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AN REVIEW ON (SMEDDS) SELF MICRO-EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

In pharmaceutical solubility is one of the biggest problem to formulate the suitable dosage form because according to new chemical (drug) entities around 40% drug exhibit poor aqueous solubility and low bioavailability. The 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. Novartis Pvt. Ltd. Neoral TM (Cyclosporine A), and Fortovase (Saquinavir), Roche Laboratories Inc. much focused on self micro-emulsifying drug delivery systems (SMEDDS). SMEDDS are surfactant, isotropic mixtures of oil, co-surfactant and drug with a unique ability to form fine oil in water micro emulsion upon mild agitation following dilution with aqueous phase. The hypothesis behind dissolution rate enhancement with SMEDDS is the spontaneous formation of the emulsion in the gastrointestinal tract which presents the drug in solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption.

Keywords: SMEDDS, Biopharmaceutical Aspects**,** Excipients.

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 solubilization in the gastrointestinal tract [1]. These drugs are classified as class II drug by Biopharmaceutical classification system (BCS), high permeability.and drugs with poor aqueous solubility. Various techniques like solid dispersion, micronization, and complexation with cyclodextrins. The problem with micronization is thermal / chemical stability, many drug may degrade and lose 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.

Complexation with cyclodextrins techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents. Realization that the oral bioavailability of poor [2] 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. Lipid suspension, solutions and emulsions have all been used to enhance the oral bioavailability but, more recently there have been much focus on the utility of self–micro emulsifying drug delivery systems (SMEDDS) [3].

Lipid Formulation Classification System

The different lipid drug delivery systems available include lipid emulsion, lipid solution, microemulsion, dry emulsion etc all these different systems and due to large number of possible[4] excipient combinations that may be used to assemble it in a single lipid-based formulations, self-emulsifying systems in particular a classification systems known as lipid formulation classification system (LFCS) [4].

Type I

This systems 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 [5,6].

Type II

Self-emulsification is generally obtained at surfactant contents above 25% (w/w). The progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface.

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Type II lipid-based formulations provide the advantage of overcoming the slow dissolution.

Type III

Type III formulations can be further segregated into Type IIIA and Type III B 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 IV

Type IV formulations does not contain natural lipids and represent the most hydrophilic formulations [7-9].

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

Biopharmaceutics Classification System (BCS) was introduced in 1995 it is based on the recognition that drug solubility/dissolution properties and gastrointestinal permeability.Some example are as follow which belongs to II, III and IV classes.

Permeability

In the absence of evidence suggesting instability in the gastrointestinal tract[9], a drug substance is considered *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered[16] dose based on mass balance determination or in comparison to an intravenous reference dose.

Solubility

A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1 to 7.5 (at 37°C) [10].

Advantages of SMEDDS

- It increases solbility , oral bioavailability, Dissolution rate dependant. The ability of SMEDDS to present the drug to GIT in solubilised and micro emulsified form (globule size between 1-100 nm) like in case of halofantrine approximately 6-8 fold increase in bioavailability of drug was reported in comparison to tablet formulation [11].
- The performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation.

Advantages of SMEDDS over Emulsion

- SMEDDS not only offer the same advantages of emulsions of facilitating the solubility of hydrophobic drugs, but also overcome the drawback of the layering of emulsions after sitting for a long time. SMEDDS can be easily stored since it belongs to a thermodynamics stable system.
- Micro emulsions formed by the SMEDDS exhibit good thermodynamics stability and optical transparency. The major difference between the above micro emulsions and common emulsions lies in the particle size of droplets[12]. The size of the droplets of common emulsion ranges between 0.2 and 10 μm, and that of the droplets of micro emulsion formed by the SMEDDS generally ranges between 2 and 100 nm are known as droplets of nano particles
- SMEDDS offer numerous delivery options like filled hard gelatin capsules or soft gelatin capsules or can be formulated in to tablets whereas emulsions can only be given as an oral solutions.

EXCIPIENTS USED IN SEDDS

Pharmaceutical acceptability of excipients and the toxicity issues of the components used makes the selection of excipients really critical. There is a great restriction as which excipeints to be used. Early studies revealed that the self-micro emulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-micro emulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient selfmicroemulsifying systems.

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 [13]. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80). Safety is a major determining factor in choosing a surfactant [14]. 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[15]. 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

Oils

The oil represents one of the most important excipients in the SMEDDS formulation not only because it can solubilize the required dose 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 triglyceride [15,16]. Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Furthermore, edible oils which could represent the logical and preferred lipid excipient choice for the development of SMEDDS are not frequently selected due to their poor ability to dissolve large amounts

of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties [17,18].

Co-solvents

The selection of surfactant and co-surfactant is crucial not only to the formation of SMEDDS, but also to solubilisation of the drug in the SMEDDS [19]. 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 cosurfactant in the self-emulsifying drug delivery systems, although alcohol- free self-emulsifying microemulsions have also been described in the literature [20]. 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.

