Review Article

Self – Micro Emulsifying Drug Delivery System: A Potential Solution to the Challenges of Oral Delivery of Poorly Water – Soluble Drugs

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ABSTRACT

The oral route is the most patronized for drug administration. However, this route is only suitable for bioactive compounds that possess adequate aqueous solubility and in vivo stability. Approximately 40% of bioactive compounds have poor aqueous solubility which limits their oral delivery. In a bid to improve the oral bioavailability profiles with minimum doses of such poorly water – soluble and lipophilic drug molecules, various approaches in drug delivery have been developed. These include rational use of surfactants, micronization, complexation with cyclodextrins, utilization of permeation enhancers, solid dispersions, nano size delivery and lipid – based systems. Recently, greater attention has been drawn to the formulation of poorly water – soluble drug molecules as self - micro emulsifying drug delivery systems (SMEDDS). The self - emulsification of SMEDDS has been argued as the basis for the observed improved oral bioavailability of drugs formulated as such. Furthermore, SMEDDS enhance oral bioavailability by facilitating the intestinal lymphatic transport mechanism and thereby avoid hepatic first – pass effect. In this article, an overview of recent advances in the study of SMEDDS and improvement of pharmacokinetic parameters of lipophilic and poorly water – soluble drug molecules is captured. This review further presents case studies in which enhanced oral bioavailability of poorly water – soluble drugs were demonstrated in vivo by using the SMEDDS technology. There is overwhelming evidence from this review to support the claim that SMEDDS do improve bioavailability of poorly soluble drugs.

Keywords: Enhanced absorption, Intestinal lymphatic pathway, Lipophilic, Oral bioavailability, Poor aqueous solubility, SMEDDS.

INTRODUCTION

The oral route of drug administration is one of the most target by many formulators for the delivery of pharmacologically active substances in the formulation technology.[1] Related advantages of the oral route include ease of administration, convenience, non – invasiveness and relative cost – effectiveness compare to other delivery routes. However the oral route may be problematic for drug molecules that are both lipophilic and poorly water – soluble. When a drug is administered per the oral route, relevant steps towards its absorption among others may include dissolution of the active compound in the gut fluid followed by permeation across the columnar absorption cell membrane of the gastro intestinal tract. Furthermore, the oral route may be limited by other associated physicochemical properties of the drug including instability and extensive first-pass metabolism, all of which decrease oral bioavailability. Approximately 40% of new chemical entities discovered are characterized with low aqueous solubility and thereby do not present themselves as potential candidates for development in oral formulations. Potential formulation challenges related to these molecules may include among others non linearity of dose - response relationship, poor rate and extent of oral absorption profile as well as high subject variability in terms of intra assay and inter assay assessment.[2] A significant influential factor for the poor oral absorption qualities of these drugs has been identified to be related to their limited solubility in the gastro intestinal tract. According to the biopharmaceutics classification system (BCS), most of these molecules belong to classes II and IV and are generally characterized by poor aqueous solubility coupled with either high and/or low gut permeability. Typical examples of drugs in this category include cyclosporine - A, saquinavir, dexamethasone and ritonavir. Others are halofantrine, tamoxifen, griseofulvin and clarithromycin. In various approaches to resolving the related formulation or delivery challenges a couple of pharmaceutical technique has been developed and advanced with the underlying mechanism of enhancing the drug's solubility and maintaining it in a solubilized state throughout its passage through the gastro intestinal tract.[3,4] Rational use of surfactants, micronization, complexation with cyclodextrins and liquisolid techniques are some of the potential strategies that have been successfully applied in this direction.[5] Others are utilization of salt formation, pH changes, use of permeation enhancers and nano size delivery.[6] Further techniques may involve the use of solid dispersions and incorporation of the actives in lipid – based systems.[7, 8] Essentially some of these approaches have been applied with considerable level of successes. However, they are not without related limitations. In the commercial manufacturing of emulsified formulations, a couple of related challenges, notably stability and manufacturing processes limitations among others may be encountered. Utilization of SMEDDS technology has emerged as one of the suitable techniques in resolving some of these challenges.[9] In recent times greater interest and/or attention has been generated in

the development of lipophilic and low solubility drug molecules in SMEDDS based on observations that both the extent and rate of oral absorption of these compounds are significantly improved when co - administered with meals rich in fats and oils. Subsequently lipid – based solutions, suspensions, emulsions and pre - concentrates have been successfully utilized as drug delivery techniques of choice to enhance the bioavailability profile of many drugs that are characterized with poor aqueous solubility. SMEDDS are isotropic systems whose fundamental components are made up of oil, surfactant, co-surfactant and the active drug. Other relevant excipients may include consistency builder, enzyme inhibitor, precipitation inhibitor, adsorbent and polymers. Self – micro emulsified formulations are physically stable and easily lend themselves to manufacture, and can be converted to solid intermediates for encapsulation into gelatin capsules. SMEDDS play vital role in the delivery of lipophilic and poorly water – soluble drugs by using lipids as carriers.[10] Upon dispersion in the gastro intestinal fluid, these systems spontaneously generate drug - containing micro emulsions with large surface area that readily transform into mixed micelles, vesicles and other related colloidal structures which possess the potential of significantly enhancing solubilization and thereby improving absorption and oral bioavailability of incorporated drugs. A further absorption enhancement by the micro emulsion may occur as a result of an enhanced digestion by the gastro intestinal endogenous enzymes. Alternatively, a possible direct absorption, devoid of the rate - determining dissolution process, from the encapsulated micro emulsified droplet due to increased partitioning of drug into the aqueous phase of the intestinal fluids may also occur.[11] Furthermore, micro emulsion may facilitate absorption via intestinal lymphatic pathway and avoidance of hepatic first pass metabolism. This concept has contributed significantly to the commercial SMEDDS formulations Sandimmune Neoral™ (Cyclosporin - A), Novir (Ritonavir) and Fortovase (Sequinavir).[12]

