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Successful development of oral SEDDS: screening of excipients from the industrial point of view

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ABSTRACT

Oral administration is the most accepted and favored route as various side effects such as fear, pain and risk of infections can be avoided resulting in a comparatively high patient compliance. However, from the industrial point of view the development of oral delivery systems is still challenging as various drugs are poorly soluble as well as slightly permeable leading to low bioavailability. As self-emulsifying drug delivery systems are able to incorporate both hydrophobic and hydrophilic drugs, these carrier systems have received more and more attention within the last years. Based on the broad range of currently available excipients, this review provides a kind of guideline for the selection of excipients useful to improve bioavailability of the drug on the one hand. As the regulatory status of potential excipients are highly important to introduce the formulation on the market, the review is focused on the other hand on excipients listed in the IIG database of the FDA by taking their corresponding maximum concentration into account. Furthermore, the issue of oral sensation and taste masking is discussed useful for the development of intraoral SEDDS.

Contents

1. Introduction

Looking at future developments, the importance of nanoparticulate systems for oral administration is constantly rising. The relevance of this topic is based on several reasons including poor solubility, poor permeability as well as poor gastrointestinal (GI)-stability leading in variations in bioavailability [1]. These major challenges have to be overcome by the development of innovative concepts. Self-emulsifying drug delivery systems so called SEDDS represent one of the most promising groups of lipophilic nanocarriers. The importance and effectiveness of these carrier systems are emphasized by a huge number of encouraging in vivo data, various patents currently pending and successful marketed products such as Sandimmune Neoral® [2,3].

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However, among the advantages of SEDDS including protective effects towards a presystemic metabolism [4–6] and sufficient permeation through the intestinal mucus gel layer in order to reach the absorption membrane [7,8], the toxicologic point of view has to be considered. There are a large number of surfactants, solvents and lipophilic components on the market, however, the regulatory status of these excipients is of great importance for the generation of novel formulations suitable to introduce these innovations on the market. Therefore, taking the regulatory aspects of SEDDS components into account from the very beginning, the establishment of a marketable product can be simplified. This review focuses on SEDDS excipients currently on the market being evaluated regarding their regulatory status for oral delivery. Furthermore, aspects which are relevant within the development process including maximum concentration of excipients as well as the impact of the excipients on the solubility of drugs are in the following highlighted.

Within the generation process of an oral delivery system, the overall goal is focused on the increase in bioavailability. Therefore, different aspects including possible interactions of SEDDS excipients with the biological environment are discussed within this review bearing in mind various in vitro and in vivo studies of orally administered SEDDS. As drug administration in the oral cavity offers several advantages like the avoidance of chemical degradation and rapid first-pass metabolism, application of SEDDS via buccal and sublingual route seems to be an innovative approach. However, in this context oral sensation and taste masking is highly important and therefore included within this review.

2. SEDDS

SEDDS are isotropic mixtures of oil, surfactant and co-solvent forming nanodroplets between 50 and 300 nm when getting in contact with body fluids. Thus, self-emulsifying systems spread rapidly in the GI-tract and the digestive flexibility of the stomach and the intestine provide the agitation necessary for self-emulsification [9]. Numerous advantages of SEDDS including physical stability, simple manufacturing process and oral application via soft or hard gelatine capsule [10] underline the intensive research within the last decades.

Current predictions suggest that over 70% of newly generated drugs are hydrophobic in nature and poorly water soluble [11]. According to the biopharmaceutical classification system (BCS), class II drugs are highly permeable across the intestinal membrane, but have limited solubility while class IV drugs bear poor solubility and permeability. Both types of drugs might lead to variations in absorption behavior and hence in oral bioavailability. Therefore, lipophilic mixtures are used to improve oral bioavailability of poorly water soluble drugs. Based on an enhancement in rate and extent of absorption, reproducible blood time profiles could already be achieved [12].

Besides, SEDDS are also able to incorporate hydrophilic drugs such as peptides via hydrophobic ion pairing [4,5,13]. Over the last view years, the development, implementation and marketing of therapeutic peptides and proteins increased significantly [14] leading in >100 peptide-based marketed drugs [15]. The reason for interest in peptides and proteins is given by their specificity to their in vivo targets resulting in high potencies of action. Despite of these advantages, low bioavailability due to enzymatic degradation, poor membrane permeability and metabolic instability have to be considered. As SEDDS can protect peptides and protein drugs towards proteolytic activity and efficiently permeate through the mucus barrier, they are a interesting tool for protein and peptide drug delivery [3]. Modification of hydrophilic drugs via hydrophobic ion pairing utilizing amphiphilic molecules is a promising strategy resulting in increased drug lipophilicity [4,13]. Evidence for the feasibility of this concept has already been provided for various peptide drugs such as leuprolide forming stable ion pairs with fatty acids, those could be dissolved in a lipophilic phase [13,16].

3. Regulatory aspects

Pharmaceutical excipients are defined in United States Pharmacopoeia (USP) as “substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system” [17]. The United States Pharmacopoeia – National Formulary (USP-NF) is additional to the European Pharmacopoeia (pH.Eur.) and the Japanese Pharmacopoeia (JP) one of the three major compendia describing the quality of substances to be regulary used in pharmaceutical products, how to test them and general conditions required to assure the quality of pharmaceutical substances. These descriptions so called monographs list the analytical specification and quality attributes and material for pharmaceutical use must comply with this monograph [18]. For an excipient listed in multiple compendia and marketed for global use, the manufacturer is advised to ascertain the conformance of the excipient to each monograph. Additionally to monographs, other specifications are available known as Drug Master File (DMF) including test methods for raw materials, description of the manufacturing process as well as safety data. Although the submission of a DMF is not prescribed by law, this document is often submitted to the Food and Drug Administration (FDA) by the excipient supplier to provide the safety and conformance with appropriate GMP requirements. The FDA maintains a quarterly updated database of excipients which have been approved and incorporated in marketed products entitled “Inactive Ingredient Guide” (IIG) (http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm). Excipients listed in this database might be preferred within the development of new delivery systems as they are already approved resulting in less work and time-consuming reviewing. Each excipient is listed by name, route, dosage form and maximum potency providing useful data for generation of novel formulations. However, based on deviations from the chemical name, this search might be challenging and laborious. The corresponding name of the excipient necessary for the FDA database is therefore included in the listed tables below. Furthermore, the maximum concentration which can be found for oral administration in the IIG database is listed. This given concentration, however, relates to the maximum amount of inactive ingredient for each dosage form containing the ingredient and does not represent the real administered amount of excipient. As SEDDS can be administered as a fluid filled in soft or hard gelatine capsule as well as adsorbed on a carrier material and pressed into tablets [19] the maximum concentrations of these two dosage forms are also provided.

4. Selection of excipients for SEDDS development

Although self-emulsifying systems have been described in detail in the literature, the generation of such a system might be challenging based on the selection of applicable excipients approved for oral delivery. It is thereby essential to identify a combination of excipients suitable to dissolve the entire drug dose in a volume appropriate for unit oral administration [10]. Furthermore, the excipients have to be chosen considering minimal self-emulsification time and droplet size in the gastric milieu for maximal absorption. Emulsifying properties of the developed SEDDS are associated with the nature of oil/surfactant pair, the surfactant concentration as well as the oil/surfactant ratio [20].

4.1. Lipophilic components

In recent years the offer of lipophilic components has grown considerably ranging from biological oils to semi-synthetic lipids [12]. Both long- and medium chain triglyceride oils differing in the degree of saturation can be used for the generation of SEDDS. Unmodified edible oils, comprising medium-chain triglycerides, provide the most natural basis for lipid vehicles and can be esteemed to be safe for oral administration based on their use in the food industry and general GRAS status. Their capacity to dissolve only small amounts of the drug and difficulties to

obtain efficient self-emulsification, however, are the reason why these oils are not the preferred choice. In contrast, modified or hydrolysed vegetable oils demonstrate higher drug solubility properties on the one hand and form good emulsification systems by combining these with non-ionic surfactants on the other hand [20]. Furthermore, their degradation products resemble the end products of intestinal digestion. An overview of available oils with the maximum concentrations listed in the IIG database are displayed in Table 1. Within the last years, these oils have been replaced increasingly by novel semi-synthetic lipid components as their amphiphilic character ensure additional surfactant properties and are therefore of great interest. Gattefossé, ABITEC, Croda and BASF are suppliers of choice within this field of excipients based on their broad range of approved lipid components for oral delivery. Regulatory status, maximal concentration, HLB-value as well as the product conditions are summarized in Table 2. This table is further subdivided into Table 2 A – D including mono-, di-, triglycerides and PEGylated lipophilic components. Thereby, glycerides are classified based on their regulatory specification regarding their mono-and diglycerides content.

Lipids can affect biopharmaceutical properties of the drugs leading to improved drug solubility in the intestinal fluid, protection of the drug against enzymatic degradation as well as the formation of lipoproteins promoting the lymphatic transport of highly lipophilic drugs [10,21]. Precipitation of poorly water soluble drugs might be affected by lipid chain length. Prasad et al. prepared various SEDDS utilizing on the one hand medium chain lipids meaning Lauroglycol FCC and Capryol 90 and on the other hand long chain lipids including Labrafil and castor oil in order to investigate precipitation of indomethacin [22]. No precipitate could be observed with long chain based SEDDS whereas medium chain based SEDDS demonstrated precipitation within 30 min of drug release. Physicochemical properties of the precipitated drug by using Raman- and IR-spectroscopy confirmed that medium chain lipids resulted in a modified indomethacin form underlining possible interactions between API and medium chain lipids. Therefore, it can be assumed that SEDDS including long chain lipids can maintain the drug supersaturation level after dilution process.

The impact of lipid excipients on bioavailability is described in detail in chapter 5.

Table 1
Overview of the available oils. NA – Not available, pH. Eur. – European Pharmacopoeia, USP NF – United States Pharmacopoeia – National Formulary, IIG – Inactive Ingredient Guide, m.p. – melting point.

