment of prostatic hyperplasia, prostate cancer, and androgenic alopecia	Not available	The dissolution test followed the standards and test methods provided by the FDA, a dissolution test was conducted according to the dissolution test method 2 (paddle method) among general test methods of the *Korean Pharmacopoeia*	Sucrose palmitine acid esters, polyoxyethylene stearates, sodium lauryl sulfate and poloxamer	The oil phase for this formulation may be soybean oil, caprylic/capric triglyceride, and propylene glycol monocaprylate. On addition, there is the inclusion of PVP as a solubilizer and binder for the dutasteride tablets. These tablets present a coating of a cellulose derivative polymer

TABLE 1: (*continued*)

36	US2011294900 (A1)	IN/2011	Oral	Diferuloylmethane (curcumin)	Proposed for anti-inflammatory, antioxidant, antiproliferative and anti-angiogenic therapy	Twenty animals were observed. Dose selected in both test and control rats was 180 mg/kg body weight. The results show that the plasma concentration obtained for the self-nanoemulsifying formulation were significantly higher than the aqueous suspension and are maintained for a longer time, thus increasing the biological half-life of the drug	The dissolution behaviors of curcumin loaded SNEDDS were studied in USP II dissolution apparatus using Japanese sinkers	Cremophor EL; if not available, one or a combination of the following may be used: hydrogenated vegetable oils, polyethoxylated castor oils or polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid esters, and polyoxyethylene castor oil derivatives	The oil phase may be selected from Captex 100, Captex 300, Captex 355, Miglyol 810, Miglyol 812, Miglyol 818, Miglyol 829, Dynacerin 660, Capryol 90, Captex 200. and Miglyol 840, or from edible oils like soybean oil. The oil with the best characteristics is propylene glycol monocaprylate (Capryol 90), given that it also acts a s a co-emulsifier for the formulation. Other co-emulsifiers that can be used are: Transcutol, Capmul, Tetraglycol, Labrafil, Lutrol F68, and Carbitol

TABLE 1: (*continued*)

	Application number (reference)	Country/ year	Administration route	Compounds	Indications or applications	Bioavailability or pharmacological assay	Release profile test	Emulsifier	Other relevant information
37	CN102247321 (A)	CN/2011	Oral	Apogossypolone	Treatment of cancer	9 male SD rats were divided into 3 groups, and were given the apogossypolone SEDDs preparation, its ordinary oral suspension, and the oral solution (30 mg/kg). After administration, the blood samples were centrifuged, extracted, and analyzed by LC-MS	Not available	Lecithin, Tween 80, Span 80, polyethylene glycol-8, glycerol caprylic acid/ caprate (Labrasol), polyoxyethylene castor oil (Cremophor EL), polyoxyethylene hydrogenated castor oil (Cremophor RH40), Pluronic F68, coconut oil C8/ C10 polyethylene glycol glycerides (Labrafac CM 10), almond oil oleic acid polyethylene glycol glycerides (including Labrafil M1944 CS, Labrafil M 2125 CS, and Labrafil M 2130 CS)	The oil phase for this formulation can be: soybean oil, peanut oil, hydrogenated corn oil, sesame oil, safflower oil, olive oil, almond oil, oleic acid polyethylene glycol glyceride, oleic acid glyceride, coconut oil, C8/C10 triglyceride, linoleic acid glyceride, lauric acid glyceride, Captex 355, and Captex 200. This invention may incorporate an alcohol as a co- emulsifier

docetaxel–cyclosporin A complex in which the system can avoid acid hydrolysis of the active substances. This is achieved by the second mechanism previously discussed, the hydrophobicity of the oil droplets hinders the activity of some enzymes by preventing the interaction between the enzyme and API.

On the other hand, a study previously reported by Bernkop-Schnürch[16] focused on the development of mucoadhesive SEDDS by the addition of hydrophobic mucoadhesive polymers generating covalent bond to the mucus. This can be achieved with thiomers, which are polymers that have thiol groups, and it depends on the cross-linking rate of the polymer chains. Furthermore, the mucus permeation abilities of SEDDSs have also been studied. Mucus permeation is reported to be better if the mean droplet size is less than 100 nm[17] and if the SEDDS is pegylated. The presence of polyethylene glycol (PEG) groups covering the oil droplets protects the SEDDS from mucolytic enzymes, thus rendering the formulation inert to the mucosal microenvironment.[18] Furthermore, the use of thiobutylamidine-dodecylamine (TBA-D), thioglycolic-acid-octylamine (TGA-O) and papain, has been registered to develop a mucolytic SEDDS.[6] These substances break disulfide bonds on the mucus and facilitate SEDDS dispersion. Only patent 8 (see Table 1), which disclosed a SEDDS for the delivery of cannabidiol, claimed the possible use of thickening and adhesive polymers to develop a mucoadhesive formulation, which in turn would allow for a delayed drug release. This is uncommon, since most of the patents aimed for immediate release rather than modified or controlled release.

Only two patents described a SEDDS with modified and controlled release features. The first one is patent 19 (see Table 1), for the controlled release of cyclosporin A. The inventors presented a hybrid system with the inclusion of nanoparticles to increase poor drug loading. Since the common loading of a regular SEDDS is determined by the lipid-surfactant-cosolvent trio, and this is specific to the identity of the API, the document stated the need to develop a uniform method to enhance drug loading independent of the physicochemical nature of the active substance, hence, the addition of the nanoparticles. In this system, the drug may be loaded in the nanoparticles, the oil phase, or both, and the nanoparticles will be dispersed in the oil. Once the formulation contacts water or an aqueous medium, the emulsion is formed, and the nanoparticles will be present in the oil droplets. Here, the free drug present in the oil will be immediately released, while the drug encapsulated in the nanoparticles will have an extended release. It takes more time for the aqueous medium to penetrate the nanoparticle. Major advantages of this method may be that the nanoparticles may be core–shell type or homogeneous, they may possess imaging and targeting properties through functionalization, and they may allow the loading of two different APIs if a combined therapy is needed. On the other hand, one of the major drawbacks identified is the use of organic solvents to disperse and load the nanoparticles. The inventors satisfactorily observed that this system increased drug loading and did not interfere with the emulsification process.

Patent 35, on its regard, presents the development of a solid SEDDS with an additional coating process form sustained release tablets. The inventors use a mixture of a water-soluble polymer such as PEG, sodium carboxymethyl cellulose, and polyacrylate, and a water-insoluble polymer such as polyvinyl chloride, and polyvinyl acetate as a first

coating, and then just the water insoluble-polymer as a second coating. The general principle as described by Efentakis and Politis[19] is simple. Once in contact with the release medium, the water-soluble polymer will swell, preventing immediate release of the SEDDS. However, broad swelling is not desirable because it may completely prevent the release, so a water-insoluble polymer is added to control the swelling. This yields a constant flux of matter from the interior of the tablet to the exterior, creating a sustained release device. A second coating of a water-insoluble polymer is added to protect the tablet from aqueous medium and delay the onset of drug release until the polymer starts breaking down.

There was one additional tactic implemented to develop a modified release SEDDS, although not as notorious as the previous two. In patent 22 (see Table 1) for the oral delivery of cannabinoids, the inventors aimed to solve the problems common to cannabis-based SEDDS, which are rapid gastric emptying while the SEDDS is in colloidal state, and irregular high peak plasma concentrations. For this, they would add amphiphilic and nonamphiphilic solutes to the formulation to induce the formation of a semisolid. This would delay the entry of water to the SEDDS, making it resistant to acid catalysis in the stomach and resulting in sustained release of the cannabinoids. The solute was ascorbyl palmitate, and once it was added in excess, it would turn the SEDDS preconcentrate from liquid to semisolid.

Another approach currently explored in the literature is formulating *in situ* zeta potential changing SEDDS, as shown by Sharifi et al.[20] The surface charge can be switched by loading the SEDDS with a compound containing an ester group susceptible to enzymatic degradation. Mucus permeation can be enhanced by changing a negatively charged droplet into a positively charged one. However, this type of technology is not yet present in the patents, as most of them characterized the formulations, identifying the value of ± 30 mV as the ideal zeta potential, but there were no references to a formulation with the ability to change this parameter on its own.

Finally, cell-penetrating SEDDS for oral gene delivery, as described by Haupstein et al.,[21] can be achieved by incorporating lipids such as lipofectin, hexylamine, dodecyltrimethylammonium ion, cetylpyridinium chloride monohydrate, stearalkonium chloride, cetrimide (using HIP), and cell-penetrating peptide HIV-1 Tat-protein 49-57 (conjugated to oleic acid) that induces clathrin- and caveolae-mediated endocytosis. None of the patents reviewed used this technology because none were concerned with the delivery of genetic material. This may suggest that research in this area is still incipient and that there may be many challenges to develop an effective manufacturing method.

