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Self-Emulsifying Drug Delivery Systems (SEDDS): An Update from Formulation Development to Therapeutic Strategies

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Abstract: Improving oral bioavailability of low poorly water soluble drugs using self emulsifying drug delivery systems (SEDDS) possess significant potential. Oral bioavailability of hydrophobic drugs can be improved using SEDDS, and appears most promising. Their dispersion in gastro intestinal (GI) fluid after administration forms micro or nanoemulsified drug which gets easily absorbed through lymphatic pathways bypassing the hepatic first pass metabolism. Parameters like surfactant concentration, oil to surfactant ratio, polarity of emulsion, droplet size and charge on droplet plays a critical role in oral absorption of drug from SEDDS. For hydrophobic drug substances that exhibit dissolution step as rate limiting for absorption, SEDDS offer an improvement in rate and extent of absorption and gives more reproducible plasma concentration time profiles. Use of combined *in vitro* dispersion and digestion methodologies has enabled a much improved understanding of role of intestinal lipid processing on solubilization behavior of lipid based drug delivery systems(LBDDS).With this we present an in-depth and advanced study on literature reports and patents starting from formulation development to therapeutic strategies through updates with recent approaches and methodologies employed in selecting the most appropriate lipid system(s), solidification techniques for transforming liquid or semi-solid SEDDS to solid SEDDS, , optimization, characterization and stability etc. The article is compiled comprehensively which will help to get information and ideas to the workers in the field of formulation of SEDDS.

Key Words: Self-Emulsifying formulation, Lipid-based Drug Delivery Systems, Bioavailability enhancement, Characterization, Hydrophobic drugs.

INTRODUCTION

The better absorbed drugs across the gastrointestinal tract (GIT) provide good oral bioavailability but have number of potentially limiting factors. These include appropriate stability and solubility in the GI fluid, reasonable intestinal permeability, and resistance to metabolism both within the enterocyte and the liver [1]. It has realized that the oral bioavailability of poorly water soluble, lipophilic drugs may be enhanced when co-administered with a meal rich in fat this has led to increase recent interest in the formulation of poorly soluble drugs in lipids as a means to enhance drug solubilisation in the GIT [2-7]. Lipid-based formulations not only

improve but normalize drug absorption, which is particularly beneficial for low therapeutic index drugs [8-10]. These formulations can also enhance drug absorption by a number of ancillary mechanisms, e. g (a) including inhibition of P-glycoprotein-mediated drug efflux and pre absorptive metabolism by gut membrane-bound cytochrome enzymes (b) promotion of lymphatic transport, which delivers drug directly to the systemic circulation while avoiding hepatic first-pass metabolism and (c) by increasing GI membrane permeability [11-15]. Modification of the physicochemical properties, such as salt formation and particle size reduction of the compound may be one approach to improve the dissolution rate of the drugs [16, 17]. However, these methods have their own limitations. In recent years much attention has focused on lipid−based formulations to improve the oral bioavailability of poorly soluble drugs .In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils, surfactant dispersions, self-emulsifying formulations, emulsions and liposomes with particular emphasis on self-emulsifying drug delivery systems (SEDDS).

Novelty Statement:

This review on Self Emulsifying Drug Delivery Systems (SEDDS) is written as these drug delivery systems have unparalleled prospect in enhancing bioavailability of low soluble drugs of biopharmaceutical classification. An extensive and updated description of literature reports on different types of self emulsifying formulations, techniques employed, characterization, optimization and application strategies are discussed comprehensively to direct the formulation scientists in formulating a stable, safe and effective self emulsifying formulation. The figures are self designed to prove the concept, mechanism and meaning of SEDDS.

SELF EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS)

SEDDS belong to lipid-based formulations. Lipid formulations can be oils, surfactant dispersions, emulsions, solid lipid nanoparticles and liposomes. SEDDS are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers. Upon mild agitation followed by dilution with aqueous media, these systems can form fine (oil in water) emulsion instantaneously. 'SEDDS' is a broad term, typically producing emulsions with a droplet size ranging from a few nanometers to several-microns. "Self-micro-emulsifying drug delivery systems" (SMEDDS) indicates the formulations forming transparent micro-emulsions with oil droplets ranging between 100 and 250 nm. "Self-nano-emulsifying drug delivery systems" (SNEDDS) is a recent term with the globule size ranges less than 100 nm [18].

A schematic about self-micro-emulsifying drug delivery systems" (SMEDDS) is shown in Figure 1. It has been suggested that self-emulsifying drug delivery systems can be prepared which, after oral administration in gelatin capsules, will emulsify within the gastric contents [19].

Advantage of self-emulsifying formulations over solid dosage formulations is the avoidance of slow drug dissolution. Distribution of the emulsion within the GIT helps to avoid the irritancy. Some marketed self emulsified dosage forms are described in Table 1.