Chemical name	Regulatory status	IIG name	Dosage form – Maximal conc.	Trade name (Company) – Examples; not exhaustive
Almond oil	Ph. Eur. (virgin, refined), USP NF (refined)	**Not listed**	–	
Castor oil	Ph. Eur. (virgin, refined, hydrogenated), USP NF (refined, hydrogenated), IIG	**Castor oil** **Hydrogenated castor oil (m. p. 83–88 °C)**	Capsule – 1.76 mg Tablet – 23.27 mg Capsule – 410.82 mg Tablet – 295 mg	Super Refined™ Castor oil (Croda)
Coconut oil	Ph. Eur.(refined), USP NF (refined, hydrogenated), IIG	**Coconut oil**	Capsule – NA Tablet – NA	Pureco® 76 (ABITEC)
Corn oil	Ph. Eur. (Maize oil – refined), USP NF (refined), IIG	**Corn oil**	Capsule – 918 mg Solution – NA Tablet – 20 mg	Super Refined™ Corn NF EP (Croda)
Cottonseed oil	Ph. Eur. (hydrogenated), USP NF (refined, hydrogenated), IIG	**Cottonseed oil** **Hydrogenated cottonseed oil (m.p. 140 °C)**	Capsule – NA Tablet – 0.16 mg Capsule – 58 mg Tablet – 402 mg	Super Refined™ Cottonseed NF (Croda) Sterotex® NF – hydrogenated (ABITEC)
Linseed oil	Ph. Eur. (virgin), USP NF (Flax seed oil)	**Not listed**	–	
Olive oil	DMF (refined), Ph. Eur. (virgin, refined), USP NF (refined), IIG	**Olive oil**	Capsule – NA Solution – 425 mg/ml	Super Refined™ Olive (Croda)
Palm oil	USP NF (hydrogenated), IIG	**Palm oil** **Listed as combination with soybean oil**	Capsule – 4 mg	
Peanut oil	DMF (super refined), Ph. Eur. (Arachis oil – refined, hydrogenated), USP NF (refined), IIG	**Peanut oil**	Capsule – 313.8 mg	Super Refined™ Peanut NF (Croda)
Rapeseed oil	Ph. Eur. (refined), USP NF (fully hydrogenated)	**Not listed**	–	Refined Rapeseed Oil EP (SIO)
Safflower oil	DMF, Ph. Eur. (refined), USP NF (refined)	**Not listed**	–	Super Refined™ Safflower USP (Croda)
Sesame oil	DMF (super refined) Ph. Eur. (refined), USP NF (refined), IIG	**Sesame oil**	Capsule – 162.5 mg Tablet – NA	Super Refined™ Sesame (Croda)
Soybean oil	DMF, Ph. Eur. (Soya-bean oil – refined, hydrogenated), USP NF (refined, hydrogenated), IIG	**Soybean oil** **Hydrogenated soybean oil (m. p. 61–68 °C)**	Capsule – 263 mg Tablet – 0.14 mg Capsule – 19.03 mg Tablet – 48 mg	Super Refined™ Soybean (Croda) Refined Soybean Oil EP (SIO) Sterotex® HM, NF – hydrogenated (ABITEC) VGB 4S – hydrogenated (SIO)
Sunflower oil	Ph. Eur. (refined), USP NF (refined)	**Not listed**		Refined Sunflower Oil EP (SIO)
Vegetable oil	DMF (hydrogenated), USP NF (hydrogenated), IIG	**Vegetable oil** **Hydrogenated vegetable oil**	Capsule – 2 mg Tablet – 25 mg Capsule – 261 mg Tablet – 240 mg	

Table 2
Overview of lipid components. NA – Not available, DMF – Drug Master File, pH. Eur. – European Pharmacopoeia, USP NF – United States Pharmacopoeia – National Formulary, IIG – Inactive Ingredient Guide, m.p. – melting point. *Mentioned within this review; however not proved for oral application.* A – monoglycerides, B – diglycerides, C – triglycerides, D – PEGylated lipophilic components.

A

Chemical name	Regulatory status	IIG name	HLB-value	Dosage form – maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
Glyceryl caprylate/caprate Type I	DMF, Ph. Eur. (Glycerol monocaprylocaprate Type I), USP NF (Glyceryl monocaprylocaprate Type I; Mono- and Di-glycerides), IIG	**Caprylic/Capric Mono/Di-Glycerides**	5–6	Capsule – 765 mg	Liquid/Semi-solid (m.p. 25 °C)	Capmul® MCM EP/NF (ABITEC) Imwitor® 742 (IOI Oleo GmbH)
Glyceryl caprylate/caprate Type II	Ph. Eur. (Glycerol monocaprylocaprate Type II), USP NF. (Glyceryl monocaprylocaprate Type II, Mono- and Di-glycerides), IIG	**Glyceryl caprylate/caprate, Glyceryl monocaprylocaprate**	–	Capsule – 374.5 mg	Liquid/Semi-solid	
Glyceryl monocaprylate Type I	DMF, Ph. Eur. (Glycerol monocaprylate Type I), USP NF (Mono- and Di-glycerides), IIG	**Glyceryl monocaprylate, Mono and diglyceride**	5–6	Capsule – 400 mg Solution – 349.1 mg/ml	Liquid/Semi-solid (m.p. 23 °C)	Capmul® MCM C8 EP/NF (ABITEC) Imwitor® 988 (IOI Oleo GmbH)
Glyceryl monocaprylate Type II	Ph. Eur. (Glycerol monocaprylate Type II), USP NF (Mono- and Di-glycerides)	**Glyceryl monocaprylate, Mono and diglyceride**	6–7	Capsule – 400 mg Solution – 349.1 mg/ml	Solid (m.p. 27–33 °C)	Capmul® 808G EP/NF (ABITEC) Imwitor® 308 (IOI Oleo GmbH)
Glyceryl monooleate Type 40	DMF, Ph. Eur. (Glycerol mono-oleate, 40), USP NF (Glycerol monooleate, 40), IIG	**Glyceryl oleate**	1	Capsule – NA Tablet – 0.15 mg	Liquid	Peceol™ (Gattefossé), Imwitor® 948 (IOI Oleo GmbH)
Glyceryl monooleate Type 60	Ph. Eur. (Glycerol mono-oleate, 60), USP NF (Glycerol monooleate, 60), IIG	**Glyceryl oleate**	3–4	Capsule – NA Tablet – 0.15 mg	Liquid/Semi-solid	Capmul® GMO 50 EP/NF (ABITEC) RHEODOL MO-60 (Kao Chemicals)
Glyceryl monooleate Type 90	Ph. Eur. (Glycerol mono-oleate, 90), USP NF (Glycerol monooleate, 90), IIG	**Glyceryl oleate**	–	Capsule – NA Tablet – 0.15 mg	Solid (m.p. 30 °C)	Cithrol™ GMO HP (Croda) Imwitor® 990 (IOI Oleo GmbH)
Polyglyceryl-10 oleate	DMF, IIG	**Polyglyceryl-10 oleate**	11	Solution – 190 mg/ml Capsule – 199.9 mg	Liquid	Caprol® PGE 860 (ABITEC)
Propylene glycol monocaprylate Type I	DMF, USP NF (Propylene Glycol Monocaprylate Type I)	**Not listed**	6	–	Liquid	Capmul® PG 8–70 NF (ABITEC) Capryol™ PGMC (Gattefossé)
Propylene glycol monocaprylate Type II	DMF, USP NF (Propylene Glycol Monocaprylate Type II)	**Not listed**	4–5	–	Liquid	Capmul® PG-8 NF (ABITEC) Capryol™ 90 (Gattefossé)
Propylene glycol monolaurate Type I	DMF, Ph. Eur. (Propylene Glycol Monolaurate Type I), USP NF (Propylene Glycol Monolaurate Type I)	**Propylene glycol monolaurate**	5	Tablet – 10 mg	Liquid	Lauroglycol™ FCC (Gattefossé)
Propylene glycol monolaurate Type II	DMF, Ph. Eur. (Propylene Glycol Monolaurate Type II), USP NF (Propylene Glycol Monolaurate Type II), IIG	**Propylene glycol monolaurate**	3–6	Tablet – 10 mg	Liquid	Capmul® PG-12 EP/NF (ABITEC) Lauroglycol™ 90 (Gattefossé)

B

Chemical name	Regulatory status	IIG name	HLB-value	Dosage form – Maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
Glyceryl monolinoleate	DMF, Ph. Eur. (Glycerol monolinoleate), USP NF (Glyceryl monolinoleate)	**Not listed**	1	–	Liquid	Maisine™ 35–1 (Gattefossé; previously Maisine™ CC)
Polyglyceryl-3 dioleate	DMF, USP NF (Polyglyceryl-3 dioleate), IIG	**Polyglyceryl-3 oleate**	3	Solution – 310 mg/ml Capsule – 330.7 mg	Liquid	Plurol® Oleique CC 497 (Gattefossé)
Propylene glycol dicaprylocaprate	DMF, Ph. Eur. (Propylene Glycol Dicaprylocaprate), USP NF (Propylene Glycol Dicaprylate/Dicaprate)	**Not listed**	1	–	Liquid	Captex® 200P (ABITEC) Labrafac™ PG (Gattefossé) Miglyol® 840 (IOI Oleo GmbH)
Propylene glycol dilaurate	Ph. Eur. (Propylene Glycol Dilaurate), USP NF (Propylene Glycol Dilaurate)	**Not listed**	2	–	Liquid	Capmul® PG-2 L EP/NF (ABITEC)

C

Chemical name	Regulatory status	IIG name	HLB-value	Dosage form – Maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
Glyceryl tricaprylate	DMF, IIG	**Tricaprylin**	–	Tablet – 0.45 mg	Liquid	Captex® 8000 (ABITEC) Miglyol® 808 (IOI Oleo GmbH)
Medium chain triglycerides	DMF, Ph. Eur. (Triglycerides, medium-chain), USP NF (Medium-chain triglycerides), IIG	**Medium-chain triglycerides**	1	Capsule – 250 mg Solution – 944.6 mg/ml Tablet – 0.34 mg	Liquid	Captex® 300 EP/NF (ABITEC) Captex® 355 EP/NF (ABITEC) Captex® 8000 (ABITEC) Kollisolv® MCT 70 (BASF) Crodamol™ GTCC (Croda) Labrafac™ Lipophile WL1349 (Gattefossé) Miglyol® 810 N (IOI Oleo GmbH) Miglyol® 812 N (IOI Oleo GmbH) Neobee® 1053 (Stepan) Neobee® M-5 (Stepan)