Pseudo Ternary Phase Diagrams

Phase diagrams are useful tools to determine the number and types of phases, the wt% of each phase and the composition of each phase at a given temperature and composition of the system. These diagrams are three-dimensional but are illustrated in two-dimensions for ease of drawing and interpretation [21]. Fig. 2 shows phase micro-emulsion /existence area for Fenofibrate SMEDDS.

EVALUTATION OF SMEDDS

Particle size

The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption [22]. Photon correlation spectroscopy (PCS) is a useful method for determination of emulsion droplet size especially when the emulsion properties do not change upon infinite aqueous dilution, a necessary step in this method. However, microscopic techniques should be employed at relatively low dilutions for accurate droplet size evaluation. Emulsion droplet polarity is also a very important factor in characterizing emulsification efficiency. The HLB, chain length and degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier have an impact on the polarity of the oil droplets [23-25].

Zeta potential

The charge of the oil droplets of SMEDDS is another property that should be assessed. The charge of the oil droplets in conventional SMEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1.0-3%, will yield cationic [26].

Biopharmaceutical Aspects

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs is well known[28]. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability *via* a number of potential mechanisms, including [27].

a) Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution [28].

b) Increases in effective luminal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilisation capacity of the GI tract

c) Changes in the biochemical barrier function of the GI tract[30]. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p glycoprotein efflux pump, and thus reduce the extent of enterocyte-based metabolism.

d) Changes in the physical barrier function of the GI tract [29-31]. Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties.

FACTORS AFFECTING SMEDDS

Polarity of the lipophillic phase

Sang-Cheol Chi, who observed that the rate of release of idebenone from SMEDDS is dependant upon the polarity of the oil phase used. The polarity of the lipid phase is one of the factors that govern the drug release from the micro emulsions [32].

Nature and dose of the drug

The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately are most difficult to deliver by SMEDDS. The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. As mentioned above if surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant [33]. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallisation could be slow in the solubilising and colloidal stabilizing environment of the gut [34].

PHARMACEUTICAL APPLICATIONS

- The lipid based formulations of HF-base afforded a 6-8 fold improvement in absolute oral bioavailability relative to previous data of the solid HF [35].

➢ An optimal paclitaxel microemulsion prepared by SMEDDS which is a mixture of paclitaxel, tetraglycol, cremophore ELP, and labrafill 1944 and a paclitaxel microemlsion containing poly(D,L-lactide –co-glycolide) (PLGA) in order to offer controlled release of paclitaxel was developed [36]. It was observed that the droplet size of microemulsion without PLGA was smaller than that of microemulsion containing PLGA by transmission electron microscopy (TEM).

➢ To study the effect of two SMEDDS containing labrasol with different dilutions on tight junctions was conducted. Changes in barrier properties of Caco-2 cell monolayers, [37] including transepithelial electrical resistance (TEER) and permeability to the paracellular marker i.e. mannitol, were assessed in response to dilutions and surfactant contents within formulations.

➢ Gentamicin was dispersed with a surfactant used for SMEDDS, labrasol, and the mixture was solidified with several kinds of adsorbents [38] microporous calcium silicate (florite RE), magnesium alumino meta silicate (Neusilin US2), and silicon dioxide (Sylysia 320).

➢ High plasma gentamicin levels were obtained the results suggest that an adsorbent system is useful as an oral solid delivery system of poorly adsorbate drugs such as gentamicin. Yet another study involved HPLC determination of anethole trithione (ATT).

➢ SMEDDS and tablets to rabbits, significant differences were found in main pharmacokinetic parameters of Tmax, Cmax and AUC0–8 between these two formulations, and a 2.5-fold enhancement of relative bioavailability of ATT was observed from the SMEDDS compared with tablets [39].

DOSAGE FORMS FROM SELF EMULSIFYING SYSTEM

➢ **Self-emulsifying tablets** The main objectives of this study were to study effect of formulation ingredients on the release rate of Ubiquinone and to evaluate an optimized selfnanoemulsified tablets formulation. The first prepared self nanoemulsion system containing Ubiquinone was prepared as nanoemulsion, this nanoemulsion was adsorbed by granular materials and then compressed to form tablets [40-42]. The optimized formulation of coenzyme Q10 self-nanoemulsified tablet dissolution profile showed that 80-90% drug release took place in 45 minute.

➢ **Self-emulsifying pellets** self-emulsifying pellets by wet granulation. Here they first developed a binder solution containing an oil (mono and diglycerides), polysorbate 80 and model drug nimesulide in different proportion. This oilsurfactant mixture was stirred then added to water to form Self- emulsifying system. Second step was to prepare granules from microcrystalline cellulose and lactose in a granulator. These binder solutions were sprayed on to the granules and pellets were formed by increasing the speed of the granulator. Pellets were able to generate significantly smaller droplets with respect to corresponding emulsions [42-46].

➢ **Self-emulsifying nanoparticle:** Nanoparticle technology can be applied to the formulation of self-emulsifying nanoparticle. One of the solvent was injection, in this method the prepared molten lipid mass contained lipid, surfactant and drug. This lipid molten mass was injected drop wise into a non-solvent system. This is filtered and dried to get nanoparticles. By this method 100 nm size particle with 70-75% drug loading efficiency was obtained [47-49].