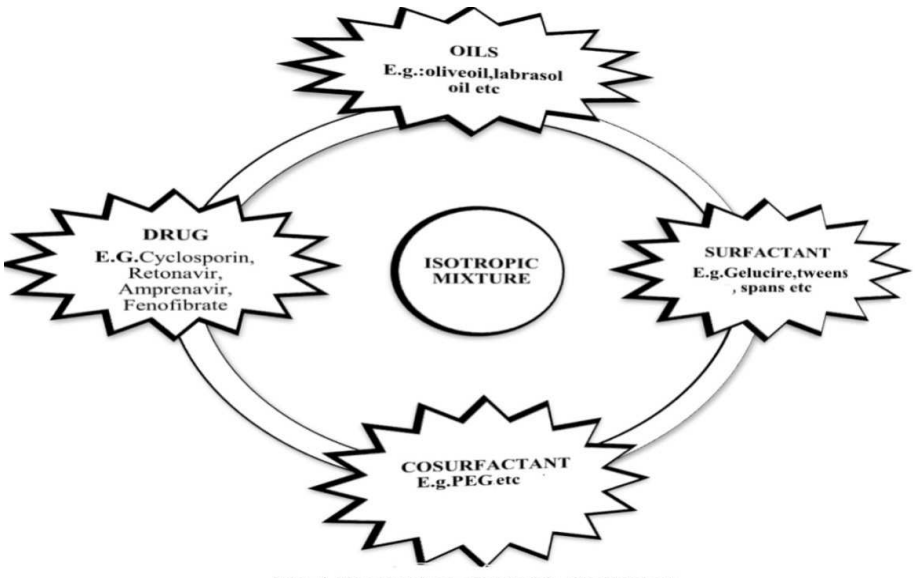

Fig.1. Illustration of what is SMEDDS

Table 1: Marketed self emulsified dosage forms

Drug name	Compound	Dosage form	Company
Neoral	Cyclosporin	Soft gelatin capsules	Novartis
Norvir	Ritonavir	Soft gelatin capsules	Abott laboratories
Fortavase	Saquinavir	Soft gelatin capsule	Hoffmann-LaRoche Inc.
Agenerase	Amprenavir	Soft gelatin capsules	Glaxosmithkline
Solufen	Ibuprofen	Hard gelatin capsules	Sanofi-Aventis
Lipirex	Fenofibrate	Hard gelatin capsules	Sanofi-Aventis

MECHANISM OF SELF EMULSIFICATION

According to Reiss, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion [20]. The free energy of a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by equation 1.

$$\Delta G = \sum N i \pi r^2 \sigma \qquad \text{Equation -1}$$

Where ΔG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius, r and σ represents the interfacial energy.

Emulsification occurs spontaneously with SEDDS because the free energy required to form the emulsion is either low or positive or negative. It is necessary for the interfacial structure to show no resistance against surface shearing in order for emulsification to take place [21, 22]. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/non-ionic surfactant) to water. This is followed by the solubilization of water within the oil phase as a result of aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interphase. Further aqueous penetration will lead to the formation of the dispersed LC phase. In the end, everything that is in close proximity with the interface will be LC, the actual amount of which depends on the surfactant concentration in the binary mixture. Thus, following gentle agitation of the self-emulsifying system, water will rapidly penetrate into the aqueous cores and lead to interface disruption and droplet formation. As a consequence of the LC interface formation surrounding the oil droplets, SEDDS become very stable to coalescence.

CHARACTERIZATION OF SEDDS

The very essence of SEDDS is self-emulsification, which is primarily assessed visually. The various ways to characterize SEDDS are compiled below [23-30].

Equilibrium phase diagram: Although self emulsification is a dynamic non equilibrium process involving interfacial phenomena, information can be obtained about self-emulsification using equilibrium phase behavior.

Turbidity measurement: This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. These measurements are carried out on turbidity meters, most commonly the Hach turbidity meter and the Orbeco-Helle turbidity meter.

Droplet size: This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nano-sizer are mainly used for the determination of the emulsion droplet size.

Electron microscopic studies: Freeze-fracture electron microscopy has been used to study surface characteristics of dispersed systems.

Zeta potential measurement: This is used to identify the charge of the droplets. In conventional SEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids.

Determination of emulsification time: The process of self-emulsification was observed using light microscopy. The mechanism of emulsification involved erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size.

Liquefaction time: This test is designed to estimate the time required by solid SEDDS to melt *in vivo* in the absence of agitation to simulated GI conditions.

Small-angle neutron scattering: Small-angle neutron scattering can be used to obtain information on the size and shape of the droplets.

Small-angle X-ray scattering: Small-angle X-ray scattering is capable of delivering structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150 nm. It is used for the determination of the microscale or nanoscale structure of particle systems in terms of such parameters as averaged particle sizes, shapes, distribution and surface-to-volume ratio.

SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM (S-SEDDS)

S-SEDDS mean solid dosage forms with self-emulsification properties. S-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, nano-particle technology).

In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres/nanoparticles and SE suppositories/implants. SEDDS are usually, however, limited to liquid dosage forms, because many excipients used in SEDDS are not solids at room temperature.

SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID/SEMISOLID SEDDS TO SOLID SEDDS

Capsule filling with liquid and semisolid self-emulsifying formulations

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. In parallel with the advances in capsule technology proceeding, liquid-Oros technology (Alza Corporation) has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SE formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pumps the drug formulation through an orifice in the hard or soft capsule. A primary consideration in capsule filling is the compatibility of the excepients with the capsule shell. The liquid/semisolid lipophilic vehicles compatible with hard capsules were listed by Cole *et al.* [31]. The advantages of capsule filling are simplicity of manufacturing, suitability for low-dose highly potent drugs and high drug loading (up to 50% (w/w) potential.

Spray drying

This technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. An illustration showing spray drying process is given under Figure 2.

Spray cooling

Spray cooling also referred to as spray congealing is a process whereby the molten formula is sprayed into a cooling chamber. Upon contact with the cooling air, the molten droplets congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms, tablets or direct filling into hard shell

capsules. Many types of equipment are available to atomize the liquid mixture and to generate droplets: rotary pressure, two-fluid or ultrasonic atomizers [31, 32].