Many of the patents presented a solid dosage form for the SEDDSs developed, mainly because liquid SEDDSs may present issues with precipitation of the API after long storage periods or when they are dispersed *in vivo*. Solid SEDDS can be made by adding adsorbent agents, such as cross-linked porous silicon dioxide, magnesium aluminum silicate, and microporous calcium silicate, to the formulation.[13] As reported by Joyce et al.,[22] the design of a hybrid drug delivery system by solidifying SEDDS may result in prolonged gastric residence, which in turn extends the absorption and dissolution time by incorporation of polymers such as hydroxypropyl methylcellulose and microcrystalline cellulose. Solid SEDDSs also improve intestinal solubility by inhibiting the precipitation

using polymeric precipitator inhibitors (polymeric nanoparticles) and modulating lipolysis of the solid carrier. They also improve drug permeability by incorporating the SEDDS preconcentrate in known permeation enhancers solid carriers such as chitosan. Of the patents reviewed, many used solid adsorbent agents, such as dextrin, mesoporous silica, silicon dioxide, magnesium stearate, dextran, and hydroxylpropyl-beta-cyclodextrin to carry the SEDDS preconcentrate. A few others use binding agents to form tablets by direct compression over the lipids in solid state. Nonetheless, liquid SEDDS was still present among the inventions. Other strategies implemented to deal with the precipitation issues include the addition of crystal growth inhibitors and cellulosic polymers to induce supersaturable SEDDS, as well as the use of several co-solvents in the formulation. The use and selection of new excipients to form solid SEDDS formulations is trending in the literature, since it offers better product stability and increased patient compliance.[23]

This supersaturable SEDDS (S-SEDDS) was specially disclosed in patents 7 and 26 (see Table 1) for the delivery of ulipristal acetate and diacerein, respectively. Here, the inventors produced a SEDDS with a lower concentration of surfactant by adding crystal growth inhibitors (CGI), such as HPMC and other cellulosic polymers, to the formulation. In this system, the drug is in amorphous form in the solid carrier, forming a hydrogen bond with the CGI to delay crystallization. When the SEDDS leaves the adsorbent, it forms an oil-in-water (O/W) emulsion once in contact with the aqueous medium, and drug molecules are further solubilized in the milk droplets. The drug then dissolves to exceed its equilibrium solubility, forming a supersaturated solution, which may increase residence time and absorption in the gastrointestinal tract.

SEDDSs may comprehend self-microemulsifying drug delivery systems (SMEDDSs) and self-nanoemulsifying drug delivery systems (SNEDDSs). Each type of SEDDS has advantages and disadvantages. Nevertheless, SNEDDSs seem to generate more interest than SMEDDS, as the majority of the inventions were the SNEDDS type of systems. This is further supported by trending research focused on SNEDDSs, as shown by Laffleur and Keckeis,[24] who present a SNEDDS as a suitable system for the delivery of talinolol and rosuvastatin calcium, which manages to improve drug payload, drug dissolution, intestinal permeation, and oral bioavailability while decreasing toxicity. Differences between each type of SEDDS are shown in Table 2.

The major representative of SNEDDSs was in patent 6 (see Table 1). This document discloses a SNEDDS formulation for the oral administration of cannabinoids. The inventors found that loading cannabis resin or a cannabinoid isolate in a SNEDDS increases drug solubility while enhancing permeation across the intestinal membrane through a wide distribution in the gastrointestinal tract. In addition, this showed a significant decrease in the food effect, associated with poor cannabinoid bioavailability. This is mainly due to the decrease in droplet size, which allowed a greater extent of absorption for the formulation created.

Another aspect relevant to the emulsion droplet size is the clarity of the emulsion formed. This becomes significant when developing an ocular formulation, as in patent 15, in which the inventors disclosed an SMEDDS formulation for ophthalmic release of lipophilic drugs. The need for the formulation to have ocular clarity while enhancing the

TABLE 2: Comparison between traditional self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery systems (SMEDDS), and self-nanoemulsifying drug delivery systems (SNEDDS)

Parameter	Conventional SEDDS	SMEDDS	SNEDDS
Droplet size (nm)	~ 300	100–250	< 100
Appearance	Murky	Clear	Clear
HLB	< 12	> 12	> 12
Oil proportion (%)	40–80	> 20	> 20
Surfactant proportion (%)	30–40	40–80	40–80

Adapted from Laffleur and Keckeis.[24]

bioavailability, permeation and ocular residence time was considered as a critical quality parameter achievable only by SNEDDS and SMEDDS. On this regard, the inventors stated that, while common and SNEDDS derived emulsions are kinetically stable systems, microemulsions derived from SMEDDSs are thermodynamically stable due to a higher concentration of water-soluble components, which in turn may provide constant ocular clarity and a desirable emulsion droplet size for ophthalmic administration.[25] The higher stability of SMEDDSs was also demonstrated in patent 10 (see Table 1) for the delivery of ospemifene, since this type of SEDDS attained the ideal zeta potential of ± 30 mV, as discussed previously.

C. Lipids in SEDDS

The structures of the lipids most used in the studied inventions are presented in Table 3, alongside their classification according to the length of the carbon chain, origin, and required hydrophilic–lipophilic balance (HLB). It is important to note that the HLB is a specific value to each surfactant that predicts the capacity of the molecule to form an emulsion by considering the number and nature of both its hydrophobic and hydrophilic functional groups. On the other hand, the required hydrophilic–lipophilic balance (RHLB) of a surfactant is the optimal value required to completely emulsify an oil phase. This value is often determined experimentally and is generally obtained by the mixture of two or more surfactants.[26]

The composition of SEDDS owes some of its success to the ability of the lipid to solubilize the API, given that it is the medium that is going to carry the poorly water-soluble drug through all the administration process until the emulsification in the gastrointestinal tract and subsequent release and absorption of the drug.

There were many oil phases claimed for each of the patents reviewed (see Table 1). The substances more commonly used, or those presenting a better formulation stability are presented in Table 3, and they can be classified as natural, semisynthetic, and synthetic. The amount and type of oil are definitive to the formulation; several of the patents struggled with this aspect. Many of the inventions revealed that the lipid has to be in the correct

TABLE 3: Structures of lipids commonly used in the inventions studied

Lipid	Classification	RHLB	Structure
Caprylic acid	MCFA, natural	—	
Capric acid	MCFA, natural	—	
Lauric acid	LCFA, natural	—	
Myristic acid	LCFA, natural	—	
Linoleic acid	LCFA, natural	—	

TABLE 3: (*continued*)

Lipid	Classification	RHLB	Structure
Eicosapentaenoic acid	LCFA, natural	—	
Docosahexaenoic acid	LCFA, natural	—	
Capmul MCM	MCFA, synthetic	3–4	
Capryol 90	MCFA, synthetic	6	

TABLE 3: (*continued*)

Isopropyl laurate	LCFA, synthetic	—	
Isopropyl myristate	LCFA, synthetic	12	
n-Butyl oleate	LCFA, synthetic	—	
Polyglycerol oleate	LCFA, synthetic	—	
Polyethylene glycol oleate	LCFA, synthetic	—	
Glyceryl monooleate (Peceol)	LCFA, synthetic	3.3	

TABLE 3: (*continued*)

Lipid	Classification	RHLB	Structure
Ethyl linoleate	LCFA, synthetic	—	
Glyceryl monolinoleate	LCFA, synthetic	4	
Lauroyl polyoxyl-32 glycerides Gelucire 44/14	LCFA, synthetic	14	R = 11 n = 32
Caprylic/capric triglyceride	MCT, synthetic	—	

TABLE 3: (*continued*)

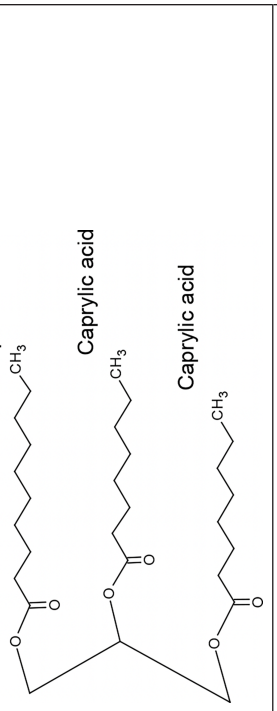
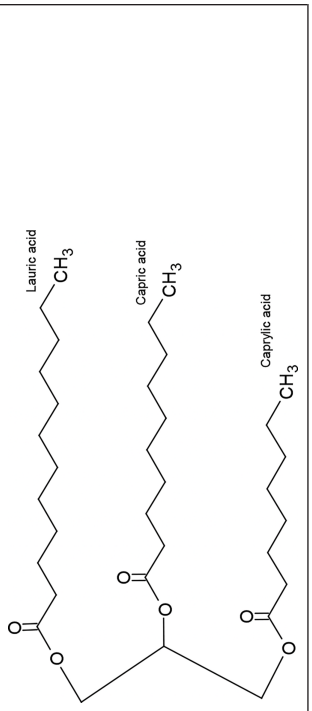
Miglyol 810	MCT, synthetic	—	
Coconut oil	MCT, natural	—	

TABLE 3: (*continued*)

