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SELF MICRO-EMULSIFYING DRUG DELIVERY SYSTEM: APPROACH TO IMPROVE SOLUBILITY AND PERMEABILITY

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ABSTRACT

Self Micro-emulsifying drug delivery systems (SMEDDS) are usually used to improve the bioavailability of hydrophobic drugs. Approximately 60-70% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. SMEDDS is isotropic (one phase system) mixture of oil or modified oils, surfactants and co-surfactants, which form the fine oil-in-water microemulsion when introduced into aqueous phase under condition of gentle agitation. The digestive motility of the stomach and intestine provide the agitation necessary for self-microemulsion *in-vivo*. Triglyceride is the one of the component of SMEDDS, which helps in the absorption of drugs from the GI tract. SMEDDS enhance the bioavailability enabling reduction in dose of the drug. SMEDDS is evaluated by various methods like visual assessment, droplet polarity and droplet size, size of emulsion droplet, dissolution test, charge of oil droplets, viscosity determination, *in-vitro* diffusion study. This article gives an overview of improvement in the rate and extent of oral absorption of drugs by SMEDDS approach. The characterization of SMEDDS and application of SMEDDS is also introduced, with particular emphasis being placed on the developments of Solid self micro-emulsifying delivery system and dosage form of SMEDDS.

INTRODUCTION

Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system. A rate limiting step for the absorption of these drugs is often their solubilisation in the gastrointestinal tract. These drugs are classified as class IV drug by biopharmaceutical classification system (BCS). Oral route is the easiest and most convenient way of non-invasive administration. Oral drug delivery systems being the most cost-effective have always lead the world wide drug delivery market. This oral route may be a problem route for drug molecules that exhibit poor aqueous solubility.[5]

A drug has to be sufficiently soluble, because with some exceptions, passive diffusion of dissolved drug molecules from high to low drug concentration is the driving force of drug absorption. Different physicochemical and physiological properties determine the reasons for poor drug absorption, which are poor water solubility, low membrane permeability, carrier mediated drug efflux, drug metabolism, and pharmacological interactions.[6] Different formulation approaches like micronization, solid dispersion and complexation with cyclodextrins have come up.[8] Indeed in some selected cases, these approaches have been successful but they offer many other disadvantages. The main problem with micronization is chemical/thermal stability; many drugs may degrade and loose bioactivity when they are micronized by conventional method, for solid dispersion the amount of carriers used is often large and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. [9]

Realization that the oral bioavailability of poor water soluble drugs may be enhanced when co-administered with meal rich in fat has led to increasing recent interest in the formulation of poorly water soluble drugs in lipids. A successful strategy to improve the oral bioavailability of poorly water soluble drugs in vivo is the use of lipid containing dosage forms. Lipid formulation can reduce the inherent limitation of slow and incomplete dissolution of poorly water soluble drugs by facilitating the formation of solubilised phases containing the drug from which absorption may occur.

