Review Article

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Self-Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability

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Oral route is prefered for drug administration, however, more than 40% of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Recently, much attention has been focused on self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly aqueous soluble drugs. SEDDS possess potential to improve oral bioavailability of poorly water soluble drugs. Following their oral administration, these systems rapidly disperse in gastrointestinal fluids, yielding micro- or nano-emulsions containing the solubilized drug. Micro/nano-emulsifed drug can easily be absorbed through lymphatic pathways, bypassing the hepatic first-pass effect, owing to their miniscule globule size. This article gives an overview of SEDDS with emphasis on different types of self-emulsifying formulations, their formulation, characterization, biopharmaceutical aspect, advantages and recent developments. Finally, the existing challenges and future aspects are pointed out.

Introduction

There has been a consistent increase in number of new chemical entities (NCEs) which possess poor aqueous solubility as a result of modern drug discovery techniques, and oral delivery of such drugs is frequently associated with low bioavailability[1, 2]. Various formulation strategies have been exploited to overcome these issues, such as salt formation, particle size reduction, use of lipidic/ surfactants systems, complexation with cyclodextrins and solid dispersions[3]. In recent years, much attention has turned to lipid based formulations to improve oral bioavailability of poorly soluble drug candidates[4]. The oral bioavailability augmentation is achieved by enhanced dissolution and solubilization of the administered drug by stimulation of biliary and pancreatic secretions, prolongation of gastric residence time, stimulation of lymphatic transport, and modulation of enterocytes-based drug transport and disposition[5].

Lipid based formulations offer a variety of options like solutions, suspensions, solid dispersions and self-emulsifying drug delivery systems (SEDDS)[2]. SEDDS have attracted considerable interest after commercial success of immunosuppressive agent cyclosporine A (Neoral®)[6] and for the two HIV protease inhibitors ritonavir (Norvir®) and saquinavir (Fortovase®)[7]. Self-emulsifying formulations comprise isotropic mixtures of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-solvent(s) which spontaneously emulsify when exposed to the fluids of the gastrointestinal tract (GIT) to form oil-in-water emulsions or micro-emulsions[4, 8-10]. 'SEDDS' is a broad term, producing crude, milky emulsions upon dispersion in water with droplet size ranging from a few nanometers to several microns. Self-microemulsifying drug delivery systems (SMEDDS) are clear, transparent micro-emulsions with droplet size ranging between 100 and 250 nm. Self-nanoemulsifying drug delivery systems (SNEDDS) are recent member to join SEDDS family. They form nano-emulsions upon dispersion in water with globule size range less than 100 nm[11]. SEDDS can be dispensed in a soft gelatin or hard gelatin or HPMC capsule.

Candidate compound selection

Lipid based formulations offer a potential platform for improving oral bioavailability of drugs especially those belonging to Biopharmaceutical Classification System (BCS) class II and class IV. A primary indication of the potential utility of lipid based formulation can be obtained by assessing the drug lipophilicity (LogP) and its solubility in pharmaceutically-acceptable lipid excipients, which should be sufficient to allow the entire dose of the drug to be administered in a single dosage unit. Another indicator of the potential for success of a lipid based formulation is the observance of a strong positive food effect when the drug is administered with a fatty meal as opposed to dosing in the fasted[12]. For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, SEDDS can offer an improvement in rate and extent of absorption resulting in reproducible blood time profiles. The systems can help in overcoming the below-mentioned problems of all the categories of BCS class drugs, as shown in Table 1. SEDDS usually provide advantage of increased drug loading capacity when compared with lipid solutions as the solubility of poorly water soluble drugs with intermediate partition

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Table 1 Application of SEDDS in relation to BCS classification[13]

BCS class	Aqueous solubility	Membrane permeability	Hurdles overcome by SEDDS
I	High	High	Enzymatic degradation, Gut wall efflux
II	Low	High	Solubilization, Bioavailability
III	High	Low	Enzymatic degradation, Gut wall efflux, Bioavailability
IV	Low	Low	Solubilization, Enzymatic degradation, Gut wall efflux, Bioavailability

coefficients (2<logP<4) are typically low in natural lipids and much greater in amphiphilic surfactants, co-surfactants and co-solvents[2].