D

Chemical name	Regulatory status	IIG name	HLB-value	Dosage frm – Maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
PEG-6 caprylic/capric glycerides	DMF, Ph. Eur. (Caprylocaproyl Macrogolglycerides), USP NF (Caprylocaproyl polyoxylglycerides), IIG	**Caprylocaproyl Macrogolglycerides**	–	Capsule – 905.81 mg	Liquid	Softigen® 767 (IOI Oleo GmbH) *Glycerox 767 HC (Croda)*
PEG-6 lauroyl glycerides	DMF, Ph. Eur. (Lauroyl macrogolglycerides), USP NF (Lauroyl polyoxylglycerides), IIG	**Lauroyl Polyoxylglycerides**	9	Capsule – 218 mg Tablet – 0.15 mg	Solid (m. p. 33–38 °C)	Labrafil® M 2130 CS (Gattefossé)
PEG-6 linoleoyl glycerides	DMF, Ph. Eur. (Linoleoyl macrogolglycerides), USP NF (Linoleoyl polyoxylglycerides), IIG	**Corn Oil PEG-6 Esters** **Linoleoyl Macrogolglycerides**	4/9	Capsule – 300 mg Capsule – 23.8 mg	Liquid	Labrafil® M 2125 CS (Gattefossé)
PEG-6 oleoyl glycerides	DMF, Ph. Eur. (Oleoyl macrogolglycerides), USP NF (Oleoyl polyoxylglycerides)	**Not listed**	4/9	–	Liquid	Acconon® AKG-6 EP/NF (ABITEC) Labrafil® M 1944 CS (Gattefossé)
PEG-8 caprylic/capric glycerides	DMF, Ph. Eur. (Caprylocaproyl Macrogolglycerides), USP NF (Caprylocaproyl polyoxylglycerides), IIG	**PEG-8 Caprylic/Capric Glycerides** **Caprylocaproyl Macrogolglycerides**	12–15	Solution – 61.2 mg/ml Capsule – 70 mg Capsule – 905.81 mg	Liquid	Acconon® MC8–2 EP/NF (ABITEC) Labrasol® ALF (Gattefossé)
PEG-32 lauroyl glycerides	DMF, Ph. Eur. (Lauroyl Macrogolglycerides), USP NF (Lauroly polyoxylglycerides), IIG	**Lauroyl PEG-32 glycerides** **Lauroyl Polyoxylglycerides**	11/14	Capsule – 218 mg Tablet – 0.15 mg	Solid (m. p. 42.5–47.5 °C)	Acconon® C-44 EP/NF (ABITEC) Gelucire® 44/14 (Gattefossé)
PEG-32 stearate	DMF, USP NF (Polyoxyl stearate Type I)	–	12		Solid (m. p. 46–50 °C)	Gelucire® 48/16 (Gattefossé)
PEG-32 stearoyl glycerides	DMF, Ph. Eur. (Stearoyl Macrogolglycerides), USP NF (Stearoly polyoxylglycerides), IIG	**PEG-32 hydrogenated palm glycerides** **Stearoyl Polyoxylglycerides**	11/13	Capsule – 4.17 mg Capsule – 480 mg Tablet – 2.6 mg	Solid (m. p. 46–51 °C)	Acconon® C-50 EP/NF (ABITEC) Gelucire® 50/13 (Gattefossé)

4.2. Surfactants

In order to develop promising oral carrier systems, various aspects have to be considered including HLB value, safety profile as well as surfactant ratio within the SEDD formulation. Surfactants, being amphiphilic in nature, are able to dissolve high amounts of hydrophobic drugs preventing precipitation within the GI-lumen [23]. In order to reduce the surface tension and forming monolayer between oil and aqueous phase, the addition of surfactants is highly important [24]. Generally, the surfactant concentration ranges from 30 to 50% w/w to form and maintain stable emulsions. Within this context the safety aspect has to be taken into account as an increased amount of emulsifier may cause GI-irritation. Hence, natural surfactants such as lecithin are more preferred with regard to their safety profile in comparison to synthetic ones. Despite of the high biocompatibility of lecithin containing phosphatidylcholine as amphiphilic structure, limited self-emulsification efficiency has been described in the literature [25]. Non-ionic surfactants demonstrating high HLB values are the most attractive emulsifiers within design of promising SEDD formulations as they are less toxic in comparison to ionic emulsifiers. The high HLB value and subsequent hydrophilicity of surfactant is of great importance to facilitate immediate formation of o/w droplets and rapid spreading of the formulation in the aqueous GI-fluid providing sufficient emulsification [20]. An overview of the available surfactants is given in Table 3 presenting the corresponding IIG name and the listed maximal concentration found in the IIG database. This table is further subdivided into Table 3 A – D containing monoglycerides, sugar-lipid based surfactants with PEG modification, polymer based surfactants and PEGylated emulsifiers. As some of the lipid components such as Acconon MC8–2 EP/Labrasol ALF exhibit also emulsification properties, these components are classified by taking the lipophilic as well as the surfactant part into account and are therefore also listed in Table 3. In order to develop SEDDS successfully, the impact of surfactants on cytotoxicity as well as permeability should be taken into account. Based on various published data, both advantages and disadvantages of well known surfactants are highlighted in chapter 6.

Table 3
Overview of the surfactants. NA – Not available, DMF – Drug Master File, pH. Eur. – European Pharmacopoeia, USP NF – United States Pharmacopoeia – National Formulary, IIG – Inactive Ingredient Guide, m.p. – melting point. *Mentioned within this review; however not proved for oral application.*
A – monoglycerides, B – sugar-lipid based surfactants with PEG modification, C – polymer based surfactants, D – PEGylated emulsifiers.

A

Chemical name	Regulatory status	IIG name	HLB-value	Maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
Propylene glycol monocaprylate Type I	DMF, USP NF (Propylene Glycol Monocaprylate Type I)	**Not listed**	6	–	Liquid	Capmul® PG 8–70 NF (ABITEC) Capryol™ PGMC (Gattefossé)
Propylene glycol monocaprylate Type II	DMF, USP NF (Propylene Glycol Monocaprylate Type II)	**Not listed**	4–5	–	Liquid	Capmul® PG-8 NF (ABITEC) Capryol™ 90 (Gattefossé)
Propylene glycol monolaurate Type I	DMF, Ph. Eur. (Propylene Glycol Monolaurate Type I), USP NF (Propylene Glycol Monolaurate Type I)	**Propylene glycol monolaurate**	5	Tablet – 10 mg	Liquid	Lauroglycol™ FCC (Gattefossé)
Propylene glycol monolaurate Type II	DMF, Ph. Eur. (Propylene Glycol Monolaurate Type II), USP NF (Propylene Glycol Monolaurate Type II), IIG	**Propylene glycol monolaurate**	3–6	Tablet – 10 mg	Liquid	Capmul® PG-12 EP/NF (ABITEC) Lauroglycol™ 90 (Gattefossé)

B

Chemical name	Regulatory status	IIG name	HLB-value	Maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
Polyoxyethylene (20) sorbitan monolaurate	Ph. Eur. (Polysorbate 20), USP NF (Polysorbate 20), IIG	**Polysorbate 20**	16.7–17	Capsule – 56.25 mg Tablet – 6 mg	Liquid	Kolliphor® PS 20 (BASF) Super Refined™ Polysorbate 20 or Tween™ 20 (Croda) Montanox™ 20 (Seppic)
Polyoxyethylene (20) sorbitan monooleate	DMF, Ph. Eur. (Polysorbate 80), USP NF (Polysorbate 80), IIG	**Polysorbate 80**	15.0	Capsule – 418.37 mg Solution – 126 mg/ml Tablet – 24 mg	Liquid	Kolliphor® PS 80 (BASF) Super Refined™ Polysorbate 80 or Tween™ 80 (Croda) Montanox™ 80 (Seppic)
Polyoxyethylene (20) sorbitan monopalmitate	Ph. Eur. (Polysorbate 40), USP NF (Polysorbate 40), IIG	**Polysorbate 40**	15.6	Solution – 0.01 mg/ml	Liquid	Tween™ 40 (Croda)
Polyoxyethylene (20) sorbitan monostearate	Ph. Eur. (Polysorbate 60), USP NF (Polysorbate 60), IIG	**Polysorbate 60**	14.9	Tablet – NA	Liquid	Kolliphor® PS 60 (BASF) Super Refined™ Polysorbate 60 or Tween™ 60 (Croda) Montanox™ 60 (Seppic)
Polyoxyethylene (20) sorbitan trioleate	IIG	**Polysorbate 85**	11.0	Solution – NA	Liquid	Tween 85
Sorbitan monolaurate	Ph. Eur. (Sorbitan laurate), USP NF (Sorbitan monolaurate), IIG	**Sorbitan monolaurate**	8.6	Capsule – 0.08 mg Tablet – 83.9 mg	Liquid, with suspended solids	Span™ 20 HP (Croda)
Sorbitan monooleate	Ph. Eur. (Sorbitan oleate), USP NF (Sorbitan monooleate), IIG	**Sorbitan monooleate**	4.3	Capsule – 153.9 mg Solution – 150 mg/ml Tablet – 7.8 mg	Liquid	Span™ 80 HP (Croda)
Sorbitan monopalmitate	Ph. Eur. (Sorbitan palmitate),USP NF (Sorbitan monopalmitate), IIG	**Sorbitan monopalmitate**	6.7	Emulsion – NA	Solid (m. p. 45–48 °C)	Span 40
Sorbitan monostearate	Ph. Eur. (Sorbitan stearate), USP NF (Sorbitan monostearate), IIG	**Sorbitan monostearate**	4.7	Suspension – 62.5 mg/5 ml	Solid (m.p. 53 °C)	Span™ 60 HP (Croda)
Sorbitan trioleate	DMF, Ph. Eur. (Sorbitan trioleate), USP NF (Sorbitan trioleate), IIG	**Sorbitan trioleate**	1.8	Capsule – NA Solution – NA Tablet – NA	Liquid	Span™ 85 (Croda)

C

Chemical name	Regulatory status	IIG name	HLB-value	Maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
Poloxamer 124 / Polyoxyethylene polyoxypropylene glycol	DMF, Ph. Eur. (Poloxamer 124), USP NF (Poloxamer 124), IIG	**Poloxamer 124**	–	Suspension – 0.09 mg/ml	Liquid	Kolliphor® P 124 (BASF; previously Lutrol® L 44) Synperonic™ PE/L 44 (Croda)
Poloxamer 188 / Polyoxyethylene polyoxypropylene glycol	DMF, Ph. Eur. (Poloxamer 188), USP NF (Poloxamer 188), IIG	**Poloxamer 188**	29	Capsule – 10 mg Solution – 10 mg/ml Tablet – 66.9 mg	Solid (m. p. 52 °C)	Kolliphor® P 188 (BASF; previously Lutrol® F 68) Synperonic™ PE/F 68 (Croda)
Poloxamer 338 / Polyoxyethylene polyoxypropylene glycol	DMF, Ph. Eur. (Poloxamer 338), USP NF (Poloxamer 338), IIG	**Poloxamer 338**	–	Capsule – 2 mg	Solid (m. p. 57 °C)	Kolliphor® P 338 (BASF; previously Lutrol® F 108) Synperonic™ PE/F 108 (Croda)
Poloxamer 407 /	DMF, Ph. Eur. (Poloxamer 407), USP NF	**Poloxamer**	18–23	Capsule – 40 mg	Solid (m.	Kolliphor® P 407 (BASF; previously