The biopharmaceutics classification system (BCS)

BCS serves as a working guideline or an experimental model that may be utilized in the assessment and evaluation of permeability and solubility parameters of drug molecules. Furthermore, the model was developed to provide requisite guidelines or aid in the regulation of post - approval changes and generic formulations. Since the oral route constitutes the principal route of delivery for majority of formulations, the BCS model utilized the oral delivery as a base or blueprint in its design. The BCS model also serves as a fundamental framework for predicting in vitro - in vivo correlations for a couple of immediate release formulations.[13] The basis of this concept is due to the recognition that drug solubility or dissolution properties and gastrointestinal permeability are the fundamental parameters governing the rate and extent of drug absorption. In the year 2000, the FDA promulgated the BCS as a science - based mechanism to allow waiver of in vivo bioavailability testing of some immediate - release solid oral dosage forms. In accordance with BCS concepts, drug substances are classified with associated respective challenges or limitations into four (4) main types as summarized in Table 1.

Table 1: Summary of the BCS indicating the four classes of bioactive molecules[14]

BCS Class	Aqueous Solubility	Membrane Permeability	Related Limitations/Challenges
Class I	High	High	Enzyme degradation, gut wall efflux.
Class II	Low	High	Solubilization and bioavailability (BA).
Class III	High	Low	Enzyme degradation, gut wall efflux, bioavailability
Class IV	Low	Low	Solubilization BA, Enzyme degradation, gut wall efflux

In practice, the model places a given drug molecule that is intended for oral dosing in one of the four categories depending on its solubility and permeability properties. If the highest clinical dose strength of a given drug molecule is soluble in 250 ml or less of aqueous media over a pH range of 1 – 7.5 at a temperature of 37° C then that drug molecule may be deemed to be 'highly soluble'. If the extent of the absorption of a given drug molecule in humans is estimated to be higher than or equal to 90% of an administered dose based on a mass balance determination or relative to a reference intravenous dose, then that drug molecule may be deemed to be 'highly permeable'.[14] A variety of methods is available for determination of permeability but the Caco - 2 cell lines technique, an assay that lends itself to high throughput automation is the type that is patronized quite often. Each BCS drug category is associated with related limitations or challenges. However delivery of relevant drug molecule in SMEDDS formulations may offer significant contributions towards development of appropriate measures in addressing some of these challenges.

The lipid formulation classification system

The lipid formulation classification system – LFCS that was established in the year 2000 serves as a fundamental guideline or a working model in the design and development of lipid – based formulations. However in the year 2006, the model was reviewed and resulted in the inclusion of an extra type of lipid – based drug delivery system.[15] On the basis of the physicochemical properties of a drug molecule, the model may be utilized in the identification and design of the most appropriate

formulation type as well as predicts probable in vivo performance of the related formulation. Furthermore the model contributes significantly to the use of systematic and rationale formulation approach that is devoid of screening iterations and provides a credible framework to guide regulatory agencies. In accordance with the LFCS model, lipid – based formulations may be classified into four (4) categories: Types I, II, III A, III B and IV as summarized in Table 2. This is conducted in accordance with their composition, globule size of dispersed phase (nm) and possible effects of dilution on their solvation efficiency. The classification may further be dependent on the significance of digestion process influence on the in vivo performance of the related formulation.

Table 2: Summary of the lipid formulation classification system – LFCS.[15]

	TYPE - I OIL	TYPE - II SEDDS	TYPE - III		TYPE – IV OIL - FREE
			III ASEDDS	III B SMEDDS	
Glycerides - (TG, DG, MG) %	100	40 – 80	40 – 80	< 20	-
Surfactants (HLB < 12) %	-	20 – 60	-	-	0 – 20
Surfactants (HLB > 12) %	-	-	20 - 40	20 - 50	20 – 80
Co-solvent – Hydrophilic %	-	-	0 - 40	20 - 50	0 – 80
Particle size (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 and potential loss of solvent capacity	Significant phase changes and potential loss of solvent capacity
Significance of digestibility	Crucial need	Not crucial but likely to occur	Not crucial but may be inhibited	Not required	Not required

Lipid – based formulation type I: These systems are usually composed of active drug(s) that is (are) uniformly dissolved and/or dispersed in triglycerides and/or mixed glycerides. They may also be delivered as oil-in-water emulsions that are stabilized by low concentrations of the related surfactant and/or co-surfactant components.[16-17] The dispersion qualities of lipid – based formulation type I systems in aqueous medium is generally poor. Furthermore for credible in vivo performance of this formulation type, active digestion by gastro intestinal tract enzymes such as pancreatic lipase and co-lipase is a requirement. Although type I lipid - based formulations appear to be simple, they are only suitable for drug candidates whose oil - solubility potential is high enough to allow complete solubilization and incorporation of the required effective or therapeutic dose in the system.