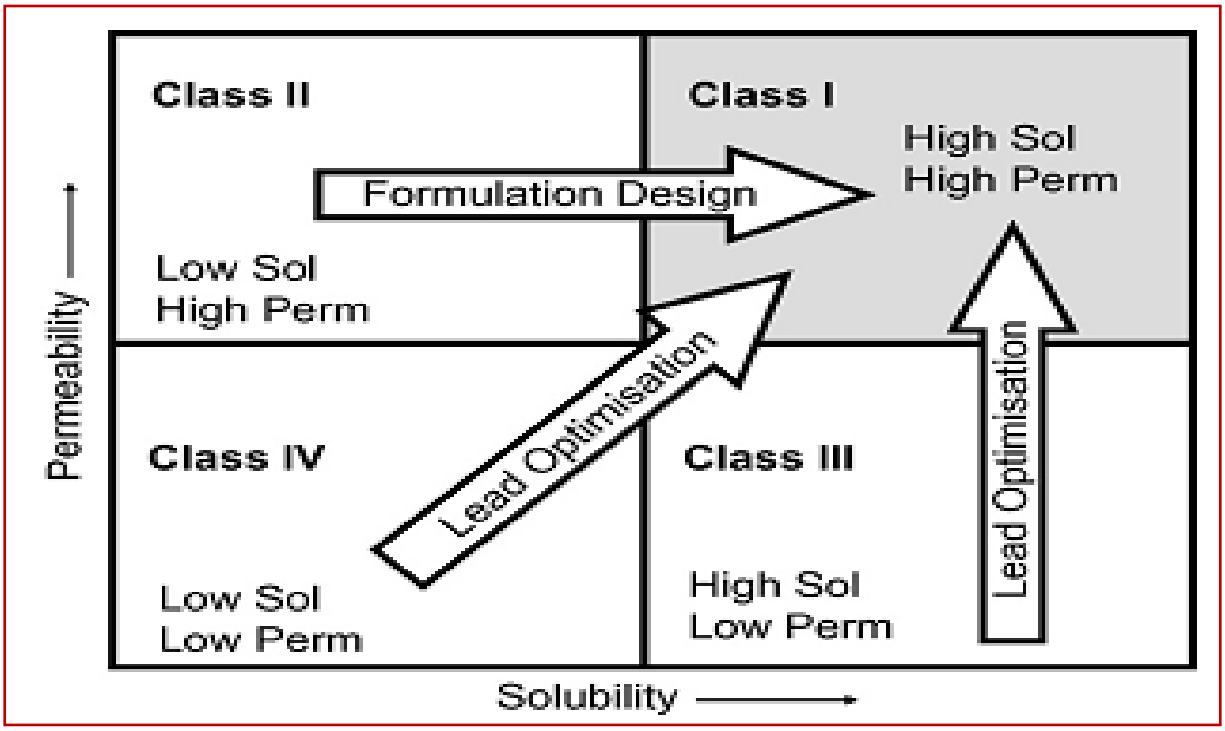
Solubility:

The Solubility of a substance at a given temperature is defined as the concentration of the dissolved solute, which is in equilibrium with the solid solute. Solubility of molecules depends on H-bond donor and acceptor properties of the molecule and of water and crystal lattice of molecule.

Table 1: Different solubility term used in the USP[11]

Descriptive term	Parts of solvent required for one part of solute	Solubility range (mg/ml)	Solubility Assigned (mg/ml)
very soluble	less than 1	>1000	1000
freely soluble	from 1 to 10	100-1000	100
Soluble	from 10 to 30	33-100	33
sparingly soluble	from 30 to 100	10-33	10
slightly soluble	from 100 to 1000	1-10	1
very slightly soluble	from 1000 to 10,000	0.1-1	0.1
practically insoluble	more than 10,000	<0.1	0.01

Figure 1: A representation of the biopharmaceutical classification system and strategy



The figure 1 indicating that absorption of a class IV drug can be markedly improved by attention to the formulation. If a class IV drug can be maintained in a solubilized state in the lumen of the gut one can achieve an absorption profile more like that of a class I drug. Formulation strategies can do little to improve the absorption of classes I and III drugs which are limited by poor membrane permeability. These are candidates for improvement the chemical level (i.e. lead optimization). SMEDDS will improve both solubility and permeability in case of BCS class II, III and IV drugs.

Lipid formulation system:

Lipid formulation system (LFS) has ability to deliver highly lipophilic drug and also increase bioavailability of these drug through various mechanisms such as transport of drug through lymphatic pathway (which bypasses hepatic metabolism), particle size reduction and increase in solubility of highly lipophilic drug in various gastric fluids[11].

Table 2: Lipid formulation classification system[6]

Typical composition (%)	Type I	Type II	Type III A	Type IIIB
1)Triglycerides or mixed Glycerides	100	40–80	40–80	20
2) Surfactants	-	20–60 (HLB ‹ 6)	20–40 (HLB ‹ 11)	20–50 (HLB ‹ 11)
3) Hydrophilic Cosolvents	-	-	0-40	0-50
Particle size of dispersion (nm)	Coarse	100–250	100–250	50–100
Significance of aqueous dilution	Limited importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity
Significance of Digestibility	Crucial requirement	Not crucial but likely to occur	Not crucial but may be inhibited	Not required and not likely to occur

In practice 'lipid' formulations are a diverse group of formulations which have a wide range of properties. This results from the blending of up to five classes of excipients Lipid formulation classification system:, ranging from pure triglyceride oils, glycerides, lipophilic surfactants, hydrophilic surfactants and water-soluble cosolvents[6].