LogP is the prime criterion for design of lipidic systems. High LogP (greater than 4) values are desirous for lipidic systems. Next physicochemical criteria that play an important role are melting point and dose. Low melting point and low dose are desirable for development of lipidic systems.

Lipid formulation classification system

Due to large number of possible combinations that may be used to assemble lipid-based formulations especially self-emulsifying systems, a classification system (Lipid Formulation Classification System – LFCS) was introduced by Pouton in 2000 and was later updated in 2006[2, 4]. This system briefly classifies lipid based formulations into four types as per their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation. The main role of lipid formulation classification system is to facilitate interpretation of *in vivo* studies more readily and identification of most suitable formulation for specific drugs with reference to their physicochemical properties[14]. Table 2 shows typical composition of various types of lipid formulations and properties of lipid based formulations.

Type I formulations comprise formulations solubilized drug in triglycerides and/or mixed glycerides or in an oil-in-water emulsion stabilized by low concentration of emulsifiers. These systems show poor initial aqueous dispersion and require digestion by pancreatic lipase/co-lipase in the GIT to produce more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase[15]. Type 1 formulations therefore are a good option for drugs having sufficient solubility in oils. Valproic acid has been formulated in soft gelatin capsule containing corn oil as lipidic component.

Type II formulations are referred to as SEDDS. SEDDS are isotropic mixtures of lipids and lipophilic surfactants (HLB<12), co-surfactant and the drug. They form oil-in-water emulsions under mild agitation following dilution with aqueous phases. Self-emulsification is generally obtained at surfactants contents above 25% (w/w). But at higher surfactants concentration (~ greater than 50-60% (w/w)), the progress of emulsification may be hindered by the formation of viscous crystalline gels at the oil/water interface[15]. No Type II formulation has been marketed till date.

Type III formulations are commonly referred as self-microemulsifying drug delivery systems (SMEDDS). They comprise of oils, hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations are further divided into Type IIIA and Type IIIB formulations. Later include higher amount of hydrophilic surfactants and co-solvents and lesser lipid content, as compared to Type IIIA. Type IIIB formulations pose greater risk of drug precipitation on dispersions given their high content of hydrophilic surfactants and co-solvents. The distinction between SEDDS (Type II) and SMEDDS (Type III) formulations is commonly made on the globule size and optical clarity of the resultant dispersion. SEDDS formulations form opaque dispersions with globule sizes > 100nm whereas SMEDDS disperse to give optically clear or slightly opalescent dispersions with globule sizes < 100nm[15]. An example of marketed Type III formulation is Neoral® (Novartis) cyclosporine formulation. This formulation comprises of corn oil glycerides, cremophor RH40, glycerol, propylene glycol and ethanol[16].

Type IV category was added to the LFCS by Pouton in 2006[4]. Type IV formulations are devoid of oils and represent the most hydrophilic formulations. They produce fine dispersions when introduced to aqueous media. A Type IV formulation is useful for drugs which are hydrophobic but not lipophilic[14]. An example of a commercial Type IV formulation is Agenerase® (GlaxoSmithKline), a capsule formulation of the HIV protease inhibitor amprenavir containing tocopherol polyethylene glycosuccinate (TPGS) as a surfactant and PEG 400 and propylene glycol as co-solvents.

Excipients classes

Lipid based excipients

The lipid based excipients encompass vegetable oils and vegetable oil derivatives.

Vegetable oils

Vegetable oils contain mixtures of triglycerides (90 to 95% w/w) but also free fatty acids, phospholipids, and non saponifiable products such as pigments and sterols or fat soluble vitamins like tocopherols and carotenoids that act as natural antioxidants. Triglycerides are classified as short (<5 carbons), medium (6-12 carbons) and long chains (>12 carbons). Some examples of vegetable oils include

Table 2 LFCS showing typical compositions and properties of lipid based formulations[4]

Increasing hydrophillic content (>> >> >> >>)					
Typical Composition	Type I	Type II	Type IIIA	Type IIIB	Type IV
Triglyceride/mised triglycerides (% w/w)	100	40-80	40-80	<20	--
Surfactants (% w/w)	--	20-20 (HLB<12)	20-40 (HLB>12)	20-50 (HLB>12)	0-20 (HLB<12) 30-80 (HLB>12)
Hydrophilic cosolvents (% w/w)	--	--	0-40	20-50	40-60
Particle size (nm)	Coarse	100-250	100-250	50-100	<50
Significance of aq. dilution	Limited importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes	High risk of precipitation
Significance of digestibility	Crucial requirement	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required

castor oil, coconut oil, corn oil, cotton seed oil, grape seed oil, olive oil and sesame oil[5].