Lipid – based formulation type II: This group of lipid - based formulations constitutes the self - emulsified drug delivery systems – SEDDS.[18]. Generally, the requisite surfactant concentration levels for effective self - emulsification is at least 25% (w/w). However, higher surfactant concentration levels of between 50% – 60% (w/w) may compromise the stability of the system. At these higher surfactant concentrations the process of self - emulsification may be impaired as a result of in situ generation of highly viscous liquid - crystalline gels at the oil/water interface.[19] One of the advantages of type II lipid - based formulation is the ability to resolve a slow dissolving step challenge which is typically observed in the dissolution and related absorption pattern of drug candidates which are characterized with poor aqueous solubility. These systems possess the propensity of significantly reducing the interfacial tension and thereby creating large interfacial areas at the oil/water interface. These processes facilitate efficient drug partitioning between the oil droplets and the aqueous phase which leads to enhanced dissolution and absorption.[20-21]

Lipid – based formulation type III: This group of lipid - based systems constitutes the self - micro emulsified drug delivery systems – SMEDDS. SMEDDS can be further sub - divided into two categories namely, type III A and type III B. Generally type III B SMEDDS are formulated with higher concentrations of hydrophilic surfactants and co – surfactants and thereby possess higher hydrophilic character than corresponding type III A formulations. Thus type III B formulations are designed in such a way that as the contents of hydrophilic surfactants and co-solvents increases that of the lipid/oil reduces. In comparing the two formulations following aqueous dilution, type III B is preferred to type III A as the former system readily and

spontaneously disperses in aqueous phase more than the latter. However, the risk of drug precipitation on dispersion of the type III B formulation is higher than that of the type III A owing to the related lower lipid/oil content. Following aqueous dilution coupled with moderate agitation formulation type III A produces fine emulsions while type III B produces transparent emulsion systems.

Lipid – based formulation type IV: This group of lipid – based formulations are usually composed of predominantly hydrophilic surfactants and co – surfactants. They do not possess any natural lipid in their composition and thereby are the most hydrophilic of all the formulations. Following aqueous dilution and moderate agitation type IV formulations readily and spontaneously form transparent systems in the form of micelle solution. Relative to the other formulations that contain simple glyceride lipids, type IV systems offer the largest drug dosing capacity. However, only a scanty report is available on the in vivo solubilization capacity of these systems. Furthermore, little information is available on whether they are equally capable of maintaining drugs with low aqueous solubility in solution throughout the gastric transit time. A typical example of type IV formulation is amprenavir (Agenerase) which contains d–α–Tocopheryl Polyethylene Glycol 1000 Succinate - TPGS as a surfactant and polyethylene glycol - PEG 400 and propylene glycol as co-solvents.[22]

Self - micro emulsifying drug delivery system (SMEDDS)

The development of SMEDDS technology, as a strategy for overcoming formulation and bioavailability challenges of lipophilic and poorly water – soluble drug molecules may principally be attributed to the formulation's self – emulsification properties. These systems are characterized by the unique ability of spontaneously forming fine oil – in - water micro emulsions upon dilution in aqueous media, such as gastro intestinal fluids, following moderate agitation.[23] Within the g.i.t., the aqueous medium requirement for self – emulsification is provided by the intestinal fluid while the requisite means of agitation is also provided by the peristalsis movements of the stomach and the intestines. One of the principal differences between self - emulsified drug delivery systems (SEDDS) and SMEDDS is that following aqueous dilution, the former typically produces opaque emulsions with an average droplet size falling within the range of 100 nm - 300 nm, while the latter produces clear micro emulsions with average droplet size of less than 50 nm.[24] Other potential characteristic dissimilarities between SEDDS and SMEDDS are as summarized and depicted in Table 3.

A lipophilic drug that is delivered as SMEDDS in small droplet size within the above – mentioned dimensions and uniformly distributed form may result in a system possessing significant enhancement of the dissolution and permeability profiles. Another characteristic feature of SMEDDS is related to their ability of providing large interfacial area between the oil and water phases leading to enhanced drug partitioning.[25] It may thereby be argued that for lipophilic and poorly water - soluble drug molecules whose rate and extent of absorption are dissolution rate-limited, their formulation and delivery in SMEDDS may offer significant enhancement in the related solubilization and oral bioavailability profile of the drug. Furthermore SMEDDS formulations may offer advantages such as potential reduction in drug dose, credible and/or reproducible blood – time profile and prevention of drug from hostile gastric environment which will further facilitate better systemic absorption.