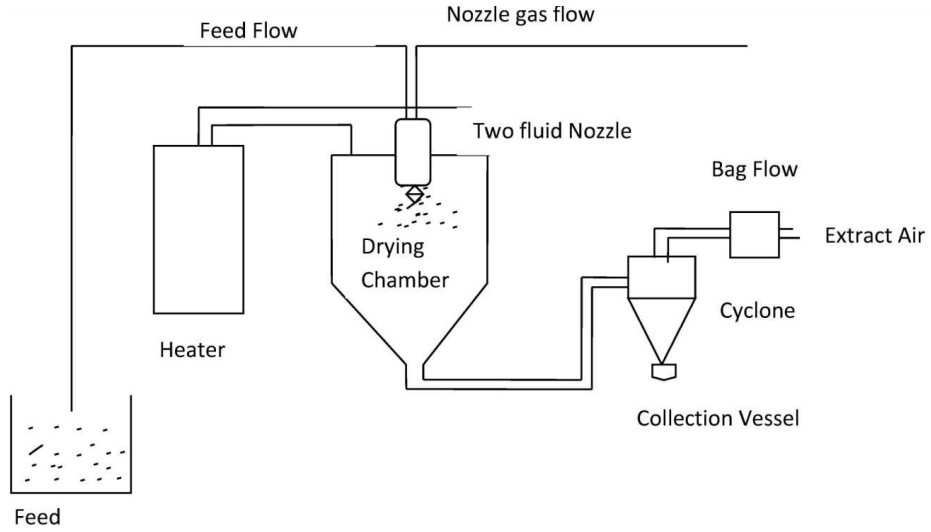

Fig.2. Spray drying process

Adsorption to solid carriers

SEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers. Solid carriers can be microporous inorganic substances, high surface area colloidal inorganic adsorbent substances, cross-linked polymers or nanoparticle adsorbents (i.g., silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and crosslinked polymethyl methacrylate). The adsorption technique has been successfully applied to gentamicin and erythropoietin with caprylocaproyl polyoxylglycerides (Labrasol) formulations that maintained their bioavailability enhancing effect after adsorption on carriers [33-35].

Melt granulation

Melt granulation or pelletization is a one step-process allowing the transformation of a powder mix (containing the drug) into granules or spheronized pellets. The technique needs high shear mixing in presence of a meltable binder. This is referred to as “pump-on” technique. Alternatively, the binder may be blended with the powder mix in its solid or semi-solid state and allowed to melt (partially or completely) by the heat generated from the friction of particles during high shear mixing referred to as “melt-in” process. The melted binder forms liquid bridges with the powder particles that shape into small agglomerates (granules) which can, by further mixing under controlled conditions transform to spheronized pellets [36-38].

Melt extrusion/Extrusion spheronization

It is a solvent-free process that allows high drug loading (60%) as well as content uniformity. Applying extrusion-spheronization, SE pellets of diazepam and progesterone and bi-layered cohesive SE pellets have been prepared [39, 40].

DOSAGE FORM DEVELOPMENT OF SOLID SEDDS

Different solid SEDDS that are developed by pharmaceutical formulators is shown as illustration under Figure 3.

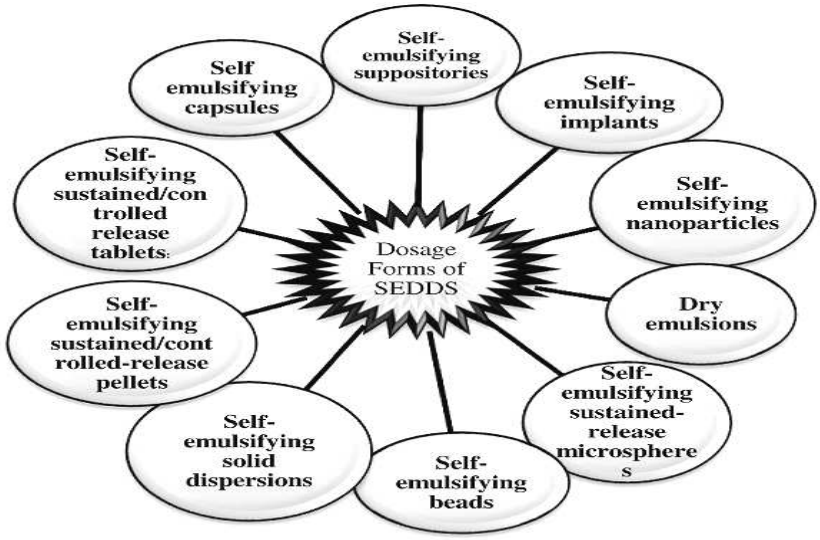

Fig.3. Illustration of dosage form development of solid SEDDS

Self-emulsifying capsules

Poor water soluble drugs can be dissolved in SEDDS and encapsulated in hard or soft gelatin capsules to produce convenient single unit dosage forms. Administration of capsules containing conventional liquid SE formulations, micro emulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the micro emulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation [41]. With the similar purpose, the supersaturable SEDDS was designed, using a small quantity of HPMC (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects [42, 43].

Dry emulsions

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation, freeze-drying or spray drying. Dry emulsion technology solves the stability problems associated with classic emulsions (phase separation, contamination by microorganism, etc.) during storage and helps also avoid using harmful or toxic organic solvents.

Self-emulsifying sustained/controlled release tablets

A gelled SEDDS has been developed by Patil et al. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release. The newest advance in the research field of SE tablet is the SE osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SES.

Self-emulsifying sustained/controlled-release pellets

Serratoni et al. prepared SE controlled-release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release. Combinations of coating and SES could control in vitro drug release by providing a range of release rates and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution [44].

Self-emulsifying solid dispersions

These formulations consist of a dispersion of the drug in an inert excipient matrix, but some manufacturing difficulties and stability problems existed. SE excipients like Gelucire1 44/14, Gelucire1 50/02, Labrasol1, Transcutol1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field. Gupta et al. prepared SE solid dispersion granules using the hot-melt granulation method. Gelucire1 50/13 was used as the dispersion carrier, whereas Neusilinee US2 was used as the surface adsorbent [45, 46].

Self-emulsifying beads

In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, Patil and Paradkar investigated loading SES into the microchannels of porous polystyrene beads (PPB) using the solvent evaporation method [46].

Self-emulsifying sustained-release microspheres

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions including tumor suppressive, antibacterial, and antithrombotic activity. You et al. prepared solid SE sustained-release microspheres using the quasi-emulsion–solvent-diffusion method of the spherical crystallization technique. With ZTO as the oil phase,. ZTO release behavior could be controlled by the ratio of hydroxypropyl methylcellulose acetate succinate to Aerosil 200 in the formulation [47].

Self-emulsifying nanoparticles

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. A second technique is that of sonication emulsion-diffusion-evaporation [48].

Self-emulsifying suppositories

Some investigators proved that S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption. The formulation included glycyrrhizin and a mixture of a C_6–C_{18} fatty acid glycerol ester and a C_6–C_{18} fatty acid macrogol ester [49].