(continued on next page)

Table 3 (*continued*)

C						
Chemical name	Regulatory status	IIG name	HLB-value	Maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
Polyoxyethylene polyoxypropylene glycol	(Poloxamer 407), IIG	**407**		Solution – 10 mg/ml Tablet – 110 mg	p. 56 °C)	Lutrol® F 127) Synperonic™ PE/F 127 (Croda)

D						
Chemical name	Regulatory status	IIG name	HLB-value	Maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
PEG-6 lauroyl glycerides	DMF, Ph. Eur. (Lauroyl macrogolglycerides), USP NF (Lauroyl polyoxylglycerides), IIG	**Lauroyl Polyoxylglycerides**	9	Capsule – 218 mg Tablet – 0.15 mg	Solid (m.p. 33–38 °C)	Labrafil® M 2130 CS (Gattefossé)
PEG-6 linoleoyl glycerides	DMF, Ph. Eur. (Linoleoyl macrogolglycerides), USP NF (Linoleoyl polyoxylglycerides), IIG	**Corn Oil PEG-6 Esters Linoleoyl Macrogolglycerides**	4/9	Capsule – 300 mg Capsule – 23.8 mg	Liquid	Labrafil® M 2125 CS (Gattefossé)
PEG-6 oleoyl glycerides	DMF, Ph. Eur. (Oleoyl macrogolglycerides), USP NF (Oleoyl polyoxylglycerides)	**Not listed**	4/9	–	Liquid	Acconon® AKG-6 EP/NF (ABITEC) Labrafil® M 1944 CS (Gattefossé)
PEG-8 caprylic/capric glycerides	DMF, Ph. Eur. (Caprylocaproyl Macrogolglycerides), USP NF (Caprylocaproyl polyoxylglycerides), IIG	**PEG-8 Caprylic/Capric Glycerides Caprylocaproyl Macrogolglycerides**	12–15	Solution – 61.2 mg/ml Capsule – 70 mg Capsule – 905.81 mg	Liquid	Acconon® MC8–2 EP/NF (ABITEC) Labrasol® ALF (Gattefossé)
PEG-15 Hydroxystearate	DMF, Ph. Eur. (Macrogol 15 Hydroxystearate), USP NF (Polyoxyl 15 Hydroxystearate)	**Not listed (intravenous – PEG-15 Hydroxystearates)**	14–16	–	Liquid/Semi-solid	Kolliphor® HS 15 (BASF; previously Solutol® HS 15)
PEG-30 castor oil	–	***Not listed***	*12*	–	*Liquid*	*ALKAMULS EL-620 (Solvay; previously Emulphor EL-620)*
PEG-32 lauroyl glycerides	DMF, Ph. Eur. (Lauroyl Macrogolglycerides), USP NF (Lauroly polyoxylglycerides), IIG	**Lauroyl PEG-32 glycerides Lauroyl Polyoxylglycerides**	11/14	Capsule – 218 mg Tablet – 0.15 mg	Solid (m. p. 42.5–47.5 °C)	Acconon® C-44 EP/NF (ABITEC) Gelucire® 44/14 (Gattefossé)
PEG-32 stearoyl glycerides	DMF, Ph. Eur. (Stearoyl Macrogolglycerides), USP NF (Stearoly polyoxylglycerides), IIG	**PEG-32 hydrogenated palm glycerides Stearoyl Polyoxylglycerides**	11/13	Capsule – 4.17 mg Capsule – 480 mg Tablet – 2.6 mg	Solid (m.p. 46–51 °C)	Acconon® C-50 EP/NF (ABITEC) Gelucire® 50/13 (Gattefossé)
PEG-35 castor oil	DMF, pH. Eur. (Macrogolglycerol Ricinoleate), USP NF (Polyoxyl 35 Castor Oil), IIG	**Polyoxyl 35 castor oil**	12–14	Capsule – 599.4 mg Solution – 515 mg/ml Tablet – 2 mg	Liquid	Cremophor EL/ Kolliphor EL® (BASF) Super Refined™ Etocas™ 35 (Croda) Acrysol™ EL-135 (Corel Pharmachem)
PEG-40 hydrogenated castor oil	DMF, Ph. Eur. (Macrogolglycerol Hydroxystearate), USP NF (Polyoxyl 40 Hydrogenated Castor Oil), IIG	**Polyoxyl 40 hydrogenated castor oil**	14–16	Capsule – 405 mg Solution – 450 mg/ml Tablet – 50 mg	Liquid/Semi-solid	Cremophor RH40 /Kolliphor RH40® (BASF) Acrysol™ K-140 (Corel Pharmachem) Croduret™ 40 (Croda) Croduret™ 50 (Croda)
D-α-Tocopherol polyethyleneglycol succinate / D-α-Tocopherol PEG-1000 succinate	DMF, USP NF (Vitamin E polyethylene glycol succinate), IIG	**Tocophersolan**	13.2	Capsule – 300 mg Solution – 120 mg/ml Tablet – 42.5 mg	Liquid/Semi-solid (m.p. 37–41 °C)	Vitamin E TPGS NF (PMC Isochem)

4.3. Hydrophilic components

Hydrophilic components meaning co-solvents are essential to dissolve large amounts of the API on the one hand and hydrophilic surfactants on the other hand as the formulation of effective SEDDS requires high concentration of emulisifier. Currently, Griesser et al. generated various ion pairs of three different therapeutic peptides meaning leuprolide (LEU), insulin (INS) and desmopressin (DES) in order to reach high payload in SEDDS [13]. Thereby, hydrophilic compounds such as Transcutol HP and propylene glycol seem to be important for the solubility of the formed complexes. Within solubility studies, presented in Table 4, the maximum concentration (5.0% m/v) of all three

Table 4
Solubility of peptide-docusate complexes in four concentrations 0.625%, 1.25%, 2.5% and 5.0% (m/v). (−) not dissolved or lower than 0.625%. Adapted by Griesser et al.

Excipient	Dielectric constant	Maximum concentration of dissolved complexes (%)		
		LEU – docusate	INS – docusate	DES – docusate
Capryol 90	6.1	5.0	1.25	2.5
Labrafac Lip. WL 1349	2.9	–	–	–
Labrafil M 1944 CS	3.7	0.625	–	–
Labrafil M 2125 CS	3.4	–	–	–
Labrasol ALF	8.1	5.0	2.5	5.0
Lauroglycol 90	4.7	5.0	–	–
Maisine CC	3.3	5.0	0.625	2.5
Peceol	3.5	2.5	2.5	2.5
Plurol Oleique CC 497	3.0	0.625	0.625	–
Propylene glycol	32.0	5.0	5.0	5.0
Tetraglycol	15.7	5.0	5.0	5.0
Transcutol HP	14.1	5.0	5.0	5.0
Tween 20	NA	2.5	–	2.5

peptide-docusate complexes could be dissolved in propylene glycol, tetraglycol and Transcutol HP. Griesser et al. pointed out that there might be a relation between the dielectric constant of various solvents and their corresponding solubilizing properties. Generally, aprotic solvents such as Labrafil M1944 CS, Maisine CC as well as Peceol demonstrated lower complex solubilizing properties underlined by low dielectric constant ranging from 2.9 to 3.7 compared to the protic solvents including Transcutol HP, tetraglycol, propylene glycol as well as Labrasol ALF. These protic components of a dielectric constant between 8.1 and 32.0 showed comparatively higher solubilizing properties as demonstrated in Table 4. As polar solvents are capable of solvating molecules through dipole interaction forces, particularly via hydrogen-bond formation, dipole moment should also be considered within the mechanism of compound solubility [26]. However, intensive research on the effect of the dipole moment on SEDDS has so far not been undertaken and only a few data are available including the dipole moment of SEDDS excipients. Therefore, an examination regarding the dipole moment of SEDDS excipients and subsequently the influence on solubility might be an interesting and useful additional tool for the successful development of SEDDS. An overview of the available hydrophilic excipients with the corresponding IIG name as well as the maximum concentration is given in Table 5. As alcohol is known to evaporate into the shells of soft gelatin or hard gelatin capsules resulting in drug precipitation, the application of alcohol has to be considered [12].

5. Impact of lipophilic excipients

In recent years various studies underlined that lipids have a major impact on the oral bioavailability by altering the biopharmaceutical properties of the drugs. Additionally to an increase in drug dissolution in the GI-fluid, the incorporated drug might be protected towards enzymatic degradation [9]. Furthermore, the oil content has an favorable effect on lymphatic transport [24]. The intestinal lymphatic system is a physiological pathway for the absorption of lipid digestion products [27]. In this context, long chain fatty acids and monoglycerides might be able to increase drug transport by the lymphatic system in the GI as these components are re-esterified in the small intestine and incorporated into chylomicron followed by secretion into the lymph vessel by exocytosis [24,28]. Chylomicron, a large lipoprotein, is not able to cross tight junction of blood capillaries; however, it can easily penetrate to lymphatic junction leading to a possible bypass of the first pass metabolism. In contrast, short and medium chain fatty acids are transported to the systemic circulation via the portal blood and only incorporated to a small extent into chylomicron [9]. Taking these aspects into account, SEDDS can be optimized accordingly resulting in higher bioavailability. Recently, Imada et al. demonstrated improved oral bioavailability of a novel antimalarial drug named N-251 by increasing lymphatic transport with long-chain fatty acid based SEDDS [29]. As shown in Table 6, various SEDDS were prepared utilizing on the one hand medium-chain fatty acids (MC-SEDDS) and on the other hand long-chain fatty acids (LC-SEDDS) and examined regarding in vivo oral absorption behavior in rats. Outcome of in vivo studies, presented in Fig. 1, revealed that SEDDS significantly improved the absorption behavior of N-251 compared to N-251 powder. Comparing MC-SEDDS and LC-SEDDS, the bioavailability of MC-SEDDS B was limited to 0.49 whereas LC-SEDDS F provided the highest bioavailability of 0.65. The improvement in bioavailability utilizing LC-SEDDS might be caused by avoiding the hepatic first-pass elimination. Therefore, the lymphatic transport of N-251 after oral administration was additionally evaluated. Significantly higher maximum mesenteric lymph node concentrations were observed for LC-SEDDS F (42.3 μg/g) compared to MC-SEDDS B (14.9 μg/ml) underlined that LC-SEDDS promotes the lymphatic transport of N-251 after the uptake of the small intestine. Charman et al. have already reported that drugs demonstrating log *P* values >5 and solubility in triglyceride of long-chain fatty acids >50 mg/ml are likely to be transported to lymphatic system [30]. It was already shown that the lymphatic transport of the lipophilic drug halofantrine was enhanced in rats by the presence of co-administered lipids, in particular by increasing the fatty acid chain length [31]. Moreover, the same API was administered orally to fasted dogs utilizing on the one hand a medium-chain formulation (Captex 355, Capmul MCM, Cremophor EL, ethanol) and on the other hand a long-chain formulation comprising soybean oil, Maisine 35–1, Cremophor EL and ethanol. Microemulsions based on long-chain glycerides resulted in a significantly higher extent of lymphatic transport of halofantrine in comparison to medium-chain formulation [31,32].