Table 3: Some characteristic differences between SEDDS and SMEDDS formulation.[26]

Character	SEDDS	SMEDDS
Appearance	Opaque	Transparent
Oil content	40 – 80% w/w	< 20% w/w
Droplet size	>100 nm	<50 nm
Phases	Biphasic	Monophasic
Stability	Unstable	Stable
Viscosity	High	Low
Interfacial tension	High	Ultra low
Energy requirement	Large energy	Low energy
Bioavailability	Low	Enhanced
Autoclaving	Not applicable	Applicable
Delivery form	Only solutions	Varieties; tablet, capsule, pellet etc.

Typical examples of drug molecules whose formulation and delivery in SMEDDS has resulted in enhanced pharmacokinetic profiles especially oral bioavailability profiles are shown in Table 4.[27] In principle the formulation of SMEDDS is comparatively simple. However, a basic and most relevant step involves the formulation excipients selection, especially the most appropriate choice of oil: surfactant mix pair and a related ratio scheme that can dissolve and maintain the therapeutic dose or concentration of the drug throughout the product's shelf – life.

Table 4: Pharmacokinetic and bioavailability profile of some poorly water – soluble drugs following administration in SMEDDS.[27.]

Compound	Pharmacokinetic observations after study
Clarithromycin	Increased Cmax, and AUC; reduced Tmax from SMEDDS.
Atovaquone	BA 3-fold higher from SMEDDS.
Cyclosporine	Increased BA and Cmax; reduced Tmax from SMEDDS Increased AUC and dose – linearity; reduced food effects from SMEDDS
Halofantrine	Tend to higher BA from LCT - SMEDDS
Ontazolast	Increased BA of at least 10 – fold from all lipid based formulations
Simvastatin	Increased BA; 1.5 – fold higher from SMEDDS formulations
Atorvastatin	BA significantly increased from all SMEDDS formulations
Itraconazole	Increased BA and reduced food effects.
Danazole	BA from LCT – solutions and LCT – SMEDDS 7 – fold and 6 – fold higher than that from MCT – SMEDDS.
Seocalcitol	BA from LCT – SMEDDS = MCT - SMEDDS

Mechanism of self – emulsification

Self – emulsification process may be expressed mathematically, by the equation provided below.

$$\Delta G = \sum N \prod r^2 \sigma$$

Where ΔG is the free energy; N is the number of droplets; r is the radius of droplet; σ is the interfacial energy.

From the above equation, the free energy of the system, which is the principal stability determinant, is directly proportional to the interfacial energy. Generally, the lower the free energy, the more stable the system. When the energy requirement for dispersion of droplets exceeds that required for droplet formation, then self – emulsification occurs.[20]. In conventional emulsions, high energy is required to produce new interface between the two immiscible phases, hence the related free energy is relatively high. Subsequently, conventional emulsions are not more stable and the two phases tend to separate. However in SMEDDS formulations, as the free energy is very low and may even become negative, new interface and emulsion formation occur instantaneously. On exposure to aqueous medium and followed with mild agitation, rapid interface is formed between the two phases. The aqueous phase progressively passes through the interface into the oil phase and becomes encapsulated in the oil phase in a drug - dissolved form until the solubilization limit is attained. Dispersed liquid crystalline phase occurs as a result of increased water penetration into the oil phase and the related quantity is dependent on the surfactant concentration. Other reports have it that when SMEDDS formulation is subjected to mild agitation, water penetration occurs spontaneously and leads to disruption of the interface with subsequent formation of liquid crystalline globules.[28] Micro emulsions are thermodynamically stable systems and thereby a credible equilibrium exists, although there is continuous exchange of matter between the two phases. Fusion of small droplets followed by fission of larger droplets into small droplets which later coagulate with other droplets constitute the apparent two different approaches of exchange of matter between the two phases.[29] These series of events subsequently lead to self – emulsification and the improved stability of the system is attributed to the dispersed liquid crystalline phase which prevents coalescence of oil globules.

Mechanism of improved oral bioavailability by SMEDDS

The enhanced oral bioavailability profiles of poorly water – soluble drug molecules delivered in SMEDDS, in the gastro intestinal structure is controlled by a couple of potential mechanisms. These may include accelerated drug dissolution processes and facilitation of the formation of solid solution within the carrier via the reduction of particle size to the molecular level.[30] Other mechanisms may involve dynamic changes in drug uptake, disposition and efflux pump systems by altering enterocyte - based as well as intestinal lymphatic transport systems.[31, 32]. Although these mechanisms are not completely understood, other potential complimentary bioavailability enhancing systems may involve the following schemes:

a) Effective alterations: Alterations in the gastric transit time offer significant influence on the bioavailability profile of drugs following oral administration. Prolonging the gastric transit time leads to a corresponding increment in the time of exposure of the drug to the absorption site. This results in increased overall dissolution, absorption and improved bioavailability profile.[33]

b) Increased solubility of drug in the intestinal lumen: Following oral administration of SMEDDS, exogenous lipid materials are introduced into the g.i.t. The presence of these materials trigger off increased secretion of endogenous lipid – based active substances such as phospholipids (PL), cholesterol (CH) etc. and bile salts (BS). Integration of these active substances/products with other intestinal materials may lead to the formation of BS/PL/CH complexes generating into intestinal mixed micelles, vesicles and other colloidal structures whose collective effects results in increased solubilization capacity of the gastro intestinal fluid. Moreover significant swelling effects on micelles, vesicles and related colloidal structures,