Self-emulsifying implants

Loomis invented copolymers having a bioresorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses.

LIPID FORMULATION CLASSIFICATION SYSTEM (LFCS)

LFCS was established by Pouton in 2000 and recently updated (2006) to help stratify formulations into those with similar component parts. The LFCS briefly classifies lipid-based formulations into four types according to their composition and the possible effect of dilution and digestion on their ability to prevent drug precipitation. A schematic illustration on lipid formulation classification system is shown in Figure 4 and ingredient proportion is given in Table 2.

Type I lipid formulations

It consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in an oil in water emulsion stabilized by low concentrations of emulsifiers such as 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin .

Type II lipid formulations

These are typically referred to as self emulsifying drug delivery systems, SEDDS which are isotropic mixtures of lipids and lipophilic surfactants (HLB<12) that self-emulsify to form fine oil-in-water emulsions

when introduced in aqueous media. Type II lipid-based formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs . Shah et al. compared the bioavailability of a drug after administration of a SEDDS formulation (comprising peanut oil and poly glycolysed glycerides as emulsifiers), a PEG 400 solution, and a capsule of 55% wet-milled spray-dried powder and a tablet of micronized drug to dogs [50]. The SEDDS formulation showed superior in vivo performance with at least 3-fold higher C_{max} and AUC when compared with the other dosage forms. Rapid release of the drug and increased drug solubilization in the gastrointestinal lumen were suggested to be responsible for the improved drug bioavailability.

Table 2: Lipid Formulation Classification System [1, 8, 21]

Composition/ Significance	**TYPE – I**	**TYPE – II**	**TYPE – IIIA**	**TYPE –IIIB**	**TYPE – IV**
% of triglycerides or mixed glycerides	100	40-80	20	<20	----
water insoluble surfactants(HLB<12)	----	20-60	----	-----	0-20
water soluble surfactants(HLB>12)	----	----	20-40	20-50	30-80
Hydrophilic co solvents	----	----	0-40	20-50	0-50
particle size of dispersion (nm)	Coarse	100-250	100-250	50-100	<50
Significance of aqueous dilution	Limited importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes & potential loss of solvent capacity	Significant phase changes & potential loss of solvent capacity
Significance of digestibility	Crucial requirement	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required

Type III lipid-based formulations

These are commonly referred to as self-micro emulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB >12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further segregated (somewhat arbitrarily) into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. Thus SEDDS formulation typically provide opaque dispersions with particle sizes >100 nm whereas SMEDDS formulations (which contain higher concentrations of hydrophilic surfactants and co-solvents) disperse to give smaller droplets with particle sizes <100 nm, and provide optically clear or slightly opalescent dispersions, more consistent with the presence of a microemulsion.

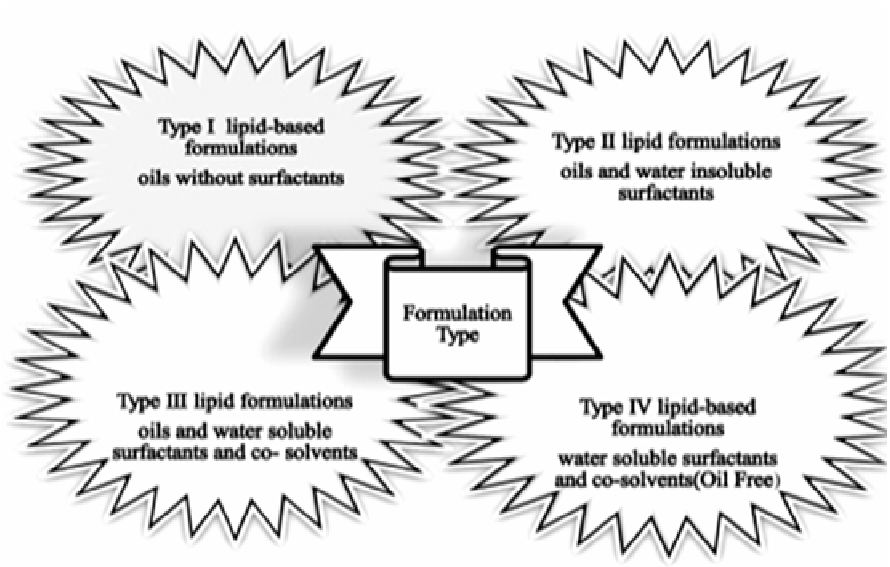

Fig.4. Schematic representation of Lipid classification system (LFCS)

Type IV lipid-based formulations

Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations offer increased drug payloads (due to higher drug solubility in the surfactants and co-solvents) and produce very fine dispersions. This leads to rapid drug release and increased drug absorption [51, 52]. An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase) which contains TPGS as a surfactant and PEG 400 and propylene glycol as co-solvents [53].

EXCIPIENTS USED IN SEDDS

Lipids/oils

The oil represents one of the most important excipients in the SEDDS formulation not only because it can solubilize marked amounts of the lipophilic drug or facilitate self-emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglycerides [54-56]. Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Medium chain triglycerides were preferred in the earlier self-emulsifying formulations because of higher fluidity, better solubility properties and self-emulsification ability, but evidently, they are considered less attractive compared to the novel semi synthetic medium chain derivatives which can be defined rather as amphiphilic compounds exhibiting surfactant properties. In such cases, the more lipophilic surfactant may play the role of the hydrophilic oil in the formulation [57, 58].

Surfactants

The surface-active agents are amphiphilic by nature, the usual surfactant concentration in self-emulsifying formulations required to form and maintain an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation. The most widely recommended ones being the non-ionic surfactants with a relatively high (HLB) hydrophilic−lipophilic balance Tween 80 [59-61].

Co-solvents

Co-solvents such as, ethanol, propylene glycol (PG), and polyethylene glycol (PEG) are suit-able for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base.

Additives

Lipid-soluble antioxidants such as α-tocopherol, β-carotene, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) or propyl gallate could potentially be included in formulations to protect either unsaturated fatty acid chains or drugs from oxidation.