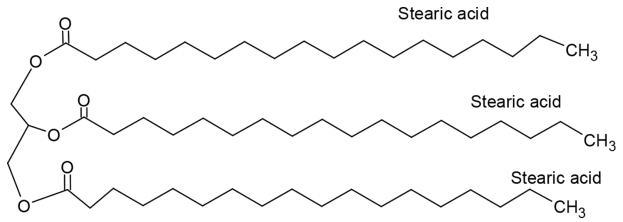
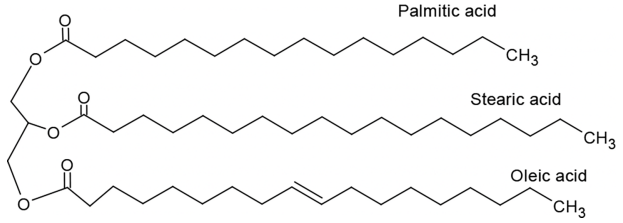
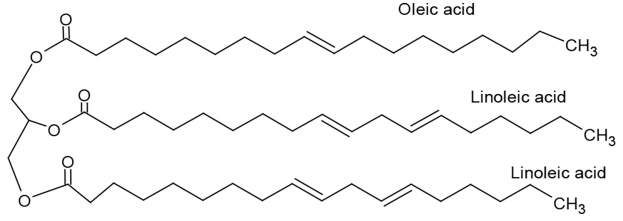
Lipid	Classification	RHLB	Structure
Hydrogenated corn oil	LCT, semi synthetic	—	 The major triacylglycerol molecules in corn oil are LLL (25%), LLO (22%), LLP (15%), OOL (11%), and PLO (10%)
Hemp seed oil	LCT, natural	—	 May also contain linoleic acid in free form or triglyceride form
Seed oils (soybean oil, sesame oil)	LCT, natural	—	 May also contain triacyclglycerols of only linoleic acid, or palmitic acid and linoleic acid in lesser proportion. Sesame oleic acid and linoleic acid are the main fatty acids with the same ratio (~ 40%). The major triacylglycerols in this oil are LLO (25%), LLL (20%), and LOO (15%)

TABLE 3: (*continued*)

Olive oil	LCT, natural	—	
Nut oils (almond and peanut)	LCT, natural	—	 68% Oleic acid, 25% linoleic acid, 5% palmitic acid, 2% palmitoleic acid and stearic acid. The main triacylglycerols in peanut oil are OOL (19%), OLL (18%), POL (13%), OOO (12%), and POO (7%)
Castor oil	LCT, natural	—	

TABLE 3: (*continued*)

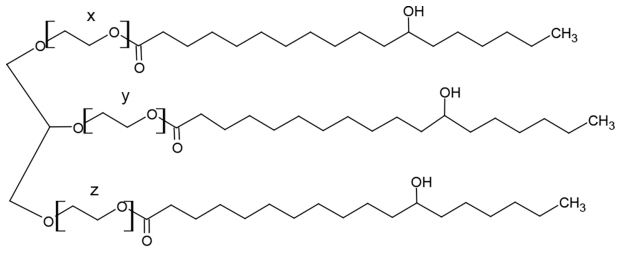
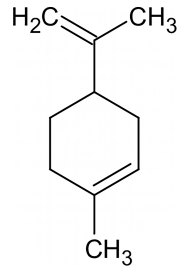
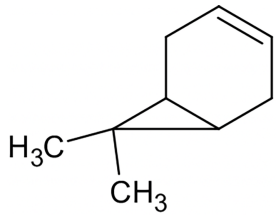
Lipid	Classification	RHLB	Structure
Polyoxyethylene hydrogenated castor oil (Cremophor RH40)	LCT, synthetic	14–16	 $x + y + z = 40$
Limonene	Terpene, natural	—	
Turpentine oil	Terpene, natural	—	 3-Carene is shown here; the oil may contain a complex mixture of terpenes.

TABLE 3: (*continued*)

Eucalyptus oil	Oxane, isoprenoid lipid, natural	—	
Squalene	Terpene, natural	—	

L, linoleic acid; LCFA, long chain fatty acid; LCT, long chain triglyceride; MCFA, medium chain fatty acid; MCT, medium chain triglyceride; O, oleic acid; P, palmitic acid; RHLB, required hydrophilic–lipophilic balance.[27]

quantity. If it is too low, it can induce poor emulsification (10%), and if it is too high (80%), may affect the organoleptic properties, producing unpleasant odor or taste (see patent 8 in Table 1).

The study by Pandey et al.[28] presents the definition of natural oils as lipids with a varying chain length and degree of unsaturation, which makes them susceptible to oxidation. This can be prevented by hydrogenation or by fractioning the oil into its constituent glycerides, thus enhancing its physical and drug absorptive properties while decreasing vulnerability to oxidation. As shown in Table 3, the hydrogenation solution against the oxidation phenomena is only approached by the inventors for a few lipids employed in the patents, such as hydrogenated corn oil, Miglyol 810, and hydrogenated castor oil (Cremophor RH 40). Most of the other inventions added antioxidants to the oil phase, such as tocopherols, butylated hydroxytoluene, and butylated hydroxyanisole, to deal with this issue. The antioxidants may even be added for both the oil and aqueous phase once the self-emulsification has taken place.

Research by Ghazani and Marangoni[27] established two principal categories for oils used in SEDDS, medium-chain triglycerides (MCTs), and long-chain triglycerides (LCTs). MCTs are small, only six to ten carbon atoms, highly soluble, mainly transported via portal circulation, and metabolized in the liver. They are considered neutral on low density lipoprotein, high density lipoprotein-cholesterol, and triacylglycerol serum concentration levels; whereas LCTs are absorbed via the lymphatic system after micellar transport at the intestinal wall and may increase plasma cholesterol. At first view, this may yield a beneficial health effect for MCTs but not for LCTs.

Triglyceride vegetable oils are often used as a base in SEDDSs, as they are considered edible and safe. One issue to consider, though, is that vegetable oils are mostly LCTs, but there are some, such as coconut oil, that are considered to be MCTs. Coconut oil is the source of glyceryl tricaprylate/caprate, a well-known and commonly used synthetic MCT for SEDDSs. The presence of numerous ester groups in triglycerides increases lipophilicity and solvent capacity to drugs. Hence, if compared by molecular weight, MCTs would have a better solvent capacity than LCT, according to the Pandey and Kohli study,[28] further supporting the beneficial effects of MCTs over LCTs. This is directly corroborated by the patents presented in this study, as a majority of them use coconut oil derivatives as the main lipid carrier, with excellent results reported. These may include Capmul MCM, Capryol 90, caprylic/capric triglyceride (Captex), and Miglyol 810.

Similarly, Nardin and Köllner[29] recently reported that edible oils, even though considered safe, have a limited capacity to dissolve drugs and a poorly efficient self-emulsification. Thus, modified and hydrolyzed vegetable oils are preferred, because they improve drug solubility and may produce an efficient self-emulsification system when combined with nonionic surfactants. Their degradation products may even resemble those obtained after normal intestinal digestion. At present, natural vegetable oils have been replaced increasingly by novel semisynthetic lipids, because they are amphiphilic, which provides an additional surfactant activity for the SEDDS and makes them attractive to researchers.[30] This is true for this review because most of the inventions

presented the use of semisynthetic lipids, as shown in Table 3. Sometimes it was hard to tell whether the formulation in the patent was constituted only by surfactants and when these structures stopped acting just as carrier lipids and started having actual active surface properties to participate in the solubilization of the drug and the emulsification process. Nardin and Köllner[29] also stated that for a given drug, LCTs such as Labrasol and castor oil may maintain drug supersaturation levels after dilution.[31] However, MCTs such as Capryol 90 and Lauroglycol have been shown to induce drug precipitation,[17] which seems to contradict the general view of these lipids presented by Pandey and Kohli.[28] This may be due to the interaction between drug and lipid, so it is necessary to choose the optimal system according to the needs of the active substance. Not all formulations are going to work for the same drug. For example, one of the patents reported Capryol 90 as the best oil phase for diferuloylmethane, a curcumin derived compound, given that it acted as an additional emulsifier or co-emulsifier.

Lipids have a major impact in increasing the oral bioavailability of drugs, altering their biopharmaceutical properties. It has been widely reported that low chain fatty acid and monoglycerides may increase drug transport by the lymphatic system, because they are re-esterified in the small intestine and taken into chylomicrons and transported into the lymph vessel via exocytosis, thus evading first pass metabolism and increasing bioavailability.[32] On the contrary, Medium chain fatty acid are transported directly to the liver and metabolized with little to no inclusion in chylomicrons. However, enzymatic lipolysis of MCTs has also been shown to keep the drug solubilized as interaction with endogenous bile salts and phospholipids may increase the solubilization of the API, resulting in an increase in its bioavailability.[33] The lymphatic route was targeted by several of the patents, especially those reporting innovative SEDDS for the oral delivery of vegetable bioactive derivatives, such as patent 21 (cinnamic acid derivatives) and patent 22 (cannabinoids).

The form in which the molecule of lipid is formulated is going to influence SEDDS metabolism as well. Patent 29 (see Table 1) describes that fatty acids in free carboxylic acid form may target binding to specific sites, but it also may prevent the molecule from crossing the cell membranes because of its susceptibility to ionization. To solve this problem, the inventors often protect the carboxylic acid groups by by converting them to esters, reducing the molecule polarity and easing its passage through lipophilic cell membranes. Once in the bloodstream, fatty acid esters can be hydrolyzed by an enterase to free carboxylic acid, regaining the target properties, or they may be metabolized in the liver.[34] This approach was common in many patents, as the inventors claimed the use of a specific fatty acid molecule and its possible derivatives as a monoglyceride, diglyceride, or triglyceride, then they would proceed to observe which one presented the best *in vivo* performance in the SEDDS.

Nevertheless, as reported by the study of Leonaviciute et al.,[15] triglycerides undergo its own kind of metabolism. They showed that the lipid phase in triglyceride form is readily degraded by the lipases, but that metabolism of the oil phase was significantly lower when there were diglycerides and monoglycerides. As a result, there needs to be a careful design of the SEDDS since this aspect may prove vital to the performance of this delivery system.