following intercalation of exogenous lipids into the bile salts, phospholipids and cholesterol structures may result in a further increase in the solubilization capacity of gastric fluid and thereby enhanced absorption rate as well as improved bioavailability profile of the incorporated drug molecule.[34]

c) Intestinal lymphatic transport mechanism: The intestinal transport mechanism of the lymphatic system lends itself as a useful tool that may be utilized to improve the oral bioavailability profile of lipophilic and poorly water – soluble drugs. A drug-loaded SMEDDS formulation that utilizes long chain triglyceride as the lipid base component may be predominantly and preferably absorbed through the lymphatic pathway (chylomicrons) instead of the portal pathway via the hepatic system. Such delivery systems avoid passage through the hepatic system and hence the first - pass metabolic effects and thereby leads to increased bioavailability. This restricted lymphatic transport is mainly due to low lymph – to - blood flow ratio. Lipid based delivery systems like lopinavir loaded solid lipid nanoparticles (SLN) was found to deliver high amount of drug in to lymphatic circulation compared to the control (pure drug) due to avoidance of first - pass extraction of the drug.[35] However SMEDDS formulations of lipophilic drugs based on medium chain triglycerides may utilize the hepatic portal system as the predominant route of absorption and may thus be exposed to the metabolic effects of the liver. Notwithstanding, the observed enhanced bioavailability profiles of some of these formulations may be attributed to a probable increase in drug dissolution that might have resulted from a large surface area generated by micro emulsification.[36] It has been established that drug molecules that possess partition coefficient (log P) values greater than 5 and quantitative solubility values of more than 50 mg/ml in triglycerides constitute potential candidates for intestinal lymphatic transport mechanism. This assertion was investigated by comparing the lymphatic transport mechanisms of dichloro diphenyl tetrachloroethane - DDT (possessing log P 6.19) and hexachlorobenzene - HCB (possessing log P 6.53). While both compounds appear to possess similar log P values, the former exhibits 13 – fold increment in triglyceride solubility over the latter, following oral administration of both compounds formulated in oleic acid. Approximately 33.5% of the administered dose of DDT was recovered in the lymph system. In the case of HCB the percentage recovery in lymph system of the administered dose was approximately 2.3%. This difference which was estimated to be significant was attributed to the 13 - fold difference in their comparative solubility in triglyceride.[37] However, drug molecules that possess both high log P values and exhibit high solubility in triglycerides are not always guaranteed to be potential candidates to be preferably transported by the intestinal lymphatic system. Penclomedine, has log P value of 5.48 and exhibits triglyceride solubility of 175 mg/ml but was observed to be poorly transported by the intestinal lymphatic transport mechanism. Approximately 3% of the administered dose was recovered in the lymphatic system in a case study.[38]. Several reports have been documented on the significant contributions offered by lymphatic transport mechanisms on enhanced bioavailability of lipid - based formulations. It is important to note that only few studies involving SMEDDS formulations have been documented so far.

d) Biochemical processes in the gastro intestinal tract – g.i.t. Alterations in the biochemical activities of the g.i.t. by administered drug loaded SMEDDS may offer significant improvement in the oral bioavailability profiles of incorporated poorly water – soluble drug molecule. It has been reported that the activities of certain intestinal efflux transporters are capable of being inhibited by some lipids, related digestion products and surfactants. The inhibitory effect is due to competition for binding with the efflux transporter and membrane perturbation caused by the formulation excipients, notably surfactants. The residence time of the drug can be prolonged by this inhibition of efflux mechanism.[39]. These attenuated activities may result in significant increase in the oral bioavailability profiles of incorporated poorly water – soluble drugs. Inhibitory effects of some lipids on p – glycoprotein efflux pump mechanisms and thus reducing the extent of enterocyte - based metabolism and subsequently leading to increased bioavailability profiles has been reported.[40]

e) Physical processes in the gastro intestinal tract – g.i.t. Alterations in certain physical barrier activities/structures in the g.i.t. following oral administration of drug loaded SMEDDS is linked to enhancement in the absorption rate and bioavailability profiles of incorporated drug. An observed enhanced permeability profile is reported to be attributable to changes in the physical barrier activities/structures, precisely opening of tight junctions in the g.i.t., produced by combined effects of lipids, related digestive products and surfactants.[41]