Formulations which comprise drug in solution in triglycerides and/or mixed glycerides are classified here as 'Type I'

- Type I formulation may well be the system of choice, in view of its simplicity and biocompatibility.
- Type II lipid formulations constitute SEDDS. Self-emulsification is generally obtained at surfactant contents above 25% (w/w). However, at higher surfactant contents (greater than 50–60% (w/w) depending on the material) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface[9].
- Type II lipid-based formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above

generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs.

- Type III lipid-based formulations, commonly referred to as self-microemulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>6) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further segregated 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. Type IIIB formulations typically achieve greater dispersion rates when compared with Type IIIA although the risk of drug precipitation on dispersion of the formulation is higher given the lower lipid content. Among the various LFS, self microemulsifying drug delivery system (SMEDDS) has gained interest after successful commercialization of cyclosporine A (Sandimmune® Neoral).

Self micro-emulsifying drug delivery systems (SMEDDS) :

SMEDDS are physically stable, isotropic mixtures of oil, surfactant, co-surfactant and solubilized drug substance which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation[13].

SMEDDS are suitable for oral delivery in soft and hard gelatin capsules. Depending on the excipient selection and relative composition of the formulation, aqueous dilution will result in spontaneous formation of lipid droplets ranging in size from approximately 100 nm (SEDDS) to less than 50 nm (SMEDDS) [8].

The optimum concentrations or concentration ranges of oil, surfactant and co-surfactant necessary to promote self-emulsification are determined by construction of a pseudo- ternary phase diagram, which should also assess the effect of drug loading on the efficiency of self-emulsification.