Strickley's survey revealed that the most frequently chosen excipients for preparing oral lipid-based formulations were dietary oils composed of medium (e.g., coconut or palm seed oil) or long chain triglycerides (e.g., corn, olive, peanut, rapeseed, sesame, or soybean oils, including hydrogenated soybean or vegetable oils), lipid soluble solvents (e.g., polyethylene glycol 400, ethanol, propylene glycol, glycerin), and various pharmaceutically acceptable surfactants (e.g., Cremophor EL, RH40, or RH60; polysorbates 20 or 80; D-α-tocopherol polyethylene glycol 1000 succinate (TPGS); Span 20; various Labrafils, Labrasol and Gelucires). Examples of surfactants, co-surfactants and co-solvents used in commercial lipid base formulations are presented in Table 3.

Table 3: Examples of surfactants, co-surfactants, and co-solvents used in commercial lipid-based formulations [62].

Excipient name (commercial name)	**Examples of commercial products in which it has been used**
Surfactants/co surfactants	
Polysorbate 20 (Tween 20)	Targretin soft gelatin capsule
Polysorbate 80 (Tween 80)	Gengraf hard gelatin capsule
Sorbitan monooleate (Span 80)	Gengraf hard gelatin capsule
Polyoxyl-35-castor oil (Cremophor EL)	Gengraf hard gelatin capsule, Ritonavir soft gelatin capsule
Polyoxyl-40-hydrogenated castor oil (Cremophor RH40)	Neoral soft gelatin capsule, Ritonavir oral solution
Polyoxyethylated glycerides (Labrafil M 2125Cs)	Sandimmune soft gelatin capsules
Polyoxyethylated oleic glycerides (Labrafil M 1944Cs)	Sandimmune oral solution
D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS)	Agenerase soft gelatin capsule, Agenerase oral solution
Co-solvents	
Ethanol	Neoral soft gelatin capsule, Neoral oral solution, Gengraf hard gelatin capsule, Sandimmune soft gelatin capsule, Sandimmune oral solution
Glycerin	Neoral soft gelatin capsule, Sandimmune soft gelatin capsule
Propylene glycol	Neoral soft gelatin capsule, Neoral oral solution, Lamprene soft gelatin capsule,Agenerase soft gelatin capsule, Agenerase oral solution, Gengraf hard gelatin capsule

Polyethylene glycol	Targretin soft gelatin capsule, Gengraf hard gelatin capsule, Agenerase soft gelatin capsule, Agenerase oral solution
Lipid ingredients	
Corn oil mono-, di-, tri-glyceride	Neoral soft gelatin capsule, Neoral oral solution
DL-α-Tocopherol	Neoral oral solution, Fortovase soft gelatin capsule
Fractionated triglyceride of coconut oil (medium-chain triglyceride)	Rocaltrol soft gelatin capsule, Hectorol soft gelatin capsule
Fractionated triglyceride of palm seed oil (medium chain triglyceride)	Rocaltrol oral solution
Mixture of mono- and di-glycerides of caprylic/capric acid	Avodart soft gelatin capsule
Medium chain mono- and di-glycerides	Fortovase soft gelatin capsule
Corn oil	Sandimmune soft gelatin capsule, Depakene capsule
Olive oil	Sandimmune oral solution
Oleic acid	Ritonavir soft gelatin capsule, Norvir soft gelatin capsule
Sesame oil	Marinol soft gelatin capsule
Hydrogenated soybean oil	Accutane soft gelatin capsule, Vesanoid soft gelatin capsule
Hydrogenated vegetable oils	Accutane soft gelatin capsule, Vesanoid soft gelatin capsule
Soybean oil	Accutane soft gelatin capsule
Peanut oil	Prometrium soft gelatin capsule
Beeswax	Vesanoid soft gelatin capsule

FORMULATION DEVELOPMENT AND CHARACTERIZATION

Successful LBDD hence requires a holistic approach to formulation. A systematic elucidation of the rationale may be achieved by

(1) Pre-selecting excipients for their fatty acid make up, melt characteristics, HLB or emulsification properties, potential effect on enterocytes based drug transport and disposition and overall digestibility.
(2) Conducting binary screening with the pre-selected excipients for drug solubility, compatibility, stability, and dissolution/dispersion properties (in biorelevant media) to identify one or more suitable systems for further studies.
(3) Identifying the formulation technique(s) suitable for the dosage form intended.
(4) Confirming the in vivo performance of the chosen formulation system(s) in appropriate animal models.
(5) Optimizing the formulation for drug loading or dissolution profile and if necessary, gain control of the oxidative and polymorphic changes [82].

Candidate compound selection

For compounds in which the primary limitation to absorption is poor aqueous solubility and slow dissolution rate, and where intestinal permeability is not a limiting factor, (e.g., biopharmaceutical classification system (BCS) Type II drugs) and for which conventional formulation approaches (e.g. salt or crystal form selection,

particle size reduction, solid dispersions or the addition of surfactants) have failed, a lipid-based formulation should be considered. A preliminary indication of the potential utility of this approach can be obtained by assessing the drug lipophilicity (e.g. octanol: water Log *p*) and particularly, its solubility in pharmaceutically-acceptable lipid excipients, which should be sufficient to allow the entire dose of 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 state. In addition, the foregoing observation may indicate the potential usefulness of a properly designed lipid-based formulation for mitigating food effect [63-65].

Dose of drug

The most difficult drugs are those which have limited solubility in both water and lipids (typically with log *P* values of approximately 2). Bioavailability may be much greater from a lipid system, which may allow pharmacological activity to be achieved with a lower dose. This is particularly important for drugs with high log *p*, when in the first instance the solvent capacity of lipid formulations appear to fall short of the required dose.

The most important consideration should be to avoid precipitation of the drug, but a secondary consideration is whether or not rapid absorption is desirable. If the drug has a low therapeutic index this may be undesirable, which argues in favour of a Type I formulation [82].