Vegetable oil derivatives

The main vegetable oil derivatives are hydrogenated vegetable oils, partial glycerides, polyoxylglycerides, ethoxylated glycerides and esters of edible fatty acids and various alcohols. Hydrogenated vegetable oils are obtained by catalytic hydrogenation of the unsaturated bonds with nickel. Examples include hydrogenated castor oil (Lubritab®, Akofine®), hydrogenated castor oil (Cutina® HM) or hydrogenated soybean oil (Hydrocote®)[5].

Partial glycerides are products of glycerolysis. The physical aspect, melt characteristics and the HLB of partial glycerides vary depending on the nature of the fatty acid(s) present and the degree of esterification with glycerol to yield mono- and diglycerides[17]. Commonly known excipients that fall under this category are glyceryl monocaprylocaprate (Capmul® MCM), glyceryl monosterate (Geleol™, Imwitor®191) and glyceryl monoleate (Peceol™).

Polyoxylglycerides (also named macrogolglycerides by EP) are a well established class of pharmaceutical excipients for enhancing solubility and bioavailability[18, 19]. They are obtained by polyglycolysis of vegetable oils with polyoxyethylene glycols (PEG) of certain molecular weight (varying from 200 to 2000 g/mol) under heating and in presence of an alkaline catalyst. Each polyoxlglycerides is composed of a defined mixture of mono-, di-, and triglycerides and mono- and diesters of PEG. They may be composed of unsaturated long chain fatty acids (LCFA) like polyoxylglycerides (Labrafil® M1944CS) and linoleyl polyoxylglycerides (Labrafil® M2125CS), saturated medium chain fatty acid esters like caprylocaproyl polyoxylglycerides (Labrasol®), lauroyl polyoxylglycerides (Gelucire® 44/14) or saturated long chain fatty acids like steroyl polyoxylglycerides (Gelucire® 50/13).

Ethoxylated lipids derived from castor oil that is rich in ricinoleic acid. They are widely used as surfactants to enhance bioavailability of poorly soluble drugs. The products representing this category are ethoxylated castor oil (Cremophor® EL) and ethoxylated hydrogenated castor oil (Cremophor® RH40 and Cremophor® RH60).

Polyalcohol esters of edible fatty acids are the largest family of vegetable oil derivatives. The alcohols may be polyglycerol (polyglyceryl oleate: Plurol™ Oleique CC497), propylene glycol (propylene glycol monocaprylate: Capryol™ 90, propylene glycol monolaurate: Lauroglycol™ 90), polyoxyethylene glycols (PEG-8 stearate: Mirj® 45, PEG-40 stearate: Mirj® 52, PEG-15 hydroxystearate: Solutol® HS15), sorbitan or monoanhydrosorbitol (sorbitan monooleate: Span® 80, polyoxyethylene-20 sorbitan monoleate or polysorbate 80: Tween® 80) or sucrose (sucrose monopalmitate: Surfhope® D-1616). They may be used as solubilizers, or as bioavailability enhancers[15].

Co-solvents

The function of co-solvents in lipid based formulations especially in SEDDS is to facilitate the dispersion process and in faster dispersion rates[10]. The co-solvents used include polyethylene glycols, ethanol, propylene glycol, and glycerol. It is important to realize that smaller quantity of co-solvents should be used in SMEDDS as larger quantities can cause drug precipitation on dispersion into aqueous phase. Table 4 lists the typical examples of excipients used in SEDDS.