Advantages of SMEDDS

SMEDDS formulations offer a couple of formulation and performance advantages over similar and related lipid – based drug delivery systems such as liposomes, nanoparticles, solid dispersions, SEDDS etc. These may include but not limited to the following:

a) Bioavailability profile enhancement: A number of drugs that are both poorly water - soluble and lipophilic in nature exhibit low oral bioavailability profiles that is governed by the related dissolution rate. The absorption rate of such drug molecules is therefore dependent on the aqueous solubility of the molecules. The cumulative effect of all these processes challenges the pharmaceutical formulator. A breakthrough in this formulation challenge seems to be the utilization of the SMEDDS technology. SMEDDS formulations possess a unique character of delivering drugs to the gastro intestinal tract in a well dissolved, uniformly dispersed and micro emulsified form (with globule size between 1 - 100 nm) and thereby generating significantly increased specific surface area in the gut. This phenomenon results in enhanced drug membrane

permeability and subsequently increased rate and extent of absorption (bioavailability). Halofantrine SMEDDS formulation exhibited approximately 6 - 8 fold enhancement in oral bioavailability compared to the conventional tablet formulation of Halofantrine.[42]

b) Manufacturing and scale - up status: In addition to the oral bioavailability enhancement, SMEDDS formulations offer another outstanding advantage over some of the other related lipid – based formulations in terms of its unique ease of manufacture and scale – up qualities. The preparation of SMEDDS involves simple procedures and equipment such as a mixer, an agitator, volumetric liquid filling machine, capping and labeling machine. The low inputs in terms of equipment need is a major underlying factor for the keen interest expressed by majority of industries that are applying and/or utilizing the SMEDDS technology.

c) Inter - assay and intra - assay subject variability and food effects:

The significantly high inter – assay and intra – assay subject variability in absorption exhibited by many drugs pose a formulation challenge in terms of drugs' in vivo performance and patients' compliance. Another major factor that may significantly influence the in vivo performance of many drugs is the presence of food materials in the gut. However, these formulation limitations may be significantly reduced by formulating such drugs in SMEDDS. There are several published reports of independence of SMEDDS performance on food effects as well as the reproducibility of credible plasma profile by SMEDDS formulations.[43]

d) No influence of lipid digestion process: The in vivo performance of many orally administered lipid – based formulations is severely influenced by a couple of gastro intestinal mediated processes. These may among others include lipolysis, emulsification by bile salts, action of pancreatic lipases/co-lipases and mixed micelle formation. However SMEDDS formulation is an exception to this limitation as they are not necessarily digested before absorption. In SMEDDS formulation, the drug is delivered in a highly solubilized and micro - emulsified form to the g.i.t which leads to an increase in the available surface area for absorption, increased drug partitioning and a further increase in drug's membrane permeability. All these phenomena cumulate in enhanced oral bioavailability of the drug.

e) Elimination of enzymatic hydrolysis of peptides and related compounds in the g.i.t. SMEDDS formulations are capable of safe delivery of macromolecules like peptides, hormones, enzyme substrates, inducers and inhibitors**,** unlike the other related lipid – based formulations. This unique character of SMEDDS makes it superior to the other oral lipid – based delivery systems. Furthermore the elimination of enzymatic hydrolysis of peptides and related compounds in the g.i.t. by SMEDDS formulations as reported in literature is another hallmark of the SMEDDS technology. The cholinesterase - induced intestinal hydrolysis of many a pro - drug can be eliminated if a tween (such as polysorbate 20) is utilized as the surfactant in the related micro emulsified formulation.[44]. The spontaneous formation of SMEDDS requires no heat energy. This makes SMEDDS the oral drug delivery system of choice for thermo labile drug molecules such as the peptides, hormones and enzymes among others.[45]

f) Influence on drug loading capacity: SMEDDS formulations offer increased loading capacity of incorporated drugs compared to conventional lipid solutions. The basis for this assertion may be attributed to a report that drug molecules that exhibit poor aqueous solubility and possess intermediate partition coefficient, log P values of between 2 and 4 are typically less soluble in natural lipids. However these molecules demonstrate high solubility in amphiphilic systems such as surfactants, co-surfactants and co-solvents.[45] However this assertion is subject to further studies and research.

Recent researches and rationale of SMEDDS in various drug categories

A couple of case studies involving recent developments and justification or rationale of SMEDDS in various drug categories were investigated. Some of the observations that were made in these investigations with the SMEDDS technology are briefly outlined below.

A study conducted by Chen Y. et al., reported that SMEDDS technology proved supreme over traditional solid dispersion – SD technology in improving solubility, dissolution, bioavailability, and intestinal permeability profiles of the poorly water – soluble and hydrophobic drug vinpocetine (VIP).[46] In solubility analysis, vinpocetine – loaded SMEDDS (VIP – SMEDDS) demonstrated a 17.3 – fold increment over that of the traditional solid dispersion (SD) delivery system. In the dissolution assessments, an improved dissolution rate of vinpocetine, coupled with better stability was observed in SMEDDS relative to the SD. In bioavailability analysis, the VIP - SMEDDS was compared to VIP crude powder and the former demonstrated a 1.89 - fold increment in the related bioavailability. However when the VIP in SD was compared to the VIP crude powder, the related bioavailability was equivalent. A 2.65 - fold improvement in apparent permeability of vinpocetine was exhibited by the VIP - SMEDDS when compared to the vinpocetine - loaded solid dispersion, VIP - SD. A 9.6 - fold widening of the width of the cell tight junctions of Caco - 2 cell monolayer was achieved when subjected to treatment with VIP - SMEDDS. However no significant change was observed when the Caco - 2 monolayer was treated with VIP – SD.