Excipient compatibility

It is well recognized that a number of lipid and some surfactant excipients are susceptible to oxidation, with the attendant formation of highly-reactive peroxide species. Peroxide formation can be detrimental not only to the stability a formulated drug substance, but has been shown to cause gelatin cross-linking, resulting in delayed disintegration of the capsule shell which in turn, may adversely affect drug release. Lipid oxidation can be controlled by limiting (when possible) the use of unsaturated lipids, by inclusion of appropriate antioxidants, or through the use of sealed hard gelatin capsule shells, which are relatively impermeable to oxygen [66-68].

Self-dispersion and sizing of dispersions

With the availability of modern Fraunhofer diffraction sizers and photon correlation spectrometers, the effect of formulation on particle size can be studied relatively easily. Optimization of SEDDS and SMEDDS is more likely to be a job for a photon correlation sizer, but if a Fraunhofer instrument is available it is advisable to use this instrument to check that there are no particles larger than 1 μm.

Phase diagrams are constructed to identify suitable mixing ratios for homogenous formulations. Equilibrium phase behavior gives spontaneous emulsification, but at least such studies enable prediction of the phases which are likely to form on dilution of SEDDS with water. Phase studies have suggested a role for liquid crystal formation in self-emulsification, and have also indicated that good formulations are usually operating close to a phase inversion region and in a region of enhanced aqueous solubilization. The enhanced solubilization is assumed to play a role in permitting more rapid penetration of water.

In vitro dispersion and digestion tests

Digestion testing is of even greater significance because it offers the opportunity to predict the fate of the formulation and drug in the intestinal lumen prior to absorption. For this purpose, *in vitro* lipolysis testing of formulations was introduced. It is becoming evident that solvent capacity can be lost on digestion, leading to drug precipitation. If the digestion experiment is followed by a centrifugation step, precipitated drug can be quantified by analyzing the contents of the pellet which sediments during centrifugation. The extent of drug precipitation upon lipolysis was indeed shown to be predictive for the ranking of formulation performance *in vivo* [69-75].

Assessment of lipid-based formulations using in vitro lipolysis

Possible changes to solubilisation capacity that occur as a result of digestion of formulation components and interaction with endogenous biliary solubilising agents (BS, PL) are assessed using an *in vitro* model of lipid digestion. To this point most of the studies in the literature have examined formulation digestion under simulated intestinal conditions, since the majority of lipid digestion is thought to occur in the intestine.

However, lipolysis is initiated in the stomach via acid-stable gastric lipase, and after oral administration of the relatively small quantities of lipid commonly contained in lipid-based formulations, gastric lipolysis may be significant [76].

In vitro lipolysis experiments suggested improved cyclosporine solubilisation in digests containing medium chain digestion products, whereas *in vivo*, oral bioavailability was higher after administration of a long chain lipid-based formulation [77]. Kaukonen et al. utilized the solubilisation behavior of a range of PWSD of increasing lipophilicity (griseofulvin, diazepam, danazol, cinnarizine and halofantrine) on digestion of simple medium chain and long chain triglyceride lipid solutions and suspensions [78]. Dahan et al. have discussed similar concepts in two recent publications exploring the oral bioavailability of vitamin D_3, progesterone, dexamethasone and griseofulvin after administration in formulations comprising a solution of drug in long (peanut oil), medium (Captex 355) and short chain (triacetin) triglyceride[79, 80].

Assessment of the efficiency of emulsification

An attempt to quantify the efficiency of emulsification of various compositions of the Tween 85 /medium-chain triglyceride system utilized a rotating paddle to promote emulsification in a crude nephelometer. This allowed an estimation of the time taken for emulsification. The samples were taken for particle sizing by photon correlation spectroscopy and self-emulsified systems were compared with homogenized systems. The most rapid emulsification occurred at an optimum surfactant content of 35% w/w, though it was concluded that all systems containing between 20-50% w/w Tween 85 emulsified very rapidly, so that this was not a crucial issue for formulation. The process of self-emulsification was observed using light microscopy. It was clear that the mechanism of emulsification involved erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size. When the surfactant content was above 50% the formation of viscous gels appeared to retard self-emulsification, though these systems produced very fine dispersions if more energy for dispersion was provided by homogenization.

Other formulation tools

Analysis of drug solubilization in bile salt–lecithin mixed micelles is a simple and effective diagnostic test. Drug solubilization can be analysed directly by spectrophotometry and by HPLC. This technique offers a quick indication of whether a drug is likely to be solubilised in the gut lumen. Aqueous dilution tests provide a simple tool for early formulation assessment. Such first solubility assessment in excipients can be obtained from turbidity measurements. The advantage of measuring turbidity is the potential for miniaturization of mixing and solubility experiments, which was recently explored in a high-throughput approach to finding lipid-based formulations [81].

BIOPHARMACEUTICAL ISSUES AND CHOICE OF FORMULATION

Biological issues in the selection of SEDDS

The rate of gastric emptying of SEDDS is similar to solutions, so that they are particularly useful where rapid onset of action is desirable. Conversely if the therapeutic index of the drug is low, the rapid onset and accompanying high T_{max} may lead to undesirable side-effects. With regard to bioavailability there are differences between formulations which contain water-soluble surfactants or co-solvents, and those which do not. These SEDDS should be preferable if the drug can be dissolved to an adequate extent. If the drug is sufficiently oil soluble a good case can be made for avoiding SEDDS completely and formulating the drug as a simple triglyceride solution, making use of lipolysis to aid dispersion of the formulation [1, 82].

Significance of droplet size

Reducing the oil content and including surfactants and co-solvents is that the droplets become less susceptible to digestion. This means that self-emulsifying systems are dependent on the initial emulsification process to produce a colloidal dispersion. It is assumed that the droplet size should be as fine as possible, and there is some evidence that this assumption holds in the case of cyclosporin A. The drug was more available from the 'Neoral' formulation than the earlier 'Sandimmune' formulation, which was a coarsely emulsifying system (Mueller et al., 1994a) [82].