Formulation and Characterization of SEDDS

Formulation of SEDDS

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble cosolvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions. The following steps should be considered in the formulation of SEDDS:

Table 3 Selected commercially available lipid based formulations with their components[11]

Generic name	Brand name/company	Dosage form	Lipidic components
Amprenavir	Agenerase/GlaxoSmithKline	SG capsule	d-alpha TPGS
Bexarotene	Targretin/Ligand	SG capsule	Polysorbate 80
Calcitriol	Rocaltrol/Roche	SG capsule,solution	Fractionated medium-chain TG of coconut oil, and palm seed oil
Carvedilol phosphate	Coreg CR/ GlaxoSmithKline	CR HG capsule	Hydrogenated castor oil, hydrogenated vegetable oil
Ciprofloxacin	Cipro/Bayer	Microcapsules for suspensions	Medium-chain TG
Cyclosporin A	Neoral/Novartis	SG capsules, oral suspensions	dl-α-tocopherol, corn oil-mono-di-TG, Cremophor RH 40
Cyclosporin A	Sandimmune/Novartis suspensions	SG capsules, oral	Labrafil M-2125CS, Labrafil M-1944CS, olive oil
Dronabiol	Marinol/Roxane and Unimed	SG capsule	Sesame oil
Dutasteride	Avodart/GSK	SG capsule	Mixture of mono- and Diglycerides of caprylic/capric acid
Fenofibrate	Lipofen/Kowa Pharmaceuticals America, Inc.	HG capsule	Gelucire 44/14
Isotretinoin	Accutane/Roche	SG capsule	Bees wax, hydrogenated oil flaxes, hydrogenated vegetable oils, soyabean oil
Lopinavir and Ritonavir	Kaletra/Abbott	Tablet, SG capsule	Span 20
Mesalamine	Pentasa/Shire US inc.	CR-capsules	Acetylated monoglyceride, castor oil
Omega-3-acid esters	Lovaza/GSK	HG capsule	α-tocopherol
Paricalcitol	Zemplar/Abbott Labroratories	SG capsule	Fractionated medium-chain triglycerides of coconut oil or palm kernel oil
Saquinavir	Fortovase/Roche	SG capsule	Medium-chain mono- and diglycerides, dl-α-tocopherol
Sirolimus	Rapamune/Wyeth-Ayerst	Oral solution	Phosal 50, PG, polysorbate 80
Tipranavir	Aptivus/Boehringer/Ingelheim	SG capsule	Cremophor EL, Medium-chain mono- and diglycerides
Tolterodine tartrate	Detrol LA/Pharmacia	ER HG capsule	Medium-chain triglycerides, Oleic acid
Tretinoin	Vesanoid/Roche	SG capsule	Beex wax, hydrogenated soybean oil flaxes, hydrogenated vegetable oils, soyabean oil
Valproic acid	Depakene/Abbott	SG capsule	Corn oil

SG, Soft Gelatin; HG, Hard Gelatin; CR, Controlled Release; TG, Triglyceride; ER, Extended Release; PG, Propylene Glycol

- The solubility of the drug in different oil, surfactants and cosolvents.
- The selection of oil, surfactant and cosolvent based on the solubility of the drug and the preparation of the phase diagram
- The preparation of SEDDS formulation by dissolving the drug in a mixture of oil, surfactant and cosolvent

Drug loading into SEDDS is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil-surfactant ratio. Thus, the design of an optimal SEDDS requires solubility screening and phase-diagram studies.

Characterization of SEDDS

Ternary Phase Diagram

Pseudo-ternary phase diagrams are often constructed for development of SEDDS, that help in determining the optimum concentrations of different excipitents necessary to obtain homogenous pre-concentates, self-emulsification ability and drug loading. Each corner of pseudo-ternary

Table 4 Examples of typical excipients used in SEDDS/SMEDDS[20]