Regarding the safety profile of the lipids, recent studies performed by Desai et al.[35] show that long-chain (LC) lipids provide less cytotoxic effect over intestinal cells than medium-chain (MC) lipids. The cytotoxic effect was observed using the Caco-2 cell line, in which they measured the tolerance of the cell membrane to lipids, lipid–surfactant association, and the end products of lipid digestion. LC SEDDSs were tolerated at tenfold higher concentration than their MC counterparts. This was a recurring concern reported by the authors of the patents, because the high concentrations of lipids in SEDDSs may irritate the gastrointestinal mucosa and induce serious toxicological effects. Furthermore, it is necessary to identify whether the permeation of the drug is increasing as a function of the SEDDS formulation or as function of intestinal epithelium degradation, possibly caused by the lipids or surfactants. In the specific case of the SEDDS for ophthalmic delivery disclosed in patent 15, the inventors carried out tolerability studies in a rabbit model, where they found that castor oil and Captex 355 had the best tolerability profile for the formulation.

On the other hand, the inventors of patents 29, 31, and 33 (see Table 1) presented a lipid phase composed of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (see Table 3), for the oral delivery of atorvastatin, acetylsalicylic acid, and the very same EPA and DHA as active principles. These lipids are omega-3 fatty acids, so the oil phase in the SEDDS is deemed safe from the beginning. The aim of the inventors was to add the therapeutic effects attributed to EPA and DHA to a SEDDS formulation containing an active principle. They claimed that these fatty acids could help prevent lipid disorders and heart disease, and so they presented patent 33 as a SEDDS for the delivery of the fatty acids alone, while submitting two more later patents that include the exact same formulation but with the addition of a statin (in patent 29) and acetylsalicylic acid (in patent 31). This is an interesting solution since trending research regarding EPA and DHA is exploring the anticancer[36] and the anti-inflammatory[37] activity these fatty acids may have. Nonetheless, studies are still needed to further assess the emulsification efficiency and performance of these types of lipids.

Additionally, Table 3 includes terpenes and essential oils as a lipid phase. This was mainly observed in patent 30 (see Table 1) for the solubilization of the chemotherapeutic drug paclitaxel, because it belongs to the terpene family. The use of this type of terpenoid lipids showed an increased solubility for paclitaxel. This can be also appreciated by the study conducted by Saneja et al.,[38] which reported the use of squalene and lemon oil in the preparation of oral delivery of cancer chemotherapeutics, such as paclitaxel and docetaxel.

The oils in each patent were selected specifically for an API based on its physicochemical properties and its highest solubility, which improved drug loading in many cases. Nonetheless, lipids play a key role in the formulation stability on the long run. Being the most abundant component in a conventional SEDDS formulation (see Table 2), they are identified as responsible for the shelf or storage stability. One of the main problems faced by the inventors in the patents was that the dissolution rate for an encapsulated or liquid SEDDS would change over time, rendering the formulation unstable after long-term storage. In patent 20 (see Table 1), they realized that the degree of

substitution of the oil phase could influence storage stability. The inventors describe the stability studies performed using PEG hydrogenated castor oil as the oil phase, where they would change the degree of substitution (PEG-10, PEG-20, PEG-30, PEG-40, PEG-50, and PEG-60), and evaluate the dissolution of the dosage form after 6 months of storage. The inventors found that PEG-40 hydrogenated castor oil (Cremophor RH 40) presented the same dissolution rate before and after 6 months of storage. They also found that a low degree of PEG substitution (PEG-10 to PEG-30) would not produce a desirable droplet size once the emulsion was formed, and that a high degree of substitution (PEG-50, PEG-60) would delay the dissolution rate because it promoted gelatin bridging on the capsules where the SEDDS was filled.

The shelf stability problem was also solved by inventors of patent 32. Here, the invention discloses a polar lipid SEDDS in which the oil phase contains Capmul MCM (see Table 1). The addition of 30% to 45% polar lipid coupled to triglycerides in a proportion of 5% significantly helped to maintain the stability after long shelf periods. This is due to the action of Capmul MCM as surfactant or cosurfactant, which eases the solubilization process of the active principle. As can be seen in Table 3, Capmul MCM possess a highly bulky hydrophilic group and a medium (C8) carbon chain, which allow for this compound to help the formation of the main surfactant micelles (Cremophor RH 40) and to form micelles of its own.

D. Surfactants and Cosurfactants in SEDDS

The surfactants are the keystone of SEDDS solubilizing capacities. They work by providing a flexible film between the aqueous and oil phases ready to distort the droplets and lower the interfacial tension. They must be of optimal lipophilic character to exert their action on the system, and thus it is important to consider a surfactant's safety, concentration, and HLB.[28] Table 4 lists the structure, HLB, and classification of the most commonly used surfactants and cosurfactants in the patents.

As shown in Table 2, SEDDSs require a high concentration of surfactant in the formulation. This causes concerns about their safety and is a limiting aspect to their use in administration routes other than oral. As reported by Psimadas et al.,[39] Cremophor EL and Cremophor RH 40 are not suitable for parenteral administration because of their toxicity. They caused dose- and time-dependent damage in endothelial and epithelial cells, being the former more sensitive to barrier disruption damage. Furthermore, inventors of patent 6 discussed the hemolysis that may occur in patients who are administered an IV dose of docetaxel without previous dexamethasone treatment, because of the high concentration of polysorbate 80 in the formulation. In this regard, concerning parenteral administration route, natural surfactants such as lecithin and phospholipids are still preferred even though they are not as efficient as synthetic surfactants in their emulsification process. This is further evidenced in patent 30, which concerns the development of an oral SEDDS for the delivery of paclitaxel, as the conventional parenteral route may cause adverse reactions in patients and prove to be inconvenient. The inventors stated that problems to be overcome by the SEDDS included the fact that direct administration

TABLE 4: Structures of emulsifiers and co-surfactants most used in the patents reviewed

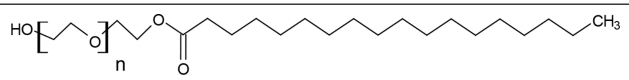
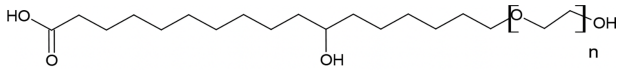
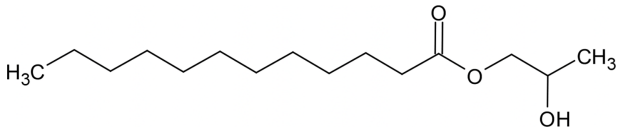
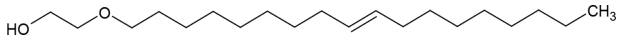
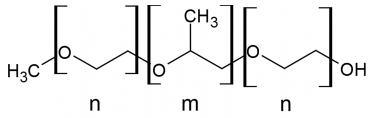
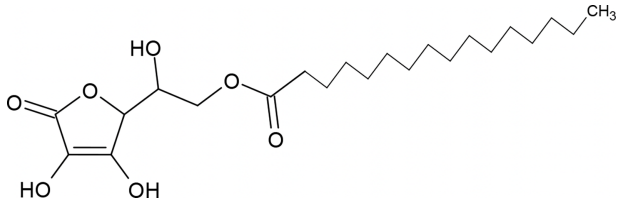
Emulsifier	HLB	Structure	Classification
PEG-32 stearate	16.9	 n = 32	Pegylated, synthetic, nonionic
Kolliphor HS 15	16	 n = 15	Pegylated, synthetic, nonionic
Lauroglycol 90	3		Synthetic, nonionic, water insoluble
Brij 97	12.4		Pegylated, synthetic, nonionic, water dispersible
Poloxamer 407	18–23	 n = 100 m = 59	Pegylated, ethoxylated, synthetic, nonionic block co-polymer, water soluble
Ascorbic palmitate	9		Semisynthetic, water dispersible

TABLE 4: (*continued*)

Span 20: sorbitan monolaurate	9		Synthetic, nonionic, water dispersible
Span 80: sorbitan monooleate	4.3		Synthetic, nonionic, water insoluble
Tween 20: polyoxyethylene sorbitan monolaurate	16.7	w + x + y + z = 20	Ethoxylated, synthetic, nonionic, water dispersible
Tween 60: polyoxyethylene sorbitan monostearate	14.9	w + x + y + z = 20	Ethoxylated, synthetic, nonionic, water dispersible

TABLE 4: (*continued*)

Emulsifier	HLB	Structure	Classification
Tween 80: polyoxyethylene sorbitan monooleate	15	w + x + y + z = 20	Ethoxylated, synthetic, nonionic, water dispersible
Lecithin	4–9		Natural

TABLE 4: (*continued*)

Labrasol	14	Ethoxylated, synthetic, nonionic, water dispersible
Labrafil M 2130 CS	9	Ethoxylated, synthetic, nonionic, water dispersible

TABLE 4: (*continued*)