The risk of precipitation

Considering the example of a hydrophobic drug dissolved in a pure co-solvent such as polyethylene glycol or propylene glycol. When the formulation is added to water the solvent capacity of the mixture falls approximately logarithmically as the formulation is diluted into water. The result is precipitation of the drug. The hydrophilic surfactant will be substantially separated from the oily components, forming a micellar solution in the continuous phase. That will depend on the log *P* of the drug, and to what extent the surfactant was contributing to its solubilization within the formulation.

Role of lipolysis and solubilization in bile

It is possible that digestion of a lipid formulation could reduce the solubility of the drug in the gut lumen, which would result in precipitation of the drug and a decrease in the absorption rate. For such compounds Type II or Type III systems might be preferable, since the presence of surfactants can inhibit digestion of the oil within the formulation (Solomon et al., 1996b; MacGregor et al., 1997). Type III systems such as 'Neoral' have been shown to act independently of bile which suggests that they are not necessarily digested before the drug is absorbed [82].

Lymphatic transport

While the primary physiological purpose of the intestinal lymphatic system is to assimilate dietary lipid from the gut, lymphatic transport can be responsible for a portion of the total uptake of hydrophobic drugs, as well. These drugs are transported to the systemic circulation in association with chylomicrons and very low density lipoproteins (VLDL) and bypass the liver and any potential for hepatic first-pass metabolism, which provides a further boost to bioavailability.

Effect of P-gp inhibition

Possible reasons for enhanced uptake of hydrophobic and/or lipophilic drugs formulated as SEDDS from the GI tract, such as a decrease in the P-gp drug efflux. In addition to a multidrug efflux pump, phase I metabolism by the intestinal cytochrome P450s is now becoming recognized as a significant factor in oral drug bioavailability [83-85]. In some cases, as shown recently, excipients incorporated in SEDDS/SMEDDS can inhibit both presystemic drug metabolism and intestinal efflux mediated by P-gp resulting in an increased oral absorption of cytotoxic drugs [86, 87].

When different doses of paclitaxel SMEDDS were co-administered with 40 mg Cs A/kg, there was a substantial increase in the Cmax and AUC values compared to those obtained with paclitaxel SMEDDS alone in rats [88].

Furthermore, when co-administered with Cyclosporin A (CsA), there was a significant improvement in the relative bioavailability of the drug in SMEDDS as compared to those of Taxol [89, 90].

Choice of non-human test species

By comparison, bile flow in the dog is more similar to that of man, suggesting that this species may be more relevant for projecting clinical performance of oral lipid-based formulations [91].

Due to lower cost and greater ease of handling, small animals (e.g., rats) usually represent the best choice for most early stage proof-of-concept investigations, while a larger animal, such as the dog, is most appropriately utilized for the final stages of testing which require evaluation of a prototype dosage form intended for administration to humans [92].

POSITIVELY CHARGED SEDDS

Positively charged emulsion droplets formed by appropriate SEDDS dilution undergo electrostatic interaction with the Caco-2 monolayer and the mucosal surface of the everted rat intestine. Positively charged droplets should be attracted to the negatively charged physiological compounds naturally occurring in lumen. It was already shown by the authors Gershanik and Benita, that larger droplets (a few microns in size range) are less

neutralized by mucin solutions of different concentrations than smaller droplets (submicron size range) formed by the same formulation.

Positively charged self-emulsifying oil formulations (SEOF), recently developed by Gershanik and Benita, and introduced a new parameter for SEDDS characterization: the charge of resulting droplets [93]. The emulsion droplets, resulting from the aqueous dilution of conventional selfemulsifying formulations formed by traditional oil/nonionic surfactant blend, in practice, carry some negative charge, possibly provided by free fatty acids present in the mixture. Incorporation of a small amount of cationic lipid (2.5±3%), oleylamine, into such an oil/surfactant system reversed the charge nature, leading to the formation of emulsion droplets which exhibit a positive zeta –potential value of about 35±45 mV. This positive zeta - potential value was also preserved after the incorporation of the model drugs [94].

IMPROVEMENT OF ORAL ABSORPTION BY SEDDS

The release of the drug compound from SEDDS takes place upon its partitioning into the intestinal fluids during droplet transport and disintegration along the GI tract. It was proposed that two main factors, small particle size and polarity of the resulting oil droplets determine the efficient release of the drug compound from SEDDS. SEDDS may be a promising alternative to orally administered emulsions because of their relatively high physical stability and ability to be delivered in standard soft gelatin capsules [95].

Effects of lipid-based excipients

Lipid-based excipients can influence oral absorption via various physiological effects such as retarded gastric emptying, stimulating bile flow and secretion of pancreatic juice, increasing the membrane lipid fluidity or acting directly onto enterocytes-based drug transport and disposition, opening of tight junctions, inhibiting efflux transporters like p-glycoprotein (P-gp), inhibiting pre-systemic metabolism or promoting the lymphatic pathway to avoid the first-pass metabolism.

Many lipid-based excipients such as glycerides, fatty acids and ionic and non-ionic surfactants are known permeability enhancers [96]. This effect can be due to increased membrane fluidity, or alternatively, excipients can open tight junctions.

Another mechanism of permeability enhancement is the interaction with efflux transporters. A well-known efflux transporter at the apical membrane of human intestine e.g., P-gp [97, 98].

Effect of lipids

Lipids exert their effects possibly through several complex mechanisms that can lead to alteration in the biopharmaceutical properties of the drug, such as increased dissolution rate of the drug and solubility in the intestinal fluid, protection of the drug from chemical as well as enzymatic degradation in the oil droplets [99, 100] and the formation of lipoproteins promoting the lymphatic transport of highly lipophilic drugs [101].

Short and medium chain fatty acids (with a carbon chain length shorter than 12 carbon atoms) are transported to the systemic circulation by the portal blood and are not incorporated to a great extent in chylomicrons [102].

In contrast, long chain fatty acids and monoglycerides are re-esterified to triglycerides within the intestinal cell, incorporated into chylomicrons and secreted from the intestinal cell by exocytosis into the lymph vessels. In addition to the stimulation of the lymphatic transport, administration of lipophilic drugs with lipids may enhance drug absorption into the portal blood then compared to non-lipid formulations [103].