Trade name	Chemical name	HLB	Regulatory status
Lipids			
Vegetable oil	Long-chain TAG	-	Oral product, GRAS, FDA IIG
Miglyol 812	Medium-chain TAG caprylic/capric TAG	-	Oral product, GRAS, FDA IIG
Tricaprylin	Medium-chain TAG	-	-
Labrafac CC	Caprylic/capric TG	-	-
Ethyl oleate	Ethyl ester of C18:1 (ω9) FA	-	FDA IIG
Captex 355	Glycerol caprylate caprate	-	GRAS, FDA IIG
Isopropyl myristate	FA ester	-	FDA IIG
Labrafac PG	PG dicaprylocaprate	-	USFA, JSFA, EP
Peceol	Glyceryl mono-oleate	3.3	GRAS, E471, EP, USP-NF, FDA IIG
Maisine 35-1	Glyceryl mono-linoleate	4	Oral product, GRAS, EP, USP-NF, E471
Imwitor 988	Caprylic/capric glycerides	3.8	USP, Ph.Eur
Akoline MCM	Caprylic/capric glycerides	5-6	-
Surfactants HLB < 12			
Tween 85	Polyoxyethylene (20) sorbitan trioleate	11	UK
Labrafil M1944CS	Oleoyl macrogolglycerides	4	EP, FDA IIG, USP NF
Labrafil M2125CS	Linoleoyl macrogolglycerides	4	EP, FDA IIG, USP NF
Lauroglycol 90	PG monolaurate	5	USFA, FCC, EFA, USP-NF
Surfactants HLB > 12			
Vitamin E TPGS	D-alpha-tocopheryl PEG 1000 succinate	13	Oral product
Cremophor EL	Polyoxyl 35 castor oil	12-14	Oral product, USP-NF, FDA IIG
Cremophor RH 40	Polyoxyl 40 hydrogenated castor oil	14-16	Oral product, USP-NF, FDA IIG
Gelucire 44/14	Lauroyl macrogolglycerides	14	EP, USP-NF, FDA IIG
Labrasol	Caprylocaproyl macrogol glycerides	14	EP, USP-NF, FDA IIG
Polysorbate 80/ Tween 80	Polyoxyethylene (20) sorbitan monooleate	15	Oral Product, GRAS, EP, USP-NF, FDA IIG
Polysorbate 20/ Tween 20	Polyoxyethylene (20) sorbitan monolaurate	16.7	Oral Product, GRAS, EP, USP-NF, FDA IIG
Co-solvents			
Ethanol	-	-	Oral product, EP, USP-NF
PEG	PEG 300 and PEG 400	-	Oral product, EP, USP-NF
Transcutol P	Diethylene glycol monoethyl ether	-	EP, FDA IIG

PG, Polyethylene Glycol; PG, Propylene Glycol; TAG, Triacylglyceride; MAG, 2-Monoacylglyceride; DAG, Diacylglyceride; FA, Fatty Acid; GRAS, Generally Recognized As Safe; E471, European Food Additive; EP, European Pharmacopoeia; USP-NF, United States Pharmacopoeia-National Formulary; FDA IIG, FDA Inactive Ingredient Guide; Ph.Eur., Pharmacopoeia Europea; USFA, United States Food Administration; FCC, Food Chemicals Codex; JSFA, Japanese Standards for Food Additives; UK, United Kingdom

diagram represents 100% of a particular component and when more than three components are used, closely related ones are grouped together as one component and treated as such in the diagram. They are generally generated by water titration method. In this method, water is incorporated to the SMEDDS pre-concentrate in drop wise manner, with gentle stirring to allow equilibration. Addition of water leads to formation of a complex systems ranging from gels to systems containing lamellar, hexagonal or cubic phases to microemulsions. The mixture is visually examined for transparency. The points from clear to turbid and turbid to clear are designated as emulsion and microemulsion[21].

Droplet size

Droplet size is important factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. It is measured by dynamic light scattering techniques. This employs the fluctuation in scattered light intensity to measure the velocity of the Brownian diffusion and consequently the dispersed droplets. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly employed for the determination of the emulsion droplet size[22, 23]. Particle size distribution can be further verified by cryogenic transmission electron microscopy (cryo-TEM). For cryo-TEM studies, samples are prepared in a controlled environment verification system. A small amount of sample is put on carbon film supported by a copper grid and blotted by filter paper to obtain thin liquid film on the grid. The grid is quenched in liquid ethane at -180ÚC and transferred to liquid nitrogen at -196ÚC. Cryo-TEM offers the advantage of visualizing the size as well as shape. Small-angle neutron scattering and Small-angle X-ray scattering can also be used to obtain information on the size and shape of the droplets.

Zeta Potential

This is used to identify the charge on droplets. The charge on the oil droplets in conventional SMEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1-3 % will yield cationic SMEDDS. Zeta potential helps to predict the stability and flocculation effect in emulsion systems. If the zeta potential falls below

a certain level, colloid will aggregate due to attractive forces. Conversely, a high zeta potential maintains a stable system[24].