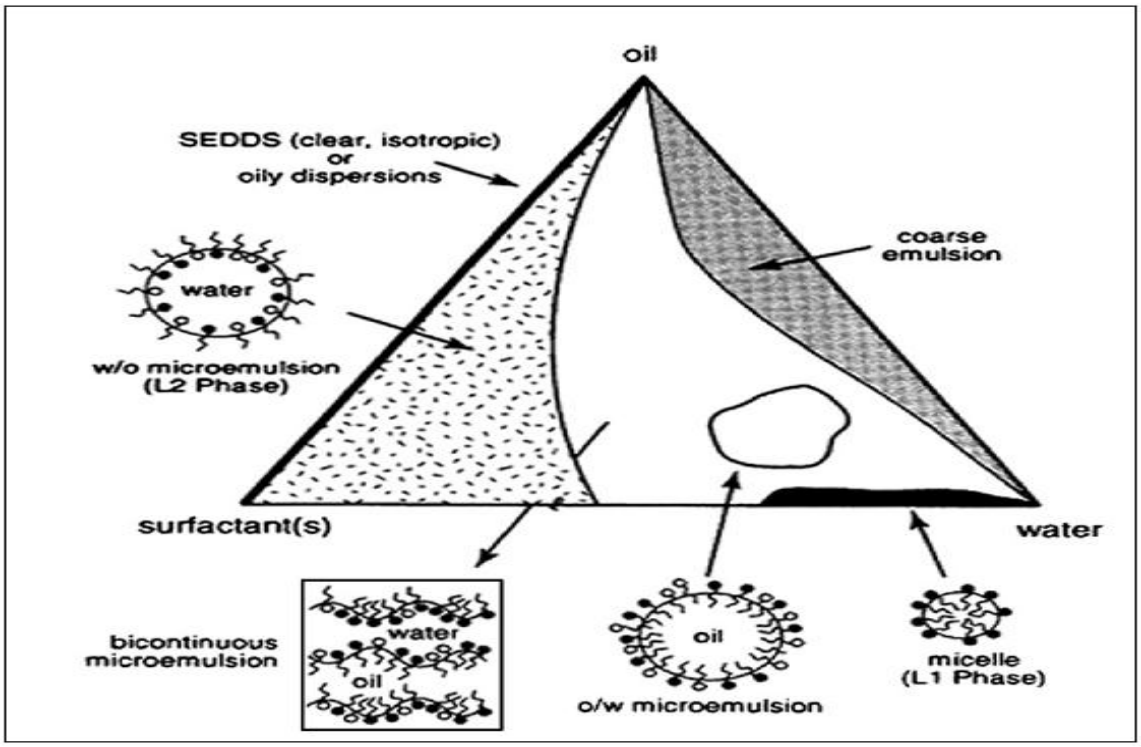


Figure 2: A schematic pseudo-ternary phase diagram of an oil/surfactant/water system with illustrating the microemulsion, emulsion, and micellar phases[13].

Excipients used in SMEDDS:

SMEDDS consists of oil, a surfactant and a co-surfactant.

I) Oil

A number of natural oils derived primarily from plant sources and processed to remove impurities or to isolate various fractions of the original product, are available and suitable for use in encapsulated oral formulation products. Naturally occurring oils and fats are comprised of mixtures of triglycerides which contain fatty acids of varying chain lengths and degrees of unsaturation. The melting point of a particular oil increases in proportion to the fatty acid chain lengths and decreases with increasing degree of unsaturation, which also increases the relative susceptibility to oxidation. Triglycerides are classified as short (< 5 carbons), medium (6–6 carbons) or long chain (> 6 carbons) and may be synthetically hydrogenated to decrease the degree of unsaturation, thereby conferring resistance to oxidative degradation. Short chain triglycerides are intestinal lumen leading to drug precipitation

Table 3: Classifications of lipids used in SEDDS [14]

Class	Chemical Name	Trade Name
LCTs	Various names	Corn oil, Soybean oil, Safflower oil
MCTs	Glyceryl tricaprylate/caprate	Fractionated coconut oil, Captex® 500, Miglyol® 810, Miglyol® 86, Neobee® M-5
Propylene glycol Esters	Propyleneglycol monocaprylate, Propylene glycol monolaurate	Capmul®PG 8, Capmul® PG 16 , Lauroglycol®
Fatty acids	cis-9 Octadecanoic acid	Oleic acid
	Hexadecanoic acid	Palmitic acid
	Octadecanoic acid	Stearic acid
Monoglycerides, or diglycerides	Glyceryl caprylate/caprate	Capmul®MCM, Imwitor® 742
	Glycerol monocaprylate	Imwitor® 308
	Glycerol monooleate	Capmul® GMO
Lipid Mixtures	SaturatedC8-C18 triglycerides	Gelucire® 33/01

II) Surfactants

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable shows in (Table 4). The most widely recommended ones are the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). The commonly used emulsifiers are various solid or liquid polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80). Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants. However, these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. Usually the surfactant concentration ranges between 30% and 60% w/w in order to form stable SEDDS. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. Surfactants are amphiphilic in nature and they can dissolve or solubilise relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SEDDS.

Table 4: Emulsifiers or surfactants used in SEEDS[15]