➢ **Self-emulsifying beads :** Self emulsifying system can be formulated as a solid dosage form by using less excipient. Porous polystyrene beads with complex internal void structures were typically produced by copolymerizing styrene and divinely benzene. It is inert and stable over a wide range of pH, temperature and humidity. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and *in vitro* drug release from SES-loaded PPB [50-53].

FUTURE ASPECTS

➢ Super saturable SMEDDS (S-SMEDDS): The toxic effects of surfactant are well known and to use these surfactants at such a high level as typically used in SMEDDS formulations can lead to GI side-effects, thus to overcome this problem and to minimize the GI side effects a new class of super saturable formulations, called as super saturable SMEDDS (S-SMEDDS) formulations, have been designed and developed [54-56].

➢ The S-SMEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Surpersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier. The S-SMEDDS formulations contain a reduced level of surfactant and a polymeric precipitation inhibitor to yield and stabilize a drug in a temporarily supersaturated state. Hydroxypropyl methylcellulose (HPMC) and related cellulose polymers are well recognized for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time periods [57-59].

➢ A supersaturable self-micro emulsifying drug delivery system (S-SMEDDS) of paclitaxel was developed employing HPMC as a precipitation inhibitor with a conventional SMEDDS formulation. *In vitro* dilution of the S-SMEDDS formulation resulted in formation of a microemulsion, followed by slow crystallization of paclitaxel on standing. This result indicated that the system

was supersaturated with respect to crystalline paclitaxel, and the supersaturated state was prolonged by HPMC in the formulation. In the absence of HPMC, the SMEDDS formulation underwent rapid precipitation, yielding a low paclitaxel solution concentration [60-62].

Table 1. Biopharmaceutical classification system (BCS)

Class I	**High solubility**	**High permeability**
Class II	Low solubility	High permeability
Class III	High solubility	Low permeability
Class IV	Low solubility	Low permeability

Table 2. Drug belongs to II, III and IV classes

Class II	**Class III**	**Class IV**
Efavirenz	Chloramphenicol	Mesylate, Furosemide
Glibenclamide	Colchicines	Albendazole
Folic Acid	Ergometrine	Didancosine
Phenytoin Sodium	Cimetidine	Azathioprinei
Carbamazepine	Hydrochloride	Acetazolamide
Dapsone	Propyl thiouracil	Indinavir

Figure 1. Processing of lipid and co-administered Drug

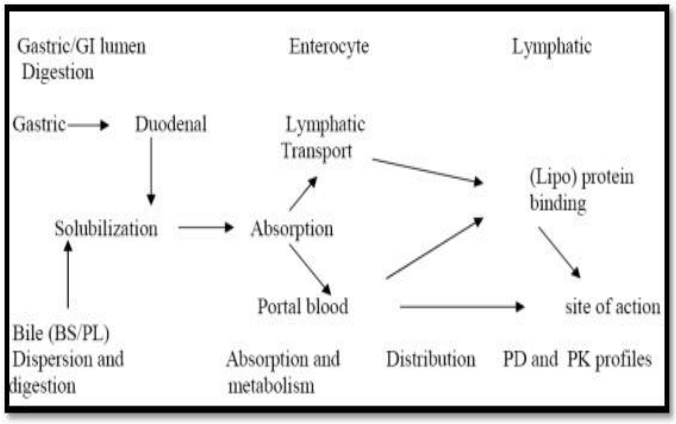
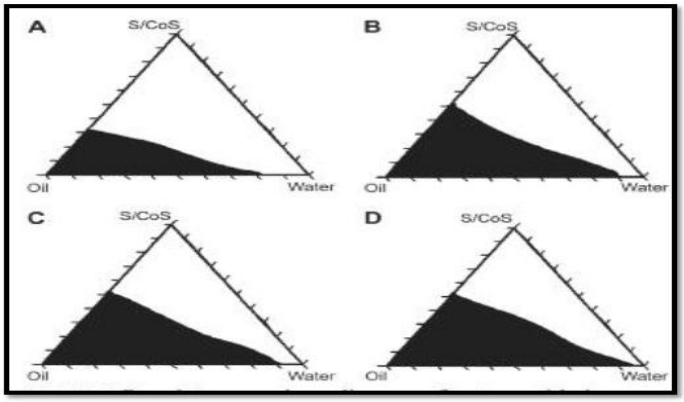


Figure 2. Shows phase micro-emulsion existence area for Fenofibrate SMEDDS



CONCLUSION

For the solubility dissolution, bioavailability and getting best therapeutics effect of poorly soluble drug Self emulsifying drug delivery system is the best solution. This is the method suited for lipophilic drugs where resulting emulsification gives faster dissolution rates and absorption. Solid SEDDS is superior to SEDDS in reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Solid SEDDS has the flexibility to develop into different solid dosage form for oral and parenteral administrations.

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