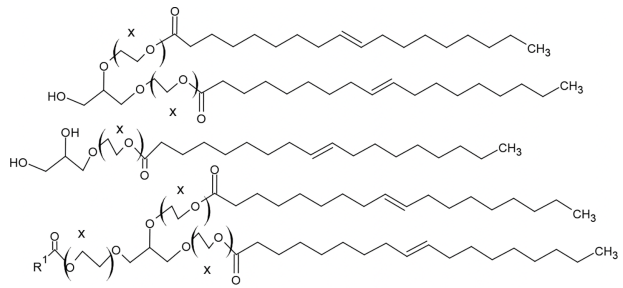
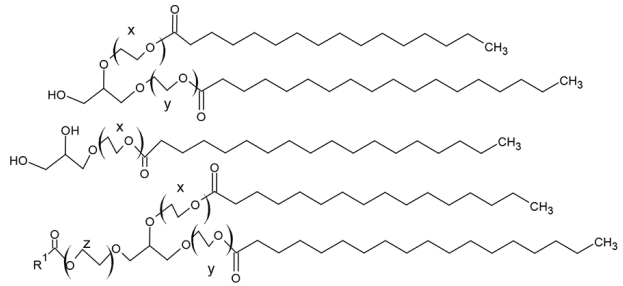
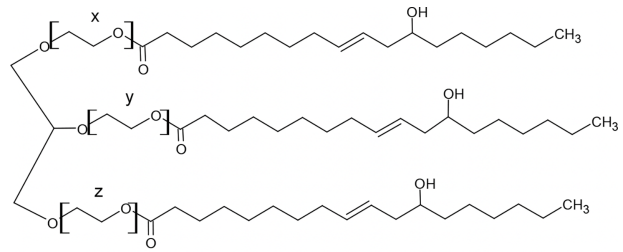
Emulsifier	HLB	Structure	Classification
Labrafil M1944 CS	4	 R1 = 17, x = 6	Ethoxylated, synthetic, nonionic, water dispersible
Gelucire 50/13	11	 R1 = 15; 17, mono (x = 32), di (x + y = 32), and triglycerols (x + y + z = 32) of C16 and C18. Contains also free PEG	Ethoxylated, synthetic, nonionic, Water dispersible
Cremophor EL	12–14	 x + y + z = 35	Ethoxylated, synthetic, nonionic

TABLE 4: (*continued*)

PEG-40 hydrogenated castor oil	14-16	x + y + z = 40	Pegylated, ethoxylated, synthetic, nonionic
Polyethylene glycol	/	n	Co-emulsifier
Propylene glycol	/		Co-emulsifier
Transcutol HP	4.2		Co-solvent
PEG 400	/		Co-emulsifier

HLB, hydrophilic–lipophilic balance.

of a regular paclitaxel formulation into the bloodstream causes severe allergic reactions, because the formulation may contain Cremophor EL, which releases histamine once it is degraded in the body. This is further supported by the study of Chowdhury et al.[40] which states that nanotechnology-based oral formulations may offer the best way to increase taxane's safety and efficacy profile.

In the current literature, safety is prioritized over emulsification efficiency. This was reported by Buyukozturk et al.,[41] who compared the toxicity between the polyethoxylated sorbitan esters (Tween) and Labrasol. They found that the presence of the sorbitan group and the low degree of esterification contributes to disruption of the intestinal wall, making the Tween surfactants highly irritable to intestinal mucosa and more toxic than Labrasol, even though they presented a higher emulsification efficiency. Thus, the use of water-soluble ester surfactants is limited by their safety profile rather than their emulsification performance. This is further supported by Mazzeti et al.,[42] as they tested the cytotoxicity of Capryol 90, Tween 80, Cremophor EL, and Labrasol for a proposed SEDDS of benznidazole. They chose Labrasol because it was less cytotoxic, even though Tween 80 was slightly more efficient at solubilizing the drug. On the other hand, even though safety cannot be neglected, a high emulsification efficiency is important and often desired by inventors. According to patent 6, adding polysorbate 80 increased the rate of self-emulsification, which in turn increased oral bioavailability, leading to reproducible plasma concentrations. They also registered disintegration times lower than 20 minutes, which is preferred over higher disintegration times that may delay the onset of drug activity. This can be one reason why Tween 80 is still one of the most frequently used surfactants in many of the patents studied, as can be seen in Table 1. It also increased compatibility with other formulation components and enhanced solubility of drugs with low water solubility.[43]

The safety issue can be resolved by decreasing the droplet size within the emulsion. As reported by Charman et al.,[44] the exposure to high local surfactant concentrations may be reduced if the droplet size is small, given that a small size encourages rapid stomach emptying and wide dispersion through the gastrointestinal tract. This remains true to the inventions, since most of them preferred the formulation with lowest droplet size achievable among a variety of options. Droplet size reduction in the patents is mainly attained by the use of the optimal lipid–surfactant–cosurfactant proportion. Nonetheless, inventors of patent 13 (see Table 1) used a high-pressure homogenization technique to diminish droplet size. They determined a pressure of 12,000 psi for the ideal droplet size and obtained a SEDDS capable of producing an emulsion with a zeta potential of −30 mV, which is considered the desirable stability.

The inventions described other ways to deal with the safety issue regarding the gastrointestinal irritation produced by the surfactants. One way is to reduce drastically the use of surfactant. In patent 7, discussed earlier, they managed to reduce surfactant concentration to 12% to 25%, which is a significant decrease relative to typical surfactant amounts (see Table 1). The inventors in patent 6 opted to use a relatively safe surfactant (PEG-32 stearate) while decreasing the concentration of polysorbate 80 to 1% to 4%, which is more prone to cause irritation in higher concentrations. This increased

the safety profile for chronic use while still attaining a SMEDDS type system. On the other hand, inventors of patent 28 (see Table 1), which presented the SEDDS for a pyrrolidine-substituted flavone, decided to use a vitamin E–derived surfactant (vitamin E polyethylene glycol succinate) in concentrations of 10% to 30% and increase the concentration of cosurfactant (PEG 100) to 20% to 40% to reduce direct toxicity.

Another approach was the development of a surfactant-free SEDDS. This type of SEDDS with no surfactant added was described in patent 27, where the inventors presented a lipid-based delivery system associated with cyclodextrins. The aim was to develop a new system allowing better encapsulation of lipophilic API by an increased solubilization in the oil phase, preventing recrystallization and eliminating the need for a surfactant. This systems works because of the structure of cyclodextrins, which are cylindrical carbohydrates with an hydrophobic cavity and an hydrophilic exterior.[45] The carbohydrate traps the active substance in its hydrophobic cavity, aiding its solubilization on the oil phase, and it further adsorbs this oil phase, forming a dry powder. The presence of the hydrophobic cavity prevents the growth of crystals and the precipitation of the drug, and once it contacts the aqueous medium, it form an emulsion. Even though no surfactant is needed to form the emulsion, the inventors claim that surfactants such as Cremophor EL may be used as permeation enhancers in a proportion no greater than 10%. This system is suitable for API sensible to light, enzymes, and oxidation, and may also incorporate hydrophilic active substances. Furthermore, this type of formulation prevents common instability phenomena normal to surfactant-based emulsions, such as creaming and coalescence.

Other of the parameters to consider is the hydrophilic–lipophilic balance (HLB), since surfactants with a high HLB value are going to be more hydrophilic and soluble in water, forming O/W emulsions, whereas surfactants with low HLB values are going to be more hydrophobic forming W/O emulsions. In the case of ethoxylated and pegylated surfactants, their solubility in water is going to increase with the degree of ethoxylation and pegylation, respectively.[46]

It is important to highlight that almost all the surfactants used for the patents and presented in Table 4 are nonionic and water soluble, with an HLB of 12 or higher. There are many patents that included only one surfactant to the SEDDS, but a combination of surfactants may also be used. Some of the inventions described the use of two surfactants, one with a low HLB (< 12) and one with a high HLB (> 12). The former would allow for a better solubilization of the hydrophobic active substance, whereas the latter would provide the desired rapid self-emulsification in water.

The type of surfactant is also vital to the behavior of the SEDDS. Nonionic surfactants are preferred because they are more stable at wider pH ranges and ionic strength than ionic ones.[17] Thus, they are more likely to be compatible with the many excipients used in a SEDDS. They are also of great interest to study the self-emulsification phenomena, given that depending on the surfactant used and the co-emulsifiers added, it is possible to obtain a self-microemulsifying formulation or a self-nanoemulsifying formulation. The work by Shakeel et al.[47] reported that for a lipid system containing Capryol-90, Capryol-PGMC, and glibenclamide, the use of Labrasol and Gelucire 44/14

produced a self-emulsifying system, and Tween 80, HCO-60, and Cremophor EL were able to produce self-microemulsifying and self-nanoemulsifying systems. In addition, a high HLB value is important because it induces spontaneous formation of O/W droplets and fast spreading of the formulation in the aqueous GI fluid.[4] This is evidenced in patent 24 (see Table 1) for the SEDDS formulation of atorvastatin calcium. While screening for the best surfactant performance and characterizing the emulsion, the inventors found that Labrasol was not able to form the desirable nanoemulsion, whereas polysorbate 20 formed the nanoemulsion with the desired quality. This may be due to the fact that polysorbate 20 has a higher HLB than Labrasol (see Table 4) and that it consists of a lone molecule, whereas Labrasol may contain monoglycerides, diglycerides, and triglycerides. The presence of many molecules may render the Labrasol micelles bulkier and less sorted than the ones formed by polysorbate 20. It may also pose some steric impediment for a cosurfactant to aid the formation of micelles, thus resulting in a larger droplet size. The capacity to form a nanoemulsion is thought to be one of the most important features to increase drug solubility and permeability.[48]

Nonionic surfactants are also of great interest to study the mucus permeation ability of a SEDDS. As stated by Rohrer et al.,[49] mucus is a complex structure containing little to no aqueous dispersion media for the SEDDS. Hence, it is important for the formulation to possess high emulsifying properties. This study proposed the use of Labrasol, Kolliphor HP, Transcutol, and PEG400 because they showed high emulsifying properties suitable for the delivery across mucosal membranes with low aqueous content. The concentration of surfactant is also important for mucus permeation. Ujhelyi et al.,[50] reported that concentrations of Cremophor RH40, Tween 80, and Labrasol of about 30% to 40% showed an increase in mucus permeation for paracellular transport in Caco-2 cell layers.