Chemical Name	Trade Name	HLB
Polyoxyethylene 20 sorbitan monolaurate	Polysorbate20 (Tween® 20)	16.7
Polyoxyethylene20sorbitan monopalmitate	Polysorbate40 (Tween® 40)	15.6
Polyoxyethylene 20 sorbitan monostearate	Polysorbate60 (Tween® 60)	14.9
Polyoxyethylene 20 sorbitan monooleate	Polysorbate80 (Tween® 80)	15.0
Sorbitan monooleate	SPAN® 80	4.30
Sorbitan trioleate	SPAN® 85	1.80
Sorbitan monostearate	SPAN® 60	4.70
Polyoxyethylene 20 sorbitan monolaurate	Polysorbate20 (Tween® 20)	16.7
Sorbitan monopalmitate	SPAN® 40	6.70
Sorbitan monolaurate	SPAN® 20	8.60
Polyoxyl 35 castor oil	Cremophor® EL	6–14
Polyoxyl 40 hydrogenated castor oil Polyoxyethylene polyoxypropylene	Cremophor® RH40	14–16
block copolymers	Poloxamer188 (Pluronic® F68)	29
	Poloxamer407 (Pluronic® 67)	22
Unsaturated polyglycolized glycerides	Labral® M265, M1944	4.0
Saturated polyglycolized glycerides	Gelucire® 44/14, 50/13	13–14
PEG-8 Caprylic/Capric glycerides	Labrasol®	14
PEG-8 Caprylic/Capric glycerides	Labrafac® CM10	10
Tocopherol PEG succinate	Vitamin E TPGS	13
Polyoxyl 40 stearate	Myrj® 52	16.9

III) Co-surfactant:

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co-surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value. At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more

surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. This process known as 'spontaneous emulsification' forms the microemulsion. However, the use of co-surfactant in self emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SEDDS but also to solubilisation of the drug in the SEDDS. Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self emulsifying drug delivery systems, although alcohol- free self-emulsifying microemulsion have also been described in the literature. Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug. On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Hence, proper choice has to be made during selection of components.[16]

Digestion and Absorption of SEDDS:

Lipids, unlike many excipients, whether present in food or as discreet pharmaceutical additives, are processed both chemically and physically within the GIT before absorption and transport into the mesenteric lymph. Indeed, most of the effects mediated by formulation-based lipids or the lipid content of food are mediated by means of the products of lipid digestion molecules that may exhibit very different physicochemical and physiological properties when compared with the initial excipient or food constituent.

- Ingested triglycerides are digested by the action of lingual lipase in the saliva and gastric lipase and the pancreatic lipase co-lipase complex in the stomach and small intestine respectively.
- These sequential processes convert essentially water-insoluble, non-polar triglyceride into progressively more polar diglycerides, monoglycerides, and fatty acids. The end point of digestion of one molecule of triglyceride is the liberation of two molecules of fatty acid and one molecule of 2-monoglyceride. In addition to the chemical breakdown of ingested lipids, the physical properties of lipid digestion products are markedly altered to facilitate absorption.

- Initial lipid digestion products become crudely emulsified on emptying from the stomach into the duodenum (because monoglycerides and diglycerides have some amphiphilic, emulsifying properties, and gastric emptying provides sufficient shear to provoke emulsification).
- The presence of partially digested emulsion in the small intestine leads to the secretion of bile salts and biliary lipids from the gallbladder that stabilize the surface of the lipid emulsion and reduce its particle size, presenting a larger lipid surface area to the pancreatic lipase/co-lipase digestive enzymes.
- In the presence of sufficient bile salt concentrations, the products of lipid digestion are finally incorporated into bile salt micelles to form a solubilized system consisting of fatty acids, monoglycerides, bile salts, and phospholipid—the so-called intestinal mixed micellar phase.