Additionally to the point of lymphatic transport, GI-lipolysis should be taken into consideration during the development process. Lipolysis is a critically important event for drug dissolution and absorption as it can be beneficial on the one hand (drug solubilization/dispersion) and negative on the other hand with respect to drug precipitation. As there is a huge number of excipients available containing ester functions, hydrolysis by various esterases might take place in the GI-tract [33]. Fernandez et al. investigated in vitro the GI-lipolysis of cinnarizine formulated in Labrasol [34]. Therefore, a two-step digestion model was used simulating the gastric phase with gastric lipase and duodenal phase with pancreatic enzymes and additionally bile [33]. As Labrasol is a macrogolglyceride composed of C8-C10 mono-, di-, and triacylglycerols, C8-C10 mono- and diesters of PEG-8 and free PEG-8 [35] it was hydrolyzed to a large extent during gastric phase; however, cinnarizine solubilization in the aqueous phase remained high. Complete digestion of monoacylglyerols and additional lipolysis of diacylglycerols as well as PEG-8-mono- and diesters were observed in the intestinal phase, but no precipitation of cinnarizine was determined. In control experiments without digestive lipases, a drastic precipitation of cinnarizine formulated in Labrasol was investigated after the pH of the reaction mixture changed to simulate intestinal conditions. Hence, enzymatic lipolysis might be required to keep the API solubilized [33,34]. The interactions between the formulation and endogenous lipids such as bile salts or phospholipids might increase the solubilization of the drug in the colloidal structures resulting in enhanced oral bioavailability [34].

6. Impact of surfactants

Additionally to lipid digestion, hydrolysis with respect to emulsifier has to be considered. Both castor oil derivates Cremophor EL and Cremophor RH40 are well known emulsifier with different melting points; therefore liquid and semisolid at room temperature, respectively [36]. Although Cremophor EL and Cremophor RH40 are from the same family of surfactants, Cremophor RH40 has a higher ethylen oxide content (40 ethylen oxide units per mol surfactant) compared to Cremophor EL based on 35 units and therefore potentially hindering

Table 5
Overview of the hydrophilic excipients NA – Not available, DMF – Drug Master File, Ph. Eur. – European Pharmacopoeia, USP NF – United States Pharmacopoeia – National Formulary, IIG – Inactive Ingredient Guide, m.p. – melting point.

Chemical name	Regulatory status	IIG name	Maximal conc.	Solid/Liquid	Trade name (Company) – Examples; not exhaustive
Acetyl tributyl citrate	Ph. Eur. (Tributyl acetylcitrate), USP NF (Acetyltributyl citrate), IIG	**Acetyltributyl citrate**	Capsule – 18.98 mg Tablet – 57.35	Liquid	Citrofol® BII (Jungbunzlauer)
Acetyl triethyl citrate	DMF, USP NF (Acetyltriethyl citrate)	**Not listed**	–	Liquid	Citrofol® AII (Jungbunzlauer)
Dimethyl sulfoxide	DMF, Ph. Eur. (Dimethyl sulfoxide), USP NF (Dimethyl sulfoxide)	**Not listed (intravenous – Dimethyl sulfoxide)**	–	Liquid	Procipient® (Gaylord Chemical)
Ethyl alcohol	DMF, Ph. Eur. (Ethanol), USP NF (Alcohol)	**Not listed (intravenous – Alcohol)**	–	Liquid	Ethanol
Ethyl oleate	Ph. Eur. (Ethyl oleate), USP NF (Ethyl oleate)	**Not listed**	–	Liquid	Crodamol™ EO (Croda)
Glycerol triacetate / 1,2,3-Propanetriol Triacetate	DMF, Ph. Eur. (Triacetin), USP NF (Triacetin), IIG	**Triacetin**	Capsule – 46.7 Tablet – 15.12 mg	Liquid	Kollisolv® GTA (BASF)
Highly purified diethylene glycol monoethyl ether	DMF, Ph. Eur. (Diethylene Glycol Monoethyl Ether), USP NF (Diethylene Glycol Monoethyl Ether)	**Not listed**	–	Liquid	Transcutol® HP (Gattefossé) CARBITOL™ (DOW Chemicals)
Polyethylene glycol 200	DMF, Ph. Eur. (Macrogols), USP NF (Polyethylene glycol), IIG	**Polyethylene glycol 200**	Capsule – NA Solution – 200 mg/ml Tablet – NA	Liquid	PEG 200
Polyethylene glycol 300	DMF, Ph. Eur. (Macrogols), USP NF (Polyethylene glycol), IIG	**Polyethylene glycol 300**	Tablet – 1.5 mg	Liquid	Kollisolv® PEG 300 (BASF) Super Refined™ PEG 300 (Croda)
Polyethylene glycol 400	DMF, Ph. Eur. (Macrogols), USP NF (Polyethylene glycol), IIG	**Polyethylene glycol 400**	Capsule – 1057 mg Solution – 8549 mg/20 ml Tablet – 105.07 mg	Liquid	Kollisolv® PEG 400 (BASF) Super Refined™ PEG 400 (Croda)
Polyethylene glycol 600	DMF, Ph. Eur. (Macrogols), USP NF (Polyethylene glycol), IIG	**Polyethylene glycol 600**	Capsule – 580.6 mg Solution – 650 mg/5 ml Tablet – 6 mg	Liquid/Semi-solid	Kollisolv® PEG 600 (BASF) Super Refined™ PEG 600 (Croda)
1,2-Propandiol	DMF, Ph. Eur. (Propylene glycol), USP NF (Propylene glycol), IIG	**Propylene glycol**	Capsule – 148.31 mg Solution – 1017.5 mg/ml Liquid – 621.6 mg/ml Tablet – 14.4 mg	Liquid	Kollisolv® PG (BASF) Super Refined™ Propylene glycol (Croda)
Propan-2-ol	DMF, Ph. Eur. (Isopropyl alcohol), USP NF (Isopropyl alcohol), IIG	**Isopropyl alcohol**	Capsule – 392.8 mg Solution – NA Tablet – 402.53 mg	Liquid	Isopropyl alcohol
Propane-1,2,3-triol (Glycerol)	DMF, Ph. Eur. (Glycerol), USP (Glycerin), IIG	**Glycerin**	Capsule – 249.1 mg Solution – 3108 mg/15 ml Liquid – 885.5 mg/ml Tablet – 16 mg	Liquid	Kollisolv® G99 (BASF) Pricerine™ 9093 (Croda) OPTIM™ Glycerine (Hedinger)
Triethyl citrate	DMF, Ph. Eur. (Triethyl citrate), USP NF (Triethyl citrate), IIG	**Triethyl citrate**	Capsule – 22.23 mg Tablet – 20.18 mg	Liquid	Citrofol® AI (Jungbunzlauer, AppliChem)

lipase access [37,38]. From the digestion point of view, Cremophor RH40 might be the more attractive choice for keeping the drug in solubilized state for a longer period compared to Cremophor EL. Cuiné et al. demonstrated in vitro that Cremophor RH40 was less effectively hydrolyzed than Cremophor EL leading in vivo to higher danazol bioavailability in beagle dogs after oral administration of SEDDS [38]. Cremophor RH40 was also identified as promising excipient for SEDDS to improve their mucus permeating properties [7]. Friedl. et al.

Table 6
Composition of MC- as well as LC-SEDDS and their corresponding droplet sizes. Indicated values are means ($n = 3$) ± SD. Adapted from Imada et al.

	MC-SEDDS A	MC-SEDDS B	MC-SEDDS C
N-251 (mg)	68	68	68
Capryol 90 (g)	0.30	0.20	0.30
Cremophor EL (g)	0.35	0.27	–
Cremophor RH40 (g)	–	–	0.35
Carbitol (g)	0.35	0.53	0.35
Mean particle size (nm)	31.8 ± 0.33	33.5 ± 0.58	30.9 ± 0.54
Polydispersity index	0.13 ± 0.01	0.12 ± 0.01	0.12 ± 0.03
	LC-SEDDS D	**LC-SEDDS E**	**LC-SEDDS F**
N-251 (mg)	68	68	68
Olive oil (g)	0.30	0.20	0.30
Cremophor RH40 (g)	0.59	0.42	0.42
Rheodol MO-60 (g)	0.13	0.21	0.21
Ethanol (g)	0.15	0.10	–
Carbitol (g)	–	–	0.10
Mean particle size (nm)	23.0 ± 0.90	32.3 ± 0.35	31.2 ± 0.09
Polydispersity index	0.18 ± 0.06	0.18 ± 0.02	0.10 ± 0.01

developed a novel mucus diffusion system whereby an increased concentration of Cremophor RH40 from 20% to 30% or up to 40% within SEDDS resulted in a two- and fourfold improvement in permeation behavior, respectively. As the mucus gel layer, a tenacious complex and

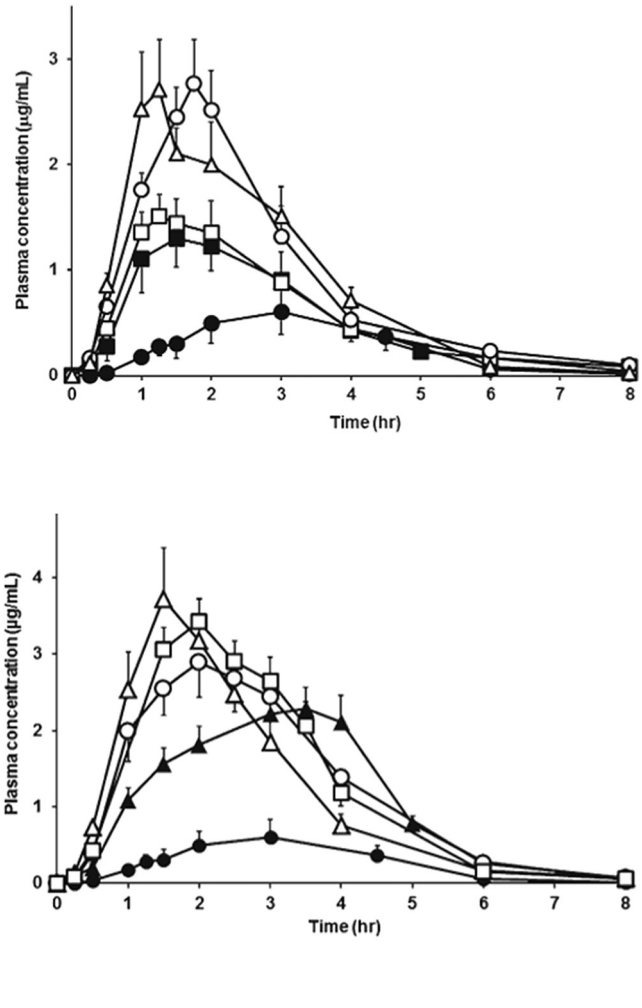

Fig. 1. (A) Plasma concentration - time profiles of N-251 after oral administration of powder (●), PEG 400 (■), MC-SEDDS A (△), MC-SEDDS B (○) and MC-SEDDS C (□) into rats. Indicated values are means (n ≥ 6) ± SD. **(B)** Plasma concentration – time profiles of N-251 after oral administration of powder (●), olive oil (▲), LC-SEDDS D (△), LC-SEDDS E (○) and MC-SEDDS F (□) into rats. Indicated values are means (n ≥ 6) ± SD. Adapted from Imada et al.