All of this very important for ophthalmic delivery. Patent 15 (see Table 1), as previously discussed, presents a SEDDS composition for the ophthalmic delivery of lipophilic drugs. The inventors stated that because of physiological conditions in the eye, such as tear drainage and poor permeability of the cornea, the bioavailability of drugs is not expected to be above 5%. Thus, rapid self-emulsification in small volumes of water and high permeation of surfactant is needed for the development of the SEDDS. For this, they stablished the need to use a surfactant with an HLB value higher than 12 and a cosurfactant with an HLB value lower than 10 (see Table 1). This would promote rapid self-emulsification while still being able to fully dissolve a lipophilic active substance.

Permeation is also definitive for the invention in patent 18 (see Table 1). The inventors disclosed a SEDDS for the delivery of coenzyme Q across the blood–brain barrier. In order to prevent a wide array of brain diseases (see Table 1), they needed the emulsion to be able to pass through the blood–brain barrier. They accomplished this by developing a SMEDDS type of system and by using Gelucire 44/14. The small droplet size and the surfactant's permeation capacity allowed for good permeation to the brain. This was subsequently confirmed in an animal model, where they measured the concentration of coenzyme Q in rat brain tissue and found it to be significantly higher than in the control group. The SMEDDS described also enhanced the brain absorption of the drug.

The metabolism of the surfactant is also an important feature. The work of Cuiné et al.[51] compared Cremophor RH40 with Cremophor EL while studying the surfactant digestion in dogs for a danazol SEDDS. They found that polyethylene glycol (PEG) units hinder lipase access to the molecule. Increase in the number of PEG units is correlated with resistance to hydrolysis. Therefore, it provides higher bioavailability. On addition, surfactants have also been found to act as modulators of P-glycoprotein (P-gp),[29] an efflux transporter responsible for poor intestinal drug uptake, because it delivers compounds back into the intestinal lumen. da Silva Junior et al.[52] demonstrated that cremophors and polyethoxylated sorbitan esters may inhibit P-glycoprotein, thus favoring drug passage through the intestinal wall and increasing its bioavailability. This problem proved significant to the inventors of patent 30 (see Table 1), because paclitaxel is a substrate of P-gp, and the use of surfactants alone was not enough to hinder P-gp activity. Therefore, they added phytosterols to inhibit the enzyme.

Another prominent feature of the SEDDS patents is the inclusion of co-emulsifiers and cosolvents in many of them. Addition of co-solvent further contributes to decrease interfacial tension without presenting toxicity issues. This increases flexibility of the interfacial film over a wider range of compositions, and in the case of medium chain alcohols (C3-C8), like those listed in Table 4, they may further reduce interfacial tension by amplifying the interface fluidity and enhancing system entropy.[53] This way, a high concentration of surfactants may not be necessary, and the emulsion formed acquires superior stability. One of the many positive effects observed in the patents whenever a cosurfactant or co-solvent was added to the formulation was the reduction in droplet size, which was often a definitive parameter to develop the best formulation. Patent 6 demonstrated that the addition of PEG 400 as a co-surfactant would yield smaller and more uniform droplets and a more stable formulation when tested in different dissolution media, so the emulsion droplet size did not change. This remained true for all the inventions when tested in different release media. Overall, there were no significant changes in particle size and emulsification efficiency.

The co-solvents are also hydrophilic components, and they may be incorporated into the formulation when the SEDDS contains large amounts of drug and surfactant.[29] They may also be used depending on the type of drug or the form employed for its solubilization. The study by Griesser et al.,[14] shows that Transcutol HP and propylene glycol are important for the solubilization of drug complexes, as in HIP, since protic cosolvents with dielectric constants between 8 and 32 (Transcutol HP, Tetraglycol, and propylene glycol) are better solubilizers than aprotic solvents with dielectric constants less than 4 (Labrafil MS1944 CS). This can be further supported by the cosolvents and co-emulsifiers presented in Table 4. The co-solvents most used in the patents were Transcutol HP and various forms of PEG.

The cosolvent concentration depends on the dissolution studies designed specifically for each invention. The inventors would build a ternary phase diagram, often fixing the amount of cosolvent and varying the amount of lipid and surfactant (or varying all three) until an ideal solubilization system was identified. This identification step was

often accomplished by the use of analytical software, and the concentration of cosolvent ranged from 10% (patent 8) to 40% (patent 28), demonstrating significant variations. Nevertheless, this was an important step as SEDDS stability fully depends on the combination of the lipid–surfactant–cosurfactant trio.

The ternary phase diagram is a useful tool to identify the concentration of surfactant, co-surfactant, and oil phase that forms the desirable stable emulsion based on the solubility studies. It can be a microemulsion or nanoemulsion, depending on the formulation and the selected excipients. To build a ternary phase diagram, a fixed ratio of surfactant to co-surfactant needs to be established, and the selected surfactant and co-surfactant must have demonstrated solubilizing capabilities for the drug of interest. The next step is to add a varying amount of oil phase and observe the characteristics of the mixture that is being formed, such as droplet size and concentration or percentage of each component. On addition, this diagram shows if the addition of the API to the mixture changes the size of the emulsion. To build ternary phase diagrams there are several analytic chemical software available, such as Chemix software.[54]

The use of other hydrophilic substances that may further contribute to the emulsification process is present as a particular case in patent 32 for the oral delivery of apogossypolone, a relatively new chemotherapeutic. The inventors described the addition of a short chain (C3-C5) polycarboxylate acid such as lactic, malic, glucic, adipic, succinic, citric, and fumaric acid. This would further stabilize the API, aiding in the solubilization process by providing flexibility to the droplets.[41]

E. Drugs in SEDDS

The drugs included in the inventions are presented in Table 5, and they belong mainly to Class II and IV of the BCS. This system was first proposed by Gordon Amidon in 1994,[55] and it comprises the grouping of all known API into four drug types or classes according to molecular solubility in water and permeation across biological membranes. Classes I and III include all drugs that are highly soluble in water, with the difference that drugs in BCS Class I are highly permeating as well, wherea those in Class III have low permeation. Class II and IV, on the contrary, cluster all those drugs that are insoluble in water, but as is the case with Classes I and III, Class II drugs have higher permeability than those in Class IV.

One of the main objectives of new drug delivery systems is to safely deliver insoluble drugs to the patient with the best possible efficacy. Thus, the development of new delivery systems, as is the case of SEDDSs, concerns itself with drugs in Classes II and IV of the BCS. Being part of Classes II and IV means that the dissolution rate is the limiting step in the absorption process. Hence, the inventors designed the SEDDS to increase dissolution rate of every compound present in Table 5. This review has already discussed the impact of the lipid–surfactant–cosurfactant trio in facilitating the solubilization and dissolution rate of poorly soluble drugs presented in the patents. However, it remains to be seen whether the nature of the drug itself can affect the performance of SEDDSs.

TABLE 5: Drugs used for the SEDDS patents classified according to their drug class

Drug class	Drug
Cannabinoids	Tetrahydrocannabinol, cannabidiol, tetrahydrocannabivarin, cannabigerol, cannabidiolic acid, tetrahydrocannabinolic acid, cannabinol
Chemotherapy agents	Docetaxel, paclitaxel, pyrrolidine substituted flavone, apogossypolone
Hypoglycemic agents	Chlorogenic acid
Immunosuppressants	Cyclosporin A
Nonsteroidal anti-inflammatory drugs	Ketoprofen, flurbiprofen, aspirin
Non-nucleoside reverse transcriptase inhibitors	Efavirenz
Phosphodiesterase inhibitors	Tadalafil
Selective estrogen receptor modulator	Ospemifene
Selective progesterone receptor modulator	Ulipristal acetate
HMG-CoA reductase inhibitors	Atorvastatin calcium, cerivastatin, fluvastatin
5-alpha-reductase inhibitors	Dutasteride
Others	Indirubin, diferuloylmethane, cinnamic amide derivatives, coenzyme Q, tocotrienols, Ziyuglicosides

The inventors of patent 23 (see Table 1) presented a SEDDS for the delivery of both pH-dependent and pH-independent drugs. For this, the developed formulation studies using danazol, indomethacin, and haloperidol as model drugs, which are a neutral molecule, cationic molecule, and anionic molecule, respectively. They found that while neutral drugs tend to dissolve in the core of the lipid drop, weakly acidic and weakly basic drugs migrate to the interface and dissolve in the surface of the droplets, affecting the size and shape. The droplets formed by indomethacin and haloperidol SEDDSs were smaller and more uniform than in the danazol SEDDS, which may indicate surface active properties and a possible action of the drug as a co-surfactant. However, both SEDDS containing the pH-dependent drugs showed to be affected by pH, as a change in the pH of the release medium would affect the drug solubility. This was especially true for the weakly acidic drug, for the release study they used a medium with a fixed pH of 6.4, and then they added the indomethacin SEDDS observing a great increase in its solubility. The next step was to increase the SEDDS concentration in the medium, but the caprylic acid in the oil phase slightly lowered the pH, causing the indomethacin to decrease its solubility, which means that the pH effect is stronger than the SEDDS solubilizing effect. Nonetheless, because they were using a buffer and the caprylic acid presents polymerization, this effect was neglected. Once this study was carried out for the haloperidol SEDDS, they did not observe a change in the solubility, because the

weakly basic drug was not affected by the same pH changes, because its pKa is 8.2, whereas the pKa of the indomethacin is 4.5. Thus, it is expected that acidic drugs will be much more sensitive to pH changes close to their pKa. The inventors also found that indomethacin and haloperidol solubility was enhanced by the formation of hydrogen bonds with caprylic acid. Therefore, the interaction between the oil phase and the drug of interest is vital to solubilization.