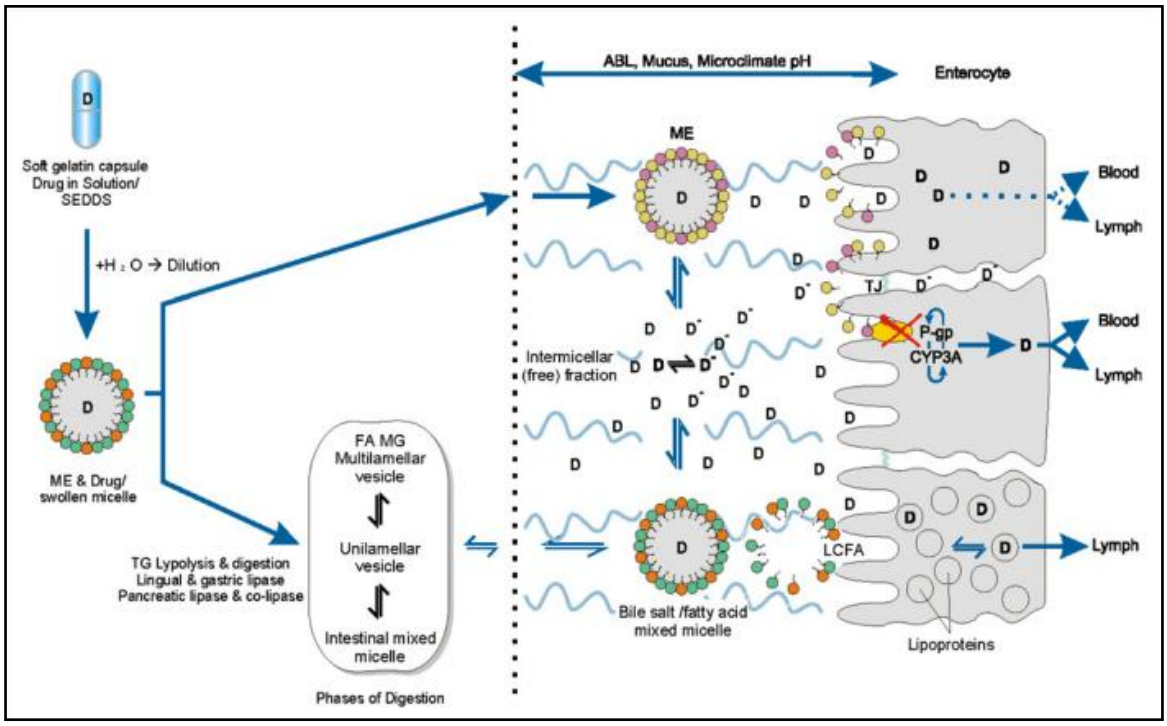


Figure 3: Release and absorption of a drug in vivo when administered as an oily dispersion. Formulation-mediated mechanisms of enhanced drug absorption include:

(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/or metabolism by gut membrane-bound CYP450 enzymes

(D) Enhanced lymphatic drug transport occurring in conjunction with stimulation of lipoprotein/chylomicrons production.

The effects of lipids on the absorption of co-administered poorly water-soluble drugs may also be classified from a mechanistic perspective as ‘‘physicochemically’’ mediated effects (solubility, dissolution, surface area) and ‘biochemically’’ mediated effects (metabolism, transport related events).[17]

Oral absorption Enhancement by Means of Physicochemical Mechanisms:

Oral absorption enhancement appears to have been mediated by way of improved drug dissolution from lipid solutions (compared with aqueous suspensions) and enhanced drug solubility in the lipid-bile salt-rich GI contents. SEDDS increases oral absorption in terms of physicochemical mechanisms by decreasing globule size and improved drug dissolution. SEDDS emulsify spontaneously when it comes in contact with gastric fluid with particle size in between 20 -200 nm.