Emulsification rate

The rate of self-emulsification is usually determined by adding a dose of the SMEDDS pre-concentrate, preferably in a capsule, to a relevant amount of water or biorelevant media. Rate of dispersion is determined by visual observation or by monitoring the change of turbidity of dispersion using a UV spectrophotometer or nephlometer.

Conductivity measurements

Conductivity measurements are able to determine the point of aqueous phase addition where the system changes from oil continuous to a water continuous phase. It also helps in monitoring percolation or phase inversion phenomena[8].

Turbidity measurement

This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time[25]. The measurements are carried out on turbidity meters for e.g. the Hatch turbidity meter and Orbeco-Helle turbidity meter[26, 27].

Biopharmaceutical aspects of SEDDS

Mechanisms underlying enhancement of drug absorption by SEDDS

Following are the mechanisms responsible for enhanced drug absorption by SEDDS,

- *In vivo* solubilization of drug: The presence of lipids in the GIT stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and Cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI mixed micelles and an increase in the solubilization capacity of the GIT. However, intercalation of administered (exogenous) lipids into these BS structures either directly or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity[19].
- Prolongation of gastric residence time: Lipids in the GI tract provoke delay in gastric emptying, i.e. gastric transit time is increased. As a result, the residence time of the co-administered lipophilic drug in the small intestine increases. This enables better dissolution of the drug at the absorptive site, and thereby improves absorption[19].
- Promotion of intestinal lymphatic transport: For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first pass metabolism[1].
- Affecting intestinal permeability: A variety of lipids have been shown to change the physical barrier function of the gut wall, and hence, to enhance permeability[28].
- Reduced metabolism and efflux activity: Recently, certain lipids and surfactants have been shown to reduce the activity of efflux transporters in the GI wall, and hence increase the fraction of drug absorbed. Because of the interplay between P-gp and CYP3A4 activity this mechanism may reduce intra-enterocyte metabolism as well[29]. Examples of surfactants with P-gp inhibitory activity include cremophor EL, labrasol, polysorbate 80, polysorbate 20 and TPGS[30].

Lipid digestion and drug solubilization in the GIT

Lipid based dosage (SEDDS) form is initially acted upon by gastric lipase. The gastric lipase digests exogenous dietary or formulation lipid. The gentle agitation and gastric emptying aids in emulsification prior to entry into duodenum. Within the small intestine, pancreatic lipase together with its co-factor co-lipase completes the breakdown of dietary glycerides to di-glyceride, monoglyceride and fatty acid. The presence of exogenous lipids in the small intestine also stimulates secretion of endogenous biliary lipids including bile salt (BS), phospholipid and cholesterol from the gall bladder. In the presence of raised BS concentrations, the products of lipid digestion are subsequently incorporated into a series of colloidal structures including multilamellar and unilammelar vesicles, mixed micelles and micelles. Together these species significantly expand the solubilization capacity of the small intestine for both lipid digestion products and drugs[15].

Circulatory uptake of drug

Both the lymph and blood vessels are present in the lamina proria underlying the intestinal absorptive cells (enterocytes) of the intestine. The rate of fluid flow in the portal blood is approximately 500 times higher than that of intestinal lymph. In contrast, following the uptake into the enterocytes, fatty acid (FA) and monoglyceride (MG) digestion products are resynthesised into triglyceride (TG) and assembled into colloidal lipoproteins (LP) within endoplasmic reticulum. These LP are exocytosed across the basolateral membrane of the enterocytes and preferentially enter the mesenteric lymph vessels due to their size which preludes easy diffusion across the vascular endothelium. Highly lipophilic drug (log P>5, and long chain TG solubility >50mg/g) may therefore access the intestinal lymph via association with developing lipoprotein[31].

Advantages of SEDDS

- Improvement in oral bioavailability: The ability of lipid based formulations to present the drug to GIT in solubilised and micro emulsified form (globule size between 1-100 nm) and subsequent increase in specific surface area, enables more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane, leading to improved bioavailability (BA). Their contribution in improvement of the oral bioavailability of several poorly water soluble drugs is summarised in Table 5.