hydrogel of glycoproteins designated mucin [39] presents the first hurdle for drug delivery, the design of SEDDS being capable of penetrating the mucus layer is of great importance in order to reach the region of underlying cells. In this context, tight junction, the component of the apical functional complex exhibiting the paracellular space in between the epithelial cells [40], should be addressed in this discussion as surfactants demonstrated an expressed effect on tight junctions of Caco-2 cell monolayer. Ujhelyi et al. examined the cellular effects of polyethylene glycol surfactants including Labrasol as well as different Polysorbates (20, 60, 80) on Caco-2 cell monolayers by TEER (transepithelial electrical resistance) measurement and lucifer yellow permeability as indicators for tight junction integrity as well as immunohistochemistry experiments [41]. Studies revealed that polyethylene glycol esters were able to influence reversible the paracellular permeability underlined by a significant reduction in TEER measurements, significant increase in lucifer yellow permeability and redistribution of junctional proteins. This outcome is in good accordance with a previously conducted study performed by Wahlang et al. investigating excipients towards enhanced permeation of curcumin [42]. Curcumin with Labrasol showed a 5.09-fold increase in P_{app} value (apparent permeability coefficient) compared to curcumin alone and the highest lucifer yellow permeation among the tested excipients. Furthermore, Labrasol caused in significant decrease in TEER values indicating opening up of tight junctions.

Moreover, surfactants are also known to be modulators of P-glycoprotein (P-gp) [43]. P-glycoprotein, an adenosine triphosphate (ATP)-dependent efflux transporter, is localized in the apical surface of epithelial tissues or cells and is the product of the multidrug resistance protein 1 (MDR1) gene [44]. This glycoprotein plays an important role in the intestinal absorption as it efflux compounds back into the intestinal lumen and is therefore responsible for poor intestinal uptake [45]. As several of marketed drugs were found to be substrates of P-glycoprotein such as atorvastatin, cyclosporine, ritonavir and tacrolimus [46], the oral pharmacokinetic parametes of these drugs are highly variable [47]. Hence, for a successful formulation design not only solubilization capacity of the surfactant should be taken into account; the bioactive nature of the surfactants should rather be exploited [9]. As some non-ionic surfactants such as Cremophors, Tweens, Solutol HS-15 and Vitamin E-TPGS (tocopheryl polyethylene glycol succinate) [43,44,48] have been reported to reduce drug efflux pumps activity, the use of these mentioned surfactants might be of great interest in order to increase oral bioavailability. Seljak et al. demonstrated that resveratrol metabolite efflux significantly decreased when the API was formulated in SEDDS [49]. Due to the extensive first-pass intestinal and hepatic metabolism of resveratrol into the metabolites resveratrol sulfate and glucuronides, plasma levels of orally administered resveratrol is below the therapeutic levels. Therefore, SEDDS compromising a mixed lipid phase (castor oil: Capmul MCM 1:1) and a mixed surfactant phase (Cremophor EL:Cremophor RH40 1:1) were developed and the metabolite fluxes during permeability experiments were determined in both directions through Caco-2 cells and rat jejunum. Outcome, shown in Table 7, underlined that in presence of API-loaded SEDDS a significant decrease of the metabolite fluxes in the secretory directions could be achieved indicating that SEDDS components may have inhibited efflux transporters. Therefore, the impact of both Cremophores, Cremophor EL and RH40, on the permeability of the well-known P-gp and multidrug resistance-related proteine (MRP) substrate rhodamine 123 was additionally investigated leading to significantly decreased efflux ratios of both substrates. Nevertheless, results achieved via cell-culture systems have to be viewed with a critical eye due to missing biorelevant factors. In order to get closer to the human intestinal milieu, Dubray et al. evaluated the impact of Gelucire 44/14 and Labrasol ALF on the secretory intestinal transport of rhodamine 123 and digoxin using a Caco-2/HT29-MTX co-culture [50]. Additionally, the effect of biorelevant media simulating the fluid in the upper small intestine in the fasted and fed status were compared with conventional saline buffer. Based

Table 7
Outcome of fluxes of resveratrol (RSV) metabolites through Caco-2 cells and rat jejunum; secretory flux to apical or mucosal side; absorptive flux to basolateral or serosal side. Adapted from Seljak et al.

	Metabolite	Apical side (nmol/h cm^2)	Basolateral side (nmol/h cm^2)	Significance
Caco-2-cells				
RSV solution	Glucuronides	2.4 ± 0.2	1.0 ± 0.2	significant
(100 μM)	Sulfate	3.1 ± 0.1	2.1 ± 0.2	significant
RSV-loaded SMEDDS (100 μM)	Glucuronides	0.6 ± 0.1	0.9 ± 0.2	not significant
	Sulfate	1.1 ± 0.3	7.8 ± 1.6	significant
RSV-loaded SMEDDS (867 μM)	Glucuronides	0.8 ± 0.0	1.4 ± 0.3	significant significant
	Sulfate	0.8 ± 0.2	1.3 ± 1.2	
Rat jejunum				
RSV solution	Glucuronides	1130 ± 12.0	614 ± 20.2	significant
(100 μM)	Sulfate	100.6 ± 14.4	36.6 ± 3.4	significant
RSV-loaded SMEDDS (100 μM)	Glucuronides	48.3 ± 7.6	846 ± 18.5	significant
	Sulfate	0.9 ± 0.2	1.0 ± 0.3	not significant
RSV-loaded SMEDDS (867 μM)	Glucuronides	137 ± 7.8	1490 ± 62.0	significant significant
	Sulfate	43.9 ± 4.1	73.6 ± 14.5	

on different results between the Caco-2 monolayer gold standard and the co-culture cell line, intestinal permeability might be influenced via various parameters. Therefore, further in vitro studies seem to be highly important to investigate the role of P-gp modulators taking the biorelevant parameters into account.

By having a closer look to in vivo studies, the enhanced oral bioavailability by SEDDS underlind the inhibitory effect of these carrier sytems to P-gp. Wang et al. investigated the effect of tocopheryl polyethylene glycol succinate (TPGS) and Cremophor EL based SEDDS on the bioavailability of tacrolimus, a substrate of P-gp, in rats. The absorption of the API from TPGS-SEDDS and Crem-SEDDS resulted in about seven- and eightfold increase in bioavailability in comparison to an API solution [47]. Furthermore, Negi et al. developed SEDDS containing Cremophor EL in order to elevate the systemic availability of irinotecan, a camptothecin derivate and substrate of P-gp [51]. As shown in Fig. 2, the area under the curve (AUC) of the API from the SEDD formulation was fourfold higher in comparison to the API suspension after oral administration to rats. Promising pharmacokinetic paramets including increased maximum concentration (C_{max}) as well as prolonged time to reach maximum concentration (t_{max}) of 6 h could be observed.

Despite of the mentioned advantage of surfactants capable to interact with the biological environment and thus enhance oral absorption, the aspect of cytotoxicity should be pointed out as an important factor within the design of promising SEDDS. Via 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and lactate dehydrogenase (LHD) assay, cytotoxicity of two tenside groups with different chemical structures and HLB values were evaluated [41]: Polyethylene glycol-based tensides including Labrasol and Polysorbates and propylene glycol-based tensides named Capryol 90, Capryol PGMC, Lauroglycol 90 and Lauroglycol FCC. Studies on Caco-2 cells indicated that polyethylene glycols are more toxic surfactants compared to propylene glycols. Polysorbates meaning Tween 20, 60 and 80 are the most toxic compounds, whereas the degree of esterification and lack of sorbit component in case of Labrasol decreased cytotoxicity compared to Polysorbates. Combinations of the mentioned surfactants (0.05% Labrasol and 0.001% Polysorbates 20, 60 and 80) did not affect the cytotoxicity than the surfactants alone. With the exception of Capryol 90, Capryol PGMC, Lauroglycol 90 and Lauroglycol FCC demonstrated no differences in effects on cell viability compared to the untreated control. However, oil-to-surfactant ratio and surfactant ratio also affected cytotoxicity shown by Buyukozturk et al. [52]. Within these studies, various formulations utilizing oils from three different structural classes (long chain triglyceride, medium chain triglyceride, and propylene glycol dicaprylate/dicaprate) and surfactants with HLB values ranging from 10 to 15 (Cremophor EL, Tween 80 and a mixture of Capmul MCM and Labrasol) were combined at three different oil-to-surfactant weight ratios (9:1, 5:1, 1:1). Despite of the oil type, the surfactant mixture of low HLB value (HLB = 10) had a toxic effect on cells at high surfactant concentrations (1:1) suggesting the importance of formulation stability for reducing cytotoxicity.