Wu L. et al., investigated the drug delivery potentials of SMEDDS, solid dispersion and ß - cyclodextrin inclusion systems on the oral bioavailability of AJS a lipophilic and poorly water - soluble novel compound.[47] A 3.4 - and 35.9 - fold increments in oral bioavailability of AJS - SMEDDS over the solid dispersion - SD and cyclodextrin inclusion systems

respectively were observed. Furthermore, the Cmax of AJS - loaded SMEDDS was approximately 2 - and 40 - times as that of the two comparators respectively. This is an evidence or practical demonstration of SMEDDS technology superiority over solid dispersion - SD and ß – cyclodextrin inclusion technology as drug delivery systems for enhancing oral bioavailability of poorly water - soluble drugs.

It has been documented that cyclosporine A – loaded SMEDDS (Neoral soft gel capsule) exhibited a 6.5 – fold increment in oral bioavailability of the poorly water – soluble drug over cyclosporine A – loaded SEDDS, (Sand - immune soft gel capsule).[48] Yocum D. E. et al., conducted a comparative study involving Neoral and Sand - immune in a safety and efficacy assessments in severe active rheumatoid arthritis. They reported that a significantly lower increase in dose from baseline was observed with Neoral. Pharmacokinetic analysis indicated a significant increase in absorption, enhanced oral bioavailability and significantly decreased variability with Neoral relative to Sand – immune.[49]

Zvonar et al. investigated a series of furosemide - loaded - SMEDDS and reported improved solubilization and permeability profiles. This study also showed that the dissolution rate of furosemide from the SMEDDS microcapsule was significantly higher than that of a reference microsphere.[50] Furthermore, an enhanced permeability of furosemide in SMEDDS formulation was observed. This was attributed most probably to the SMEDDS formulation capability of altering apical membrane fluidity, opening tight junctions and inhibiting efflux transporters that were responsible for furosemide transfer in the gut.[51]

The formulation and evaluation of curcumin – SMEDDS in liquid and pellet forms were investigated by Setthacheewakul S. et al. In a drug release or dissolution study, the curcumin – loaded SMEDDS in liquid and pellet formulations exhibited a 16 – fold increment over that of the curcumin aqueous suspension. Pharmacokinetic analysis revealed a 14 - and 10 - fold greater oral absorption from liquid and pellet curcumin - SMEDDS formulations respectively, over the curcumin aqueous suspension. In a stability study, the curcumin - loaded SMEDDS liquid and pellets formulations demonstrated good stability under intermediate and accelerated testing conditions over a period of six months.[52] This study illustrates the potential of the SMEDDS technology in improving the oral delivery of hydrophobic and poorly water – soluble drugs such as curcumin.

Factors affecting SMEDDS performance

Identifiable and variable factors that may affect the performance of SMEDDS may include but not limited to the following:

a) Therapeutic concentration of drug molecule (Drug dose): The effective therapeutic concentration of the drug molecule is one of the important factors that influence the performance of SMEDDS formulations. Generally drug molecules requiring larger effective therapeutic concentrations do not present as potential candidates for SMEDDS development. However if such drug molecule exhibits extreme solubility in the lipid phase, it may be recommended for development and delivery by SMEDDS. Drugs molecules with log P values of approximately 2 and poorly water – soluble are most difficult to develop and formulate in SMEDDS.

b) Lipid/oil solubility of drug molecule: The capability of a SMEDDS formulation to maintain the incorporated drug in solid solution or solubilized state depends to a larger extent on the lipid or oil solubility qualities of the drug molecule. When the contribution offered by surfactant/co - surfactant mix to drug's solubilization is significant, then dilution of such SMEDDS formulation may result in significant decrease in the solubilization potential of the system. This may subsequently lead to crystallization or precipitation of the drug molecule from the system. To assess the possibility of drug precipitation in the g.i.t. following oral administration, equilibrium solubility measurements techniques are employed. Within the solubilizing and colloidal solubilizing environment in the g.i.t., precipitation or crystallization of certain drug molecules could be extremely slow and under these conditions a 'super saturated' system may be produced. Report has it that after initial emulsification in lipid – based formulations, a precipitated drug can remain in a super saturated state for up to twenty four hours while the attainment of solubility equilibrium may take up to five days.[4] It may thereby be argued on this basis that in such formulations drug absorption in the gut might take place long before or even be completed before a possibility of drug precipitation. Indeed documented reports show that super saturation could actually enhance the rate and extent of absorption by increasing the thermodynamic activity of the drug. However there is the urgent need for further studies to investigate and predict the fate of drug loaded SMEDDS formulations in relation to the super saturation concept as available report in this domain is scanty.

c) Polarity status of lipid phase: The nature and magnitude of the polarity of the oil/lipid phase is one of the principal factors governing the performance of drug loaded lipid – based formulations. Essentially, the type of forces existing in the system as well as the affinity of drug molecules for oil or water phase is highly dependent on the polarity factor. In a given SMEDDS formulation, a direct relationship has been established to exist between the polarity of the system and rate of drug molecules release.[21]. This assertion was observed and further reported in a study that involved investigations into the relationships between polarity and drug release rate in idebenone - loaded SMEDDS. It was observed that the formulation that possessed the highest polarity was associated with the highest drug release rate.[53]

Notwithstanding the above - mentioned related challenges of SMEDDS, these formulations have a couple of breakthrough potentials as far as drug delivery in the pharmaceutical industry is concerned. Recent researches in SMEDDS technology may include but not limited to the

delivery of drug molecules like curcumin, vinpocetine, ariethole trithione, ritonavir, saquinavir and halofantrine. Others are paclitaxel, idebenone, cyclosporine and alprostadil, some of which are indicated earlier in this review.