Table 5 Examples of SEDDS/SMEDDS describing oral bioavailability enhancement of poorly water soluble drugs

Compound	Formulations(s)	Study design	Observation after Study	References
Cyclosporin	Neoral (SMEDDS)	Relative BA in humans	Increased BA and C_{max} and reduced T_{max} and SMEDDS	33
Ontazolast	Soyabean oil emulsion, drug solution in peceol	Absolute BA in rats	BA increases at least 10-fold from all lipid based formulations	18
Vitamin E	SEDDS or soybean oil (LCT) solution	Relative BA in humans	BA 3-fold higher from SEDDS	34
Coenzyme Q10	SMEDDS	Relative BA in dogs	BA 2-fold higher from SEDDS	1
Simvastatin	SMEDDS	Relative BA in dogs	BA 1.5-fold higher from SMEDDS	35
Progesterone	SEDDS	Relative BA in dogs	BA 9-fold higher from SEDDS	36
Carvediol	SEDDS	Relative BA in dogs	BA 4-fold higher from SEDDS	37
Silymarin	SMEDDS, PEG 400 solution	Relative BA in rabbits	BA approximately 2 and 50-fold higher from SMEDDS than that of PEG 400 solution	38
PNU-91325	Supersaturable SEDDS compared to cosolvent (PG)	Relative BA in rats	5-6 fold enhancement in oral bioavailability for Supersaturable SEDDS relative to cosolvent	39
Zeodary tumeric oil	Self-emulsifying sustained release microspheres	Relative BA in rabbits	Bioavailability enhancement of 135.6% with respect to the Conventional liquid SEDDS	40
Curcumin	Pelleted SMEDDS	Relative BA in rats	10-11 fold enhancement in oral bioavailability for pelleted SEDDS relative to curcumin aqueous suspension	41

BA, Bioavailability; PEG, Poly Ethylene Glycol; PG, Propylene Glycol; LCT, Long Chain Triglyceride

- Ease of manufacture and scale-up: Ease of manufacture and scale-up is one of the most important advantage that makes lipid based formulations unique when compared to other bioavailability enhancement techniques like solid dispersions, liposomes and nanoparticles. Lipid based formulations require very simple and economical manufacturing facilities for large-scale manufacturing.
- Reduction in inter-subject and intra-subject variability and food effects: There are several drugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is a major factor affecting the therapeutic performance of the drug in the body.
- Prevention of enzymatic hydrolysis in GIT: One unique property that makes lipid based formulations superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis[32].
- Increased drug loading capacity: Lipid based formulations especially SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient ($2<\log P<4$) are typically low in natural lipids and much greater in amphiphilic surfactants, co-surfactants and co-solvents[2].

Recent developments

Supersaturable SEDDS

Supersaturable SEDDS formulations are SEDDS formulations having reduced amount of surfactant, and a crystal growth inhibitor such HPMC.

The cellulosic polymers are excellent crystal growth inhibitors and are effective in prolonging the supersaturated state of the drugs in GIT. The ability to generate a supersaturated state with HPMC with the S-SEDDS formulations may be due to the formation of widely spaced cellulosic-polymer network that is formed by the HPMC chains in water. HPMC chain may inhibit nucleation, as well as crystal growth by adsorption of the HPMC molecules onto the surface of the nuclei, or onto the surface of crystals[42]. The reported formulations of S-SEDDS in literature are given for paclitaxel[42] and PNU-91325[39].

Solid SEDDS

This approach enables the development of solid dosage forms (tablets, capsules) using a liquid SEDDS for a poorly water-soluble drug. Solid SEDDS mean solid dosage forms with self-emulsification properties. Solid SEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion and nanoparticle technology). They combine the advantages of SEDDS (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance)[43].

Conclusion

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDS, which have been shown to substantially improve oral bioavailability. Their efficiency is case specific, thus their proper characterization is of utmost importance. Lipid based formulations are still not very widespread as commercial formulations, despite their great success in bioavailability enhancement of poorly soluble drugs. This can be attributed to lack of proper understanding of development and manufacturing process to physical and chemical stability issues. Effective *in vitro* tests should be utilized which can predict *in vivo* performance of this fascinating and diverse group of formulations.

Future focus should be on understanding of the role of individual lipids and surfactants in the formulation of SEDDS with regard to dispersion process, the structure of the formed emulsion particle and drug solubilization.

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