7. Administration in the oral cavity

Delivery of drugs to the oral cavity has attracted particular attention due to the high vascularisation of the oral mucosa allowing the direct passage of drugs to the systemic circulation [53,54]. Furthermore, the oral mucosa presents a reduced enzymatic activity in comparison to the ones in the GI-tract [55]. Within the oral mucosal cavity, the delivery

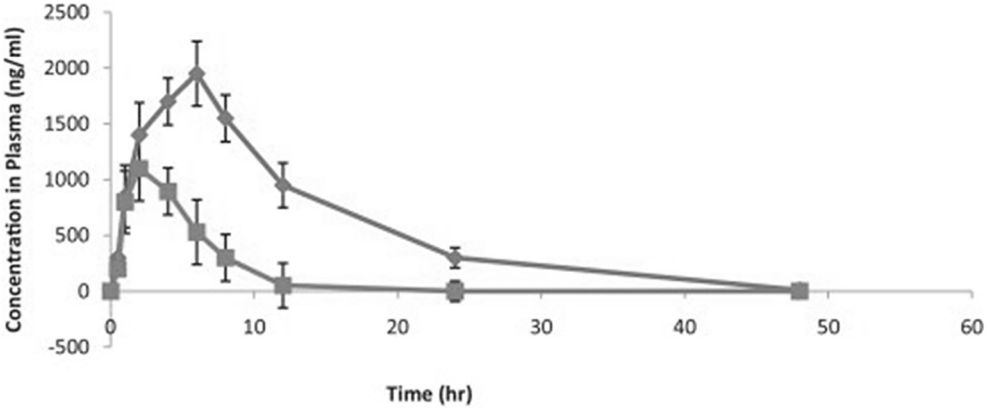

Fig. 2. Plasma concentration–time profiles of irinotecan in rats after oral administration of free irinotecan suspension (■) and SEDDS (♦). Indicated values are means (n=6) ± SD. Adapted from Negi et al.

Table 8
Range of excipients tested regarding odor, oral sensation and taste (++: good tolerable, +: tolerable,-: non-tolerable).

Organic solvents/surfactants	Odor	Oral sensation	Taste	Additional information
Capmul MCM EP	+	−	−	bitter
Capmul PG-8 NF	+	−	−	extreme bitter
Capmul PG-12 EP/NF	+	+	−/+	bitter
Cremophor EL	+	+	+	
Corn Oil	++	++	++	
Labrafac Lipophile WL1349	++	++	++	
Labrafac PG	++	++	++	
Labrafil M 1944 CS	++	++	++	
Labrafil M 2125 CS	++	++	++	
Labrasol ALF	+	+	+	bitter
Maisine CC	++	++	++	
Oleic acid	++	++	++	
Olive oil	++	++	++	
Peceol	++	++	++	
PEG 300	+	−/+	−/+	
PEG 400	+	−/+	−/+	
Plurol Oleique CC 497	++	++	++	
Propylene glycol	+	++	++	
Span 20	++	+/++	+/++	
Span 80	+	−/+	−/+	bitter
Transcutol HP	+/++	+	+/++	
Tween 20	+	+	+	bitter
Tween 60	+	+	+	bitter
Tween 80	+	+	+	bitter

of drugs is classified into two categories meaning local and systemic delivery either via the buccal or sublingual mucosa [53]. The sublingual route is generally employed for the delivery of high permeable drugs in order to achieve an immediate systemic effect and hence often used in the treatment of acute disorders [55]. In contrast, as a prolonged release of drugs is required within the treatment of chronic disorders, the buccal mucosa is the more attractive route for drug administration considering its lower permeability [54,55]. Furthermore, the application of SEDDS might be a promising strategy as it has been demonstrated that lipophilic drugs can be effectively brought into intimate contact with the absorptive membrane when they are formulated into a self-emulsifying system [56]. In this context, the aspect of oral sensation of the SEDDS excipients is highly important within the development process.

8. Oral sensation and taste masking

Patients, in particular children, are extremely sensitive to taste and actively refuse unpalatable dosage forms [57]. As many APIs are bitter by nature, the excipients of the developed SEDDS should not support the unpleasant taste, they should rather provide acceptable sensation during application resulting in high patient compliance. Oils such as olive oil as well as corn oil are pleasant in taste and advisable as lipid excipient to generate SEDDS. However, semi synthetic and synthetic components are the more problematic excipients of the SEDD formulation leading to some extent to bitter sensation. Hence, a range of excipients tested within healthy human volunteers regarding odor, oral sensation and taste is presented in Table 8 [58]. Thereby a small amount of 50 μl of surfactant or solvent was applied into the mouth.

Additionally to excipients demonstrating an almost neutral sensation after administration, taste masking by the addition of flavors is recommended when drugs exhibiting an unpleasant taste should be enclosed in a delivery system. Cirri et al. developed a liquid spray formulation by using SEDDS for the poor water soluble drug xibornol suitable for the local treatment of infection and inflammation of the throat and dental care [59]. The final SEDDS containing Labrafil M1944, Transcutol, Labrafac PG and a hydrophilic co-solvent (propylene glycol or PEG 200) consist additionally of sodium saccharinate, ammonium glycyrrhizinate and mint essence in order to allow tolerable organoleptic properties. Possible irritation, taste and compliance were tested within 10 healthy human volunteers. Based on the sweet smell and taste as well as the lack of any collateral effects, SEDDS containing xibornol were well accepted and therefore suitable as liquid spray. Furthermore, Monteagudo et al. optimized microemulsions and SEDDS containing phenobarbital regarding taste by using strawberry along with banana and tutti-frutti flavors plus mint flavors. The taste masking evaluation was performed by using an electronic tongue, an analytical system providing a fast, objective and simple assessment exhibiting correlations to human taste panel evaluation [60]. The same analytical method was used to evaluate the taste masking efficiency of SEDDS loaded orodispersible tablets for cyclosporine. The SEDD formulation alone containing 31.3% of orange oil, 60.2% of Emulphor EL-620 and 8.5% Capmul MCM C8 was also tested and compared with cyclosporine solution. Outcome revealed efficiency of SEDDS and SEDDS loaded tablets to supress the unpalatable taste of cyclosporine [61]. Moreover, Hasan et al. incorporated aqueous flavors within oil vehicle as an approach for taste masking of bitter drugs. Self-microemulsifying system comprimising of the oil component Crodamol GTCC, co-surfactant Glycerox 767 HC and surfactant Croduret 40 in the ratios of (6/5/40) as well as (10/40/50) have demonstrated capacity to solubilize strawberry flavor, sucrose, citric acid and the bitter-taste drug paracetamol [62].

9. Conclusion

Taking several advantages of SEDDS into account including protective effect towards a presystemic metabolism, sufficient permeation through the mucus gel layer, incorporation of hydrophilic as well as hydrophobic active compounds and simple manufacturing process, SEDDS are currently one of the most promising carrier sytems for oral administration and are likely the basis of different products in the future. Various SEDD formulations have been described in literatures and intensivly investigated regarding emulsification time, droplet size and stability as well as drug payload. However, from the industrial point of view, the aspect of regulatory status is of great importance and hence, excipients should be selected according to the listed solvents, surfactants and co-surfactants provided by the IIG database of the FDA. Besides, emphasis can be placed on excipients which are able to influence for instance P-glycoprotein and lymphatic transport to increase the oral bioavailability of the drug. Although the delivery of SEDDS to the oral cavity is a quite new field, the interest in the development of such carrier systems will be likely increasing within the next years considering the advantages of this route of application. Therefore, first impulses including oral sensation important for the selection of excipients suitable for drug delivery to the oral cavity are given within this review.

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References

[1] A. Bernkop-Schnürch, Nanocarrier systems for oral drug delivery: do we really need them? Eur. J. Pharm. Sci. 49 (2) (2013) 272–277.
[2] S.I. Jethara, A.D. Patel, M.R. Patel, Recent patents survey on self emulsifying drug delivery system, Recent Pat. Drug Deliv. Formul. 8 (3) (2014) 233–243.
[3] G. Leonaviciute, A. Bernkop-Schnürch, Self-emulsifying drug delivery systems in oral (poly)peptide drug delivery, Expert Opin Drug Deliv. 12 (11) (2015) 1703–1716.
[4] O. Zupancic, J.A. Griebetainger, J. Rohrer, et al., Development, in vitro and in vivo evaluation of a self-emulsifying drug delivery system (SEDDS) for oral enoxaparin administration, Eur. J. Pharm. Biopharm. 109 (2016) 113–121.
[5] G. Leonaviciute, O. Zupancic, F. Prüfert, J. Rohrer, A. Bernkop-Schnürch, Impact of lipases on the protective effect of SEDDS for incorporated peptide drugs towards intestinal peptidases, Int. J. Pharm. 508 (1–2) (2016) 102–108.
[6] G. Hetenyi, J. Griesser, M. Moser, F. Demarne, V. Jannin, A. Bernkop-Schnürch, Comparison of the protective effect of self-emulsifying peptide drug delivery systems towards intestinal proteases and glutathione, Int. J. Pharm. 523 (1) (2017) 357–365.