Effect of surfactants

Surfactants increase the permeability by interfering with the lipid bilayer of the single layer of the epithelial cell membrane, which with the unstirred aqueous layer, forms the rate-limiting barrier to drug absorption/diffusion. Therefore, most drugs are absorbed via the passive transcellular route.

Surfactants partition into the cell membrane and disrupt the structural organization of the lipid bilayer leading to permeation enhancement. They also exert their absorption enhancing effects by increasing the dissolution rate of the drug [104-107].

BIOAVAILABILITY ENHANCEMENT

Oral drug bioavailability of a chemically stable drug is limited by its solubility and its permeability. Poor drug absorption therefore can be caused by inadequate rate and extent of drug dissolution and or low permeation. Accordingly as per the biopharmaceutical classification system, a drug on the basis of these solubility and permeability characteristics classified in to four possible categories, class I to IV.

Bioavailability of poorly soluble class II drugs, on the contrary is dependent on their aqueous solubility/ dissolution rate. As these drugs tend to exhibit dissolution limited bioavailability, the in vivo physiological response is well correlated with the invitro dissolution, resulting eventually in good in vitro/in vivo correlations (IVIVC).

For accomplishing better solubility or dissolution rate of class II drugs use of techniques like micronization, co solvents, micellar solubilization, solid dispersions and complexation has been employed with fruition [108]. A report on bioavailability enhancement using self emulsifying formulation by different workers is presented in Table 4.

Table 4: Literature updates on various reports of bioavailability enhancement using self-emulsifying formulations.

Drug	Enhancement	With reference to	Species	References
Acyclovir	3.5 fold	Pure drug solution	Male albino rats	109
Anethole trithione	2.5 fold	Tablets	Rabbits	110
Atorvastatin	1.5 fold	Conventional tablet	Beagle dogs	111
Bicalutamide	2 fold	Suspension	Rats	112
Carvedilol	4.13 fold	Commercial tablet	Beagle dogs	113
Carvedilol	1.56 fold	Luode (a commercial tabet)	Beagle dogs	114
Danazold	2 fold	Pure surfactant solution	Beagle dogs	74
Fenofibrate	1.075 fold	Tricor tablets	Human	81
Gentamycin	5 fold	I.V saline	Beagle dogs	33
Insulin	1.15 fold	Subcutaneous injection	Beagle dogs	115
Itraconazole	1.9-2.5 fold	Sporanox capsules	Humans	116
Itraconazole	2 fold	Solid dispersion	Rats	117
Ketoconazole	2 fold	Pure drug	Rats	118
Ketoprofen	1.13 fold	Pure drug	Humans	119
Mitotane	3.4 fold	Lysodren	Rabbits	120
Nimodipine	2.6-6.6 fold	Conventional tablet	New Zealand Male rabbits	121
Nimodipine	4.6 fold 1.91 fold 1.53 fold	Suspension Oily solution Micellar solution	Male rabbits	121
Nitrendipine	1.6 fold	Conventional tablet	Beagle dogs	122
Silymarin	3.6 fold	Legalon capsule	Rats	123
Oleanolic acid	2.4 fold	Tablet	Rats	124
Simvastatin	1.5 fold	Zocor tablets	Beagle dogs	125
Tretinoin	1.67 fold	Commercial capsule formulation	Beagle dogs	126

CONCLUSIONS

Poor drug solubility is a frequently encountered problem for pharmaceutical formulation scientists as it affects the drug ability of a new chemical entity (NCE). Since most of the new chemical entities synthesized, nearly

half (50% of) are hydrophobic, the use of lipid based delivery systems (SEDDS) has become increasing popular for pre-clinical studies to therapeutic strategies. The design of SEDDS, SMEDDS, SNEDDS and Micellar systems presents enough of choices that appear equivalent on surface and are usually selected empirically. The use of natural and semi synthetic/ synthetic lipids has gained much academic and commercial interest as a potential formulation for the therapeutic strategy for improving the oral bioavailability of low soluble drugs. Lipid-based systems are a promising choice for the delivery of hydrophobic drug substances. These systems avoid the dissolution step upon oral administration and bypass first pass effect. The several mechanisms to improve the bioavailability of hydrophobic drugs may be, e.g., a)increased membrane fluidity facilitating transcellular absorption, b)opening of tight junctions to allow paracellular transport, c)inhibition of P-glycoprotein-mediated drug efflux and/metabolism by gut membrane- bound CYP450 enzymes, d)enhanced lymphatic transport occurring in conjunction with stimulation of lipoprotein/chylomicron production. Further reasons may be facilitation of *in vivo* dispersion through added surfactant, lypolysis of constituent lipids etc. SEDDS being the most dispersed of all appear the most promising.

Lack of drug precipitation up on aqueous dilution plays the predominant role in many cases. Attention needs to be given to the susceptibility of these systems for precipitation *in vivo* upon oral administration, there remains a need to have predictive ability and objective parameters for assessing this risk. Some *in vitro* models can be extrapolated to predict the relative tendency of formulations for *in vivo* drug precipitation. Use of some polymeric hydrophilic excepients in the formulation can help prevent or delay drug precipitation by the formation of a supersaturated state up on aqueous dilution. Regarding the physical and chemical stability of drugs solubilized in lipid excepients have yet not been adequately established. Moreover, lipid excepients themselves may subject to cause physical changes or chemical degradation over time, which could potentially impact drug stability and formulation performance.

This review presents, the current strategies and considerations for successful developments of LBDDS/SEDDS with hope that they can serve as the ground work for many more success in the field. Now there are new techniques being used to convert liquid or semisolid SEDDS formulations into powders or granules which can be further processed in to conventional “powder-fill” capsules or compressed in to tablets. SEDDS can overcome the limitations for marketing the many drugs in future. Efforts toward formulation development of SEDDS will help to improve the bioavailability of many hydrophobic drugs.

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