



A REVIEW ON SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM: AN APPROACH TO ENHANCE THE ORAL BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

Technology Catalysts International reported in 2002 that approximately 35-40% of all new chemical compounds suffer from poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low oral bioavailability. Several strategies to improve the solubility and dissolution of poorly water soluble drugs have