Increasing the dissolution rate of an API will in turn increase its bioavailability. As more of the drug is dissolved, a higher concentration can reach the site of action and add to the therapeutic response. Many of the inventors in the patents considered that an increase in bioavailability would permit a reduction of the surfactant concentration and API dose. This is specifically the case of patents 24 and 25 (see Table 1). The first presents a SEDDS for the delivery of atorvastatin calcium. The inventors point out that if bioavailability is increased, optimization of the SEDDS could reduce the dose and therefore the amount of surfactant needed to solubilize it, because it directly depends on the amount of the drug to be loaded. This way, the surfactant toxicity issue discussed previously could be solved. In addition, patent 25 presents a SEDDS for the oral delivery of efavirenz, an antiretroviral drug commonly used to treat AIDS. The inventors of this SEDDS were concerned with the high risk of significant adverse effects of efavirenz, so they aimed for a dose reduction that would still yield efficacious plasma concentrations. Up-to-date research on efavirenz published by Chaivichacharn et al.[56] has shown that the safety profile of the drug is not acceptable and that it presents high interindividual variability in plasma concentrations, leading to unpredictable efficacy and toxicity. The approach taken with efavirenz by formulating it into a SEDDS opens the possibility to do the same with other drugs that may present the same problems.

The solubilization performance of a SEDDS also depends on the loading of the drug. As discussed in patent 36 (see Table 1), it is common to measure the solubility of the drug in every component of the formulation and then calculate the amount of drug to be added to the SEDDS. Nevertheless, the method's biggest disadvantage, as can be appreciated in the study by Narang et al.,[57] is that part of the drug may be precipitated once the SEDDS contacts the aqueous medium *in vivo*. This is because surfactants and cosurfactants undergo molecular rearrangement after contact with water and momentarily lose their ability to solubilize the drug. The problem was solved in the patents by measuring the drug solubility on the blank emulsion formed by the SEDDS and then calculating the amount of drug to be incorporated in the system, since measuring only the solubility of the drug on the SEDDS beforehand would often present higher solubility values compared to the solubility observed once the emulsion was formed in aqueous medium.

Many of the inventions reviewed only load the SEDDS with one drug. Nonetheless, there are others with two active principles. Using two drugs in the same SEDDS would possibly increase the bioavailability of one of them, or it could deliver a combined therapy for a specific pathology. The first is the case of patent 11, which adds cyclosporin A to a docetaxel SEDDS to increase the bioavailability of the latter drug. As determined by Mei et al.,[58] this is due to activity of cyclosporin A as an inhibitor of efflux pumps in the

gastrointestinal drug barrier, the most common of them being P-gp, as previously discussed. However, cyclosporin A also depresses the immune system, and this may cause clinical complications for the patients. To reduce adverse effects, the addition of other efflux pump inhibitors is preferable even though they are not considered an API per se, and this can be seen in other patents (see Table 1). Additionally, patent 14 discloses the delivery of dutasteride and tadalafil to treat prostate hyperplasia, since the combination of both a 5-alpha-reductase inhibitor and a 5-phosphodiesterase inhibitor have a higher treatment efficacy than monotherapy. This way, SEDDS with two active principles may increase patient compliance, since there is no need to take different dosage forms.

There may also be SEDDS for natural extract delivery, as is the case of patent 16, which discloses the delivery of ziyuglycosides. The inventors described the alcoholic extraction of glycosides from *Sanguis sylvestris*, a plant regularly used in Chinese traditional medicine. Once extracted, the glycosides were ready to be incorporated into a SEDDS, and no additional steps compared to the other patent were taken. This invention is reported to be the first to develop a SEDDS for a natural extract of *S. sylvestris*, and it invites more research into the delivery of natural extracts through SEDDS. Literature of this topic in general is very limited at the moment. Work by Echeverry et al.[59] belongs to this type of research into SEDDS. The publication deals with the delivery of a *Passiflora ligularis* extract through a self-emulsifying drug delivery system in which particular characteristics of natural extracts are highlighted. The main issues addressed in this study are how to enhance mucus permeation with suitable excipients, and how the solubility studies may affect the excipient selection based on the major constituents of the extract. For the scope of this study in particular, a flavonoid rich natural extract showed better solubility and stability when dissolved in castor oil, Cremophor EL, and propylene glycol. Thus, they were selected as the oil phase, surfactant, and co-surfactant, respectively.

F. Pharmacokinetics and Animal Models

A minority of the patents studied in this review reported pharmacokinetic data on the formulations. Pharmacokinetic parameters of the drugs orally administered as SEDDS were compared to the conventional dosage form commercially available, more commonly a tablet or an emulsion. Table 6 presents the differences between the parameters measured for each formulation of the same pharmaceutically active principle.

The studies in each case were carried out by comparison to the regular dosage form available in the market, and they comprise only the SEDDS that exhibit an immediate drug release. Pharmacokinetic studies for those SEDDS that can be considered to have a modified or controlled release were not published in the patents reviewed, and specific information of the pharmacokinetic parameters is not available for all the inventions.

The results shown in Table 6 satisfactorily confirm that bioavailability is increased for each drug in the table. The pharmacokinetic parameters that account for this increase in bioavailability are AUC, C_{max}, and T_{max}. The area under the curve (AUC) is a parameter to estimate the extent of a product bioavailability. It is calculated by mathematical

TABLE 6: Pharmacokinetic parameters after oral administration of a conventional delivery system and SEDDS for a given active pharmaceutical ingredient (API)

	Pharmacokinetic parameter (units)	**Conventional dosage form**	**SEDDS**	**Animal model**
Indirubin (patent 13)	AUC_{∞} (μg·h/L)	134.109	238.413	Rat
	T_{max} (h)	15	2	
	C_{max} (μg/L)	5.4	22.35	
Sildenafil (patent 3)	T_{max} (h)	0.56	2.25	Rat
	C_{max} (μg/mL)	0.011	0.084	
	AUC (μg·h/mL)	0.024	0.352	
Cannabidiol (patent 8)	AUC (mg·h/mL)	1.389	2.435	Rat
	T_{max} (h)	3.05	2	
	C_{max} (ng/mL	302	519	
	$T_{½}$ (h)	6.14	6.04	
	F	4.9%	39%	
Coenzyme Q (patent 18)	AUC (N.R.)	2.656	14.36	Rat
	C_{max} (N.R.)	0.374	1.547	
Cinnamide derivative (patent 21)	AUC (ng·h/mL)	12498	42637	Rat
	MRT (min)	131	105	
	$T_{½}$ (min)	76,5	58,9	
	Cl (mL/min)	421	125	

TABLE 6: (*continued*)

Atorvastatin calcium (patent 24)	AUC (ng·h/mL)	663.3	2289.5	Rat
	C_{max} (ng/mL)	258.6	113.2	
	T_{max} (h)	0.76	0.73	
	MRT (h)	3.54	2.36	
	Relative F (%)	—	345.17	
Diacerein (patent 26)	C_{max} (µg/mL)	3.058	5.35	N.R.
	T_{max} (h)	5.39	1.25	
	AUC_o (µg·h/mL)	22.688	27.149	
	AUC_φ (µg·h/mL)	22.816	27.332	
Diferuloylmethane (patent 36)	K_{el} (1/h)	0.0553	0.1717	Rat
	T_{max} (h)	1	0.25	
	C_{max} (ng/mL)	14.63	120.825	
	AUC (ng·h/mL)	59.5488	240.78	
	AUMC (ng·h·h/mL)	252.8	728.2	

N.R., not reported.

models once the concentration versus time curve is established. A larger AUC means that the drug achieves higher concentrations or that it stays longer in the organism; hence, its absorption is enhanced. Different types of AUC can be observed, such as AUC_{φ}, AUC_{o} and AUC_{∞}. They may present different values, and this is due to the different mathematical models used to calculate them. This way, statistical analysis yields a better quality of data. On addition, C_{max} is the maximum concentration reached in plasma, and T_{max} is the time it takes for the drug to reach this maximum concentration. These two parameters can also be considered involved in the absorption process and are vital to determine the absorption rate of a drug if needed.[60] As can be seen in Table 6, all SEDDSs present a significantly greater AUC and C_{max}, and a lower T_{max} compared to regular dosage forms. This means that SEDDS manages to deliver the drug faster to its maximum concentration and further confirms the solubilizing power of the SEDDS as more drug is available for absorption. However, careful attention needs to be paid to the therapeutic window of the drug. The aim is to reach a C_{max} who falls in it, since a C_{max} above the minimal toxic concentration threshold is not desired for the risk of adverse effects, and a C_{max} below the minimum effective concentration threshold, even if it is superior to the conventional dosage form, is not enough to meet therapeutic requirements. As a result, once an increase in bioavailability is observed for a SEDDS, the dosage should be optimized.