Super - saturable SMEDDS (s – SMEDDS)

Surfactants and co-surfactants which constitute relevant components of SMEDDS development are established to be related with various levels of formulation limitations including stability and undesirable toxic effects. In an attempt to address this and other related limitations, new techniques in SMEDDS formulations have been introduced into the pharmaceutical industry. This has led to the design and development of the super - saturable self - micro emulsified drug delivery systems (s - SMEDDS).[54] The underlying principle of the s - SMEDDS approach is that on exposure to aqueous medium such as the gastro intestinal fluid a protracted supersaturated system of the incorporated drug and the formulation is generated from which enhanced absorption of the drug may be achieved. In the supersaturated state, the thermodynamic activity of the lipophilic drug is extended beyond its solubility limit, paving the way for an increased driving force for enhanced absorption and improved bioavailability profile.[54] Principal formulation constituents of s - SMEDDS include the lipophilic drug, surfactant/co-surfactant in reduced concentrations and a polymeric precipitation - inhibitor or crystallization – inhibitor. In practice commonest precipitation inhibiting agents that may be utilized include polymeric hydroxy propyl methyl cellulose (HPMC) and related polymeric cellulose materials. The precipitation inhibiting agent is intended to facilitate the generation and stabilization of the drug in the temporarily supersaturated form for prolonged period of time.[55]. A typical example of this class of formulation is paclitaxel – s-SMEDDS whose development utilized HPMC as the precipitate inhibiting agent. A comparative dissolution and pharmacokinetic study between paclitaxel – s-SMEDDS and paclitaxel – SMEDDS formulations was performed. Following in vitro aqueous dilution, the s - SMEDDS formulation yielded a clear micro emulsion which on standing for a specified period of time produced a slow crystallization or precipitation of paclitaxel crystals. This observation is an indication that a supersaturated system of paclitaxel was produced and the rate of precipitation was prolonged by the incorporated HPMC. However the conventional SMEDDS formulation underwent rapid precipitation following in vitro aqueous dilution, yielding a solution of low paclitaxel concentration. This observation was attributed to the absence of polymeric HPMC and hence the absence of super saturation in this system. The comparative pharmacokinetic study revealed significant supremacy of the paclitaxel - loaded s - SMEDDS formulation over the conventional paclitaxel - loaded SMEDDS formulation. While approximately a 10 - fold higher maximum plasma drug concentration (Cmax) and a 5 - fold higher oral bioavailability of value 9.5% were observed in the s - SMEDDS formulation, the orally administered control Taxol formulation exhibited an oral bioavailability value of approximately 2.0% of the administered dose. Furthermore the conventional SMEDDS formulation that was produced without HPMC showed a bioavailability value of approximately 1%.[55] In the development of s - SMEDDS formulation, utilization of polymeric HPMC as crystallization inhibitor compels a significant reduction in the concentration of surfactant required. This allows the production and stabilization of a temporary supersaturated solution with enhanced solubilization potential. Under these circumstances, a high free drug concentration would be produced via the generated and stabilized supersaturated solution in vivo. This would lead to a related increase in the driving force for enhanced absorption and bioavailability profile.[54]. An added formulation advantage offered by s - SMEDDS formulation approach over conventional SMEDDS formulation is related to a better toxicity/safety profile assessment. This is attributed furthermore to the significant reduction in the concentration of surfactant requirement in the s - SMEDDS approach. The mechanisms of the precipitation inhibition as well as the generation and stabilization of super saturation by the polymeric cellulose materials are not clearly understood. Although intensive investigations are currently underway, better and clearer understanding of these mechanisms continue to remain a challenge.[24]. There is therefore the urgent need for further and extensive investigations into these limitations so as to facilitate appropriate development of the s - SMEDDS technology.

CONCLUSIONS

SMEDDS technology is a promising delivery mechanism for improving oral bioavailability as well as other pharmacokinetic profiles of drug molecules that are lipophilic and poorly water - soluble. With rational application of this technology, the oral delivery of poorly water – soluble and lipophilic drugs can be made possible since SMEDDS have demonstrated the potential of significantly enhancing the oral bioavailability profiles of such molecules. Therapeutic drug dose reduction, reproducible plasma drug concentration – time profiles, selective targeting of drug towards specific sites in the gut and protection of drugs from the hostile environment in the gut are further advantages offered by the SMEDDS technology. With future developments, SMEDDS appear a huge potential to making significant contributions in resolving the delivery challenges that are associated with oral formulation of poorly water - soluble drugs, especially the BCS classes II and IV drugs which may further be hydrophobic.

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