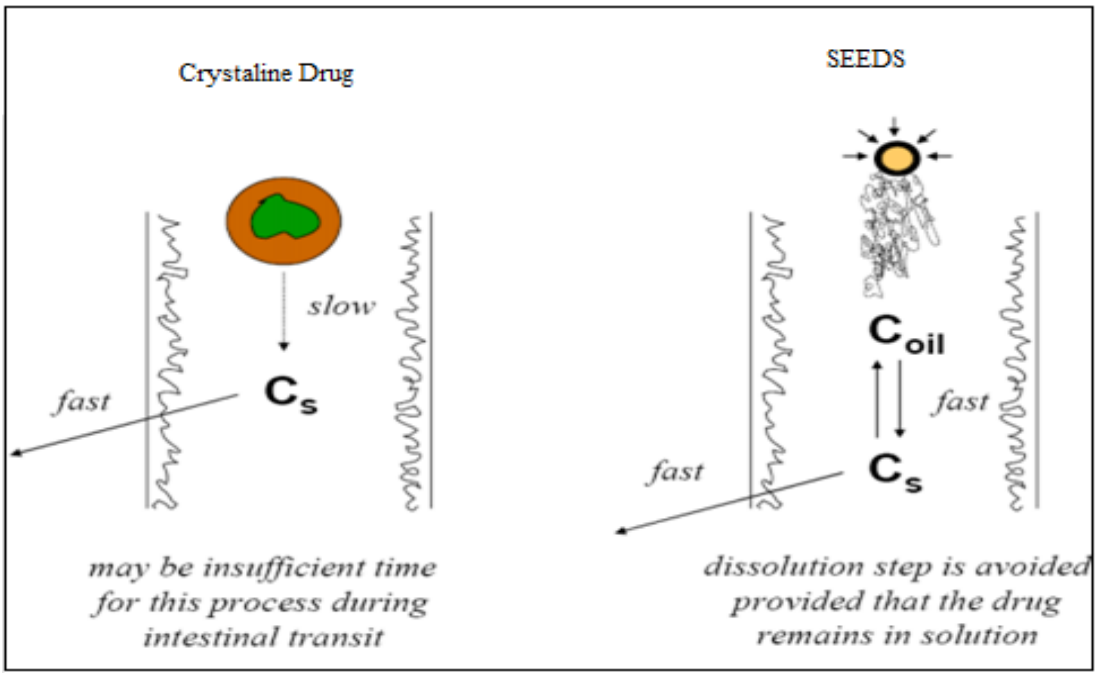


Figure 4: SEDDS avoiding dissolution step[18]

A recent literature survey has described in some detail the potential for many lipids to inhibit both CYP3A-based metabolic processes and p-glycoprotein–mediated anti-transport processes. The literature survey indicate that the use of essential oils to improve bioavailability and presents data detailing the inhibitory capacity of essential oils using in vitro drug metabolism screens. Surfactants found in many dispersed lipid formulations have also been shown to inhibit the extent of p-glycoprotein–mediated efflux.

Lipids and Targeting to the intestinal lymph

- As described previously, digested dietary lipids (in the form of fatty acids and monoglycerides) are absorbed into the enterocyte, re-esterified to form triglyceride, and subsequently assembled into colloidal lipid aggregates or prelipoproteins.
- Prelipoproteins then fuse with the basolateral membrane of the enterocyte, facilitating entry into the lamina propria. The colloidal structure and size of intestinal lipoproteins subsequently precludes their absorption into the blood capillaries (because the capillaries of the small intestine have a continuous ‘‘tight’’ endothelial structure).
- The structure of the intestinal lymphatic vessels, however, is notably different, and lymphatic endothelial cells have relatively open intercellular junctions. Estimates of intercellular junctional distances range from several microns to 15–20 nm and consequently, intestinal lipoproteins are almost exclusively absorbed into the intestinal lymphatics.
- The collecting lymphatic from the small intestine and the ascending and transverse colon join to form the superior mesenteric lymph duct, which runs by means of the thoracic lymph into the systemic circulation directly, illustrating that drugs that are transported to the systemic circulation by means of the intestinal lymph avoid the first-pass metabolic effects inherent in absorption by means of the portal blood.
- Because drug access to the intestinal lymphatic primarily depends on drug association with lymph lipoproteins, compounds that are inherently lymph directing or ‘‘lymphotropic’’ must be extremely lipophilic.[19]

ADVANTAGES OF SEDDS:

Improvement in Solubility and bioavailability:

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of class-IV drug (low solubility/low permeability). In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate oil-in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore, increase in AUC i.e. bioavailability and C max is observed with many drugs when presented in SEDDS.[27]

Ease of manufacture and scale-up:

Ease of manufacture and scale-up is one of the most important advantage that makes SEDDS unique when compared to other drug delivery systems like solid dispersions, liposomes,

nanoparticles, etc., dealing with improvement of bio-availability. SEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of industry in the SEDDS.[28]

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. Several research papers specifying that, the performance of SEDDS is independent of food and, SEDDS offer reproducibility of plasma profile are available.

Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT:

One unique property that makes SEDDS 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. The intestinal hydrolysis of prodrug by cholinesterase can be protected if polysorbate 20 is emulsifier in micro emulsion formulation. These systems are formed spontaneously without aid of energy or heating thus suitable for thermo labile drugs such as peptides.[36]

No influence of lipid digestion process:

Unlike the other lipid-based drug delivery systems, the performance of SEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SEDDS are not necessarily digested before the drug is absorbed as they present the drug in micro-emulsified form which can easily penetrate the mucin and water unstirred layer.[29, 37]

Increased drug loading capacity:

SEDDS 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.[30]

Protection against Biodegradation:

The ability of self emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic pH in stomach, enzymatic degradation or

hydrolytic degradation etc. Such drugs when presented in the form of SMEDDS can be well protected against these degradation processes as liquid crystalline phase in SMEDDS might be an act as barrier between degrading environment and the drug. Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an acid environment. When the drug was formulated in a Galacticles™ oral lipid matrix system (SEDDS formulation) and compare with a commercial formulation, it showed the good plasma profile as compare to reference formulation. The oral bioavailability of undegraded acetylsalicylic acid is improved by 73% by the Galacticles™.[38]

Oral Lipid Matrix System formulation compared to the reference formulation. This suggests that the SMEDDS formulation has a capacity to protect drugs from degradation in the GI tract. Super-saturated SMEDDS contain a reduced amount of a surfactant and a water soluble cellulosic polymer (or other polymers) to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. The SEDDS formulations can result in enhanced oral absorption as compared with the related self micro-emulsifying drug delivery systems (SMEDDS) formulation and the reduced surfactant levels may minimize gastrointestinal surfactant side effects. Oral drug delivery systems are designed address the varied challenges in oral delivery of numerous promising compounds including poor aqueous solubility, poor absorption, and large molecular size. These are both liquid and powder-in-capsule products comprising our self-emulsifying liquid crystalline nano-particles (LCNP) technology (featuring Cubosome®, Hexosome®, and Flexosome™).Liquid crystalline nano-particles (LCNPs) are excellent solubilizers. Compared with conventional lipid or non lipid carriers, LCNPs show high drug carrier capacity for a range of sparingly water-soluble drugs. For drugs susceptible to *in-vivo* degradation, such as peptides and proteins, LCNP vehicles protect the sensitive drug from enzymatic degradation. The LCNP systems also address permeability limitations by exploiting the lipid-mediated absorption mechanism. For water-soluble peptides typical bioavailability enhancements range from twenty to more than one hundred times. In an alternative application large proteins have been encapsulated for local activity in the gastrointestinal tract.[31]

DRAWBACKS OF SMEDDS:

One of the obstacles for the development of self micro-emulsifying drug delivery systems (SMEDDS) and other lipid-based formulations is the lack of good predicative in vitro models for assessment of the formulations. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug. To

mimic this, an *in-vitro* model simulating the digestive processes of the duodenum has been developed. This *in-vitro* model needs further development and validation before its strength can be evaluated. Further development will be based on in-vitro and in-vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested *in-vivo* in a suitable animal model. Future studies will address the development of the *in-vitro* model. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered. Moreover, volatile co-solvents in the conventional self micro-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs. [32, 39]

CONCLUSION:

Self micro-emulsifying drug delivery systems are way for the formulation of drug compounds with poor aqueous solubility. The oral delivery of such drugs can be made possible by SMEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SMEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs. As improvements or alternatives of conventional liquid SMEDDS, S-SMEDDS are superior in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Numerous studies have confirmed that SMEDDS substantially improved solubility/dissolution, absorption and bioavailability of poorly water-soluble drugs. It is also worth pointing out some issues to which much attention should be paid, for example physical aging phenomenon associated with glyceride, oxidation of vegetable oil , and interaction between drugs and excipients . Selection of suitable excipients is the main hurdle of developing S-SMEDDS. Thus, these aspects should represent the major future working directions for S-SMEDDS. Thus major breakthroughs are still required for proper development of SMEDDS.

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CONFLICT OF INTEREST:

Authors declare no conflict of interest.

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