[7] H. Friedl, S. Dünnhaupt, F. Hintzen, et al., Development and evaluation of a novel mucus diffusion test system approved by self-nanoemulsifying drug delivery systems, J. Pharm. Sci. 102 (12) (2013) 4406–4413.
[8] J. Griesser, G. Hetenyi, H. Kadas, F. Demarne, V. Jannin, A. Bernkop-Schnürch, Self-emulsifying peptide drug delivery systems: how to make them highly mucus permeating, Int. J. Pharm. 538 (1–2) (2018) 159–166.
[9] M.A. Rahman, A. Hussain, M.S. Hussain, M.A. Mirza, Z. Iqbal, Role of excipients in successful development of self-emulsifying/microemulsifying drug delivery system (SEDDS/SMEDDS), Drug Dev. Ind. Pharm. 39 (1) (2013) 1–19.
[10] S. Gupta, R. Kesarla, A. Omri, Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems, ISRN Pharm. 2013 (2013), 848043. .
[11] J. Khan, T. Rades, B. Boyd, The precipitation behavior of poorly water-soluble drugs with an emphasis on the digestion of lipid based formulations, Pharm. Res. 33 (3) (2016) 548–562.
[12] K. Kohli, S. Chopra, D. Dhar, S. Arora, R.K. Khar, Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability, Drug Discov. Today 15 (21−22) (2010) 958–965.
[13] J. Griesser, G. Hetenyi, M. Moser, F. Demarne, V. Jannin, A. Bernkop-Schnurch, Hydrophobic ion pairing: key to highly payloaded self-emulsifying peptide drug delivery systems, Int. J. Pharm. 520 (1–2) (2017) 267–274.
[14] A.A. Kaspar, J.M. Reichert, Future directions for peptide therapeutics development, Drug Discov. Today 18 (17–18) (2013) 807–817.
[15] D.J. Craik, D.P. Fairlie, S. Liras, D. Price, The future of peptide-based drugs, Chem. Biol. Drug Des. 81 (1) (2013) 136–147.
[16] F. Hintzen, G. Perera, S. Hauptstein, C. Müller, F. Laffleur, A. Bernkop-Schnürch, In vivo evaluation of an oral self-microemulsifying drug delivery system (SMEDDS) for leuprorelin, Int. J. Pharm. 472 (1–2) (2014) 20–26.
[17] A.C. Carmen Alvarez-Lorenzo, Smart materials for drug delivery, The Royal Soc. Chem 2 (2013) 4 chapter 2.
[18] QUALIFICATION OF EXCIPIENTS FOR USE IN PHARMACEUTICALS, The International Pharmaceutical Excipients Council, 2008.
[19] Y. Ito, T. Kusawake, M. Ishida, R. Tawa, N. Shibata, K. Takada, Oral solid gentamicin preparation using emulsifier and adsorbent, J. Control. Release 105 (1–2) (2005) 23–31.
[20] T. Gershanik, S. Benita, Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs, Eur. J. Pharm. Biopharm. 50 (1) (2000) 179–188.
[21] D.J. Hauss, S.E. Fogal, J.V. Ficorilli, et al., Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor, J. Pharm. Sci. 87 (2) (1998) 164–169.
[22] D. Prasad, H. Chauhan, E. Atef, Studying the effect of lipid chain length on the precipitation of a poorly water soluble drug from self-emulsifying drug delivery system on dispersion into aqueous medium, J. Pharm. Pharmacol. 65 (8) (2013) 1134–1144.
[23] J. Wadhwa, A. Nair, R. Kumria, Emulsion forming drug delivery system for lipophilic drugs, Acta Pol. Pharm. 69 (2) (2012) 179–191.
[24] B. Chatterjee, S. Hamed Almurisi, A. Ahmed Mahdi Dukhan, U.K. Mandal, P. Sengupta, Controversies with self-emulsifying drug delivery system from pharmacokinetic point of view, Drug Delivery. 23 (9) (2016) 3639–3652.
[25] P.P. Constantinides, Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects, Pharm. Res. 12 (11) (1995) 1561–1572.
[26] M.D. Limbani, L.D. Patel, Studies on drug solubilization and role of lipid vehicle in pseudo ternary phase diagram in formulation development of SNEDDS containing poorly water soluble drug, Int. J. Pharm. Sci. Rev. Res 40 (2) (2016) Article No. 43.
[27] I. Cherniakov, A.J. Domb, A. Hoffman, Self-nano-emulsifying drug delivery systems: an update of the biopharmaceutical aspects, Expert Opin. Drug Deliv. 12 (7) (2015) 1121–1133.
[28] J.Y. Kiyasu, B. Bloom, I.L. Chaikoff, The portal transport of absorbed fatty acids, J. Biol. Chem. 199 (1) (1952) 415–419.
[29] C. Imada, T. Takahashi, M. Kuramoto, et al., Improvement of oral bioavailability of N-251, a novel antimalarial drug, by increasing lymphatic transport with long-chain fatty acid-based self-nanoemulsifying drug delivery system, Pharm. Res. 32 (8) (2015) 2595–2608.
[30] W.N.A. Charman, V.J. Stella, Estimating the maximal potential for intestinal lymphatic transport of lipophilic drug molecules, Int. J. Pharm. 34 (1) (1986) 175–178.
[31] S.M. Caliph, W.N. Charman, C.J. Porter, Effect of short-, medium-, and long-chain fatty acid-based vehicles on the absolute oral bioavailability and intestinal lymphatic transport of halofantrine and assessment of mass balance in lymph-cannulated and non-cannulated rats, J. Pharm. Sci. 89 (8) (2000) 1073–1084.
[32] S.-M. Khoo, D.M. Shackleford, C.J.H. Porter, G.A. Edwards, W.N. Charman, Intestinal lymphatic transport of halofantrine occurs after oral administration of a unit-dose lipid-based formulation to fasted dogs, Pharm. Res. 20 (9) (2003) 1460–1465.
[33] F. Carriere, Impact of gastrointestinal lipolysis on oral lipid-based formulations and bioavailability of lipophilic drugs, Biochimie 125 (2016) 297–305.
[34] S. Fernandez, S. Chevrier, N. Ritter, et al., In vitro gastrointestinal lipolysis of four formulations of piroxicam and cinnarizine with the self emulsifying excipients labrasol and Gelucire 44/14, Pharm. Res. 26 (8) (2009) 1901–1910.
[35] S. Fernandez, V. Jannin, S. Chevrier, Y. Chavant, F. Demarne, F. Carrière, In vitro digestion of the self-emulsifying lipid excipient Labrasol® by gastrointestinal lipases and influence of its colloidal structure on lipolysis rate, Pharm. Res. 30 (12) (2013) 3077–3087.
[36] I. Matsaridou, P. Barmpalexis, A. Salis, I. Nikolakakis, The influence of surfactant HLB and oil/surfactant ratio on the formation and properties of self-emulsifying pellets and microemulsion reconstitution, AAPS PharmSciTech 13 (4) (2012) 1319–1330.
[37] S. Kollipara, R.K. Gandhi, Pharmacokinetic aspects and in vitro-in vivo correlation potential for lipid-based formulations, Acta Pharm. Sin. B 4 (5) (2014) 333–349.
[38] Cuiné JF, McEvoy CL, Charman WN, et al. Evaluation of the impact of surfactant digestion on the bioavailability of danazol after oral administration of lipidic self-emulsifying formulations to dogs. J. Pharm. Sci. 97(2):995–1012.
[39] H.H. Sigurdsson, J. Kirch, C.-M. Lehr, Mucus as a barrier to lipophilic drugs, Int. J. Pharm. 453 (1) (2013) 56–64.
[40] F. Laffleur, A. Bernkop-Schnürch, Strategies for improving mucosal drug delivery, Nanomedicine (Lond). 8 (12) (2013) 2061–2075.
[41] Z. Ujhelyi, F. Fenyvesi, J. Váradi, et al., Evaluation of cytotoxicity of surfactants used in self-micro emulsifying drug delivery systems and their effects on paracellular transport in Caco-2 cell monolayer, Eur. J. Pharm. Sci. 47 (3) (2012) 564–573.
[42] B. Wahlang, D. Kabra, Y.B. Pawar, K. Tikoo, A.K. Bansal, Contribution of formulation and excipients towards enhanced permeation of curcumin, Arzneimittelforschung 62 (2) (2012) 88–93.
[43] D.M. Woodcock, M.E. Linsenmeyer, G. Chojnowski, et al., Reversal of multidrug resistance by surfactants, Br. J. Cancer 66 (1) (1992) 62–68.
[44] H. Zhang, M. Yao, R.A. Morrison, S. Chong, Commonly used surfactant, Tween 80, improves absorption of P-glycoprotein substrate, digoxin, in rats, Arch. Pharm. Res. 26 (9) (2003) 768–772.
[45] J.B. da Silva Junior, T.M. Dezani, A.B. Dezani, C.H. dos Reis Serra, Evaluating potential P-gp substrates: main aspects to choose the adequate permeability model for assessing gastrointestinal drug absorption, Mini Rev Med Chem. 15 (10) (2015) 858–871.
[46] M.-L. Chen, Lipid excipients and delivery systems for pharmaceutical development: a regulatory perspective, Adv. Drug Deliv. Rev. 60 (6) (2008) 768–777.
[47] Y. Wang, J. Sun, T. Zhang, H. Liu, F. He, Z. He, Enhanced oral bioavailability of tacrolimus in rats by self-microemulsifying drug delivery systems, Drug Dev. Ind. Pharm. 37 (10) (2011) 1225–1230.
[48] K. Katneni, S.A. Charman, C.J. Porter, Impact of cremophor-EL and polysorbate-80 on digoxin permeability across rat jejunum: delineation of thermodynamic and transporter related events using the reciprocal permeability approach, J. Pharm. Sci. 96 (2) (2007) 280–293.
[49] K.B. Seljak, K. Berginc, J. Trontelj, A. Zvonar, A. Kristl, M. Gasperlin, A self-microemulsifying drug delivery system to overcome intestinal resveratrol toxicity and presystemic metabolism, J. Pharm. Sci. 103 (11) (2014) 3491–3500.
[50] O. Dubray, V. Jannin, F. Demarne, Y. Pellequer, A. Lamprecht, A. Béduneau, In-vitro investigation regarding the effects of Gelucire® 44/14 and Labrasol® ALF on the secretory intestinal of transport of P-gp substrates, Int. J. Pharm. 515 (1–2) (2016) 293–299.
[51] L.M. Negi, M. Tariq, S. Talegaonkar, Nano scale self-emulsifying oil based carrier system for improved oral bioavailability of camptothecin derivative by P-Glycoprotein modulation, Colloids Surf B Biointerfaces. 111 (2013) 346–353.
[52] F. Buyukozturk, J.C. Benneyan, R.L. Carrier, Impact of emulsion-based drug delivery systems on intestinal permeability and drug release kinetics, J. Control. Release 142 (1) (2010) 22–30.
[53] V.F. Patel, F. Liu, M.B. Brown, Advances in oral transmucosal drug delivery, J. Control. Release 153 (2) (2011) 106–116.
[54] A.C. Silva, D. Santos, D. Ferreira, C.M. Lopes, Lipid-based nanocarriers as an alternative for oral delivery of poorly water- soluble drugs: peroral and mucosal routes, Curr. Med. Chem. 19 (26) (2012) 4495–4510.
[55] S. Rossi, G. Sandri, C.M. Caramella, Buccal drug delivery: a challenge already won? Drug Discov. Today Technol. 2 (1) (2005) 59–65.
[56] B. Whittle, G. Guy, Liquid Spray Formulations for Buccal Delivery of Cannabinoids, Google Patents, 2013.
[57] M. Maniruzzaman, J.S. Boateng, B.Z. Chowdhry, M.J. Snowden, D. Douroumis, A review on the taste masking of bitter APIs: hot-melt extrusion (HME) evaluation, Drug Dev. Ind. Pharm. 40 (2) (2014) 145–156.
[58] Internal report No. 25071412, ThioMatrix Forschungs- und Beratungs GmbH, 2017.
[59] M. Cirri, P. Mura, P.C. Mora, Liquid spray formulations of xibornol by using self-microemulsifying drug delivery systems, Int. J. Pharm. 340 (1–2) (2007) 84–91.
[60] E. Monteagudo, M. Langenheim, C. Salerno, F. Buontempo, C. Bregni, A. Carlucci, Pharmaceutical optimization of lipid-based dosage forms for the improvement of taste-masking, chemical stability and solubilizing capacity of phenobarbital, Drug Dev. Ind. Pharm. 40 (6) (2014) 783–792.
[61] A.S. Zidan, B.M. Aljaeid, M. Mokhtar, T.M. Shehata, Taste-masked orodispersible tablets of cyclosporine self-nanoemulsion lyophilized with dry silica, Pharm. Dev. Technol. 20 (6) (2015) 652–661.
[62] N.M. Hasan, Flavored self microemulsifying lipid formulations for masking the organoleptic taste of pharmaceutical actives, J. Appl. Pharm. Sci 5 (11) (2015) 127–134.