There is also the estimation of the area under the moment curve (AUMC), which is defined as the total area under the curve of the plot of concentration/time versus time, which is regarded as the first moment. This parameter helps to determine other drug characteristics, such as the mean residence time (MRT), the apparent elimination rate constant, and the apparent volume of distribution at the steady state.[61] The MRT is the mean time a drug spends in the body after entering the circulation. It includes the time spent in the blood and in peripheral tissues, and it may be used to determine the elimination rate and clearance.[62] These two parameters can be regarded as a method to estimate drugs distribution prior to the elimination phase.

Other pharmacokinetic parameters included are the half-life of the drug, elimination rate, and clearance. The half-life of a drug is defined as the time it takes for the concentration of the drug in the bloodstream to be reduced to half, and it is closely related to the elimination rate, which is the speed at which the drug is metabolized and excreted from the body.[63] In addition, clearance is a measure of the quantity of drug eliminated from a given volume of fluid per unit of time. These three parameters define the elimination phase of the drug and are also relevant to the bioavailability. A rapid elimination of the SEDDS expressed by high values of the elimination rate and low values of MRT are not desired if optimal concentrations are not reached beforehand, since this would mean that the formulation is being metabolized without sufficient amount of drug reaching the action site. On the contrary, if better bioavailability is achieved, inferior MRT values and higher elimination rate values could prove beneficial, as the drug would exert its effect and then leave the system without accumulation. This is the case for the atorvastatin calcium and the cinnamide derivative SEDDS, as they have lower values of MRT compared to the common dosage form while still attaining higher bioavailability. This could probe very useful if the SEDDS is to be administered to a patient with polymedication.

The half-life may also be used to estimate the spacing between numerous administrations of a dosage form and for the design of a dosing regimen.[64] As shown in Table 6, this was the pharmacokinetic parameter less affected by the SEDDS, as can be seen for the delivery of cannabidiol and the cinnamic acid derivative. As reported by Delavenne and Dargaud et al.,[60] this parameter depends on the clearance and volume of distribution, and its estimation is complicated because it depends on many factors inherent to the pharmaceutical composition, the nature of the drug, and interindividual variability. The half-life is one of the parameters especially affected by the limit of quantification of the instrumentation used. Any information below this limit is going to be missing, but this can be resolved by integrating a null value, imputing the missing values using fixed values, or developing specific statistical analysis to account for the missing information.

Only two of the patents directly reported the value of the bioavailability, F. The first of them is patent 8 for the delivery of cannabidiol. In this document the inventors established the value of F by the traditional method considering the AUC of IV administration and reporting the value as a percentage. On the other hand, inventors of patent 24 for the delivery of atorvastatin calcium determined the bioavailability of the SEDDS relative to the established bioavailability of the conventional dosage form, reporting that it was 345.17% higher.

The administration of SEDDS can reduce interindividual variability on the bioavailability of poorly water-soluble drugs that is directly related to food intake or dietary status. Drugs in BCS Class II are often taken with food to increase the residence time and because some of the fatty components in the food may aid their absorption. This was especially true for diacerein (see Table 6). Nonetheless, as described in patent 26 (see Table 1), when formulated into a SEDDS this food effect was neglected. As confirmed by AboulFotouh et al.,[65] the presence of food would help solubilize the drug, so the absorption depended on the amount of fat a meal could contain. Thus the bioavailability was not constant for different individuals. Nonetheless, the use of SEDDSs overcomes the dissolution step in the stomach, rendering the drug ready to be absorbed in uniform quantities.

Most of the pharmacokinetic studies were carried out in rat models, and even though there were some inventors who used dog or guinea pig models, the specific data was only reported for rats. However, the inventors did not describe whether they used a compartmental or noncompartmental approach to determine the pharmacokinetic parameters.

As reported by Araya et al.,[66] the main differences between animal models is the way the SEDDS is administered and the sampling blood volume available for analysis. In this study, they demonstrated the formation of an O/W microemulsion in the gastrointestinal tract in both animals, and they observed an increase in intestinal absorption and bioavailability. However, the full evaluation for a more complex dosage form could only be carried out in the dog model. Although rats were administered a powder SEDDS, dogs could be administered a soft gelatin capsule filled with the SEDDS. This way, the disintegration of the capsule and the liberation behavior could also be examined. Moreover, the study on animal models allows for direct comparison to *in vitro* dissolution tests. The study revealed that the drug's

dissolution was higher in the *in vitro* test than in the gastrointestinal tract of the animal, even though the SEDDS clearly showed increased absorption and bioavailability. This may indicate that for the studies reported in Table 6, the *in vivo* liberation of the complete dosage form remains to be tested, as the inventor did not elaborate on this aspect.

Other differences between animal models are the cost and time of the study. Rats are more easily prepared for experimental observation, and dogs may consume more time and money. The time at which the drug is evenly distributed in rat bloodstream has been calculated to be less than 2 minutes, whereas the time for this to happen in dogs and larger mammals could be 10 minutes or more. As a result, pharmacokinetic parameters on larger mammals are more difficult to establish with precision. On top of that, subsequent administrations may be made in rats after short periods of time, whereas in dogs the administrations may be spaced for a week or even longer.[62,66] This could be the main reason why the rat model is preferred, as it could ease the patent registration and submission processes, which can be long and exhaustive.

Further aspects to consider are the differences between the values of pharmacokinetic parameters that can be observed for the same species. Vasconcelos et al.[67] observed that for a different strain of rat, the values of AUC were not reproducible, so the exposure of a drug depends on the genetic variation and the group of animals selected. This is important, since pharmacokinetic studies of the same drug using the same animal model are not going to be directly comparable, and caution must be exercised. Nonetheless, the inventors of the patents did not directly compare the SEDDS developed to other studies but to the conventional dosage form.

G. Release Profile Test

The release profile tests reported for the inventions were only dissolution assays of the SEDDSs. The inventors proceeded according to pharmacopeial methods available for each of the countries of origin. They measured the disintegration time, the cumulative dissolution of the drug, and the emulsification time of the SEDDS in aqueous medium (see Table 1). For this, the inventors would build a calibration curve to test the dissolution of the drug, and some of them would even characterize the emulsion formed in different dissolution media. The media most commonly used were neutral aqueous solution, hydrochloric acid medium, and phosphate buffer medium, and they did not find significant differences in the emulsification performance for the SEDDS.

Nevertheless, detailed drug release analysis was absent in all of the patents. Even though the majority of them were immediate release, and only a few attained controlled release, no drug release model is proposed, and no release kinetics are discussed in the inventions. These types of studies must be done for SEDDS because a dosage form is bound to influence the release kinetics of a drug directly affecting the bioavailability and effectivity of treatment.[55,68] Understanding the release mechanism of SEDDSs could help increase optimization of formulation and develop new treatments.

The release mechanism of the SEDDS is discussed by Bernkop-Schnürch et al.[70] The authors suggest that drug release from SEDDS is explained by a diffusion mechanism, and it is mostly controlled by the body. Because SEDDSs are not matrix systems, release control phenomena such as swelling and hydration of the matrix, dissolution of the drug, and erosion are not going to occur.[69] As a result, the underlying mechanism is the diffusion of the drug to the surface of the droplets, where, once the interfacial barrier is surpassed, it reaches the aqueous medium. Moreover, the parameter directly involved in the mechanism is going to be the partition coefficient, log D, between the oil phase of the SEDDS and the release medium. This means that once the emulsion is formed in the gastrointestinal tract, the drug is going to move out of the droplets until it reaches an equilibrium. Then, the biological membrane is going to absorb it, causing further concentration of the drug to leave the droplets and reestablish this equilibrium. Therefore, drug release from SEDDS is going to be controlled by the absorption rate of the mucosa.

This study also proposes a method for determining the log D of the SEDDSs. The authors proposition is to measure the drug solubility in the SEDDS, and then measure the drug solubility in the release medium. They described the optimal value of log D to be between 3 and 5, since values lower than 3 would present immediate release with risk of precipitation, and values above 5 would render the drug too attached to the oil, which may interfere with diffusion and decrease the quantity absorbed.[70] However, no information regarding the log D is disclosed in the patents, and release kinetics are still in need of more studies.

IV. CONCLUSIONS

Self-emulsifying delivery systems are becoming more relevant because of their obvious beneficial properties, such as increasing bioavailability of drugs in BCS Classes II and IV, ease of formulation, and relatively safe profile. SEDDSs are also a flexible dosage form that may allow for dosing optimization, controlled release, and hybrid formulation to develop new drug delivery systems. As a result, the inventions reviewed manage to meet the novelty requirements in improving drug solubilization, enhancing formulation stability and compatibility, improving the metabolism, and dealing with toxicity issues. However, available technology is not at hand with current research, since the patents undergo a long process before being published. So there may be a significant gap in time between state-of-the-art SEDDS research and the marketed products. Nonetheless, there may be many more patent submissions for these systems in the coming years since its advantages outweigh any other concern as reviewed in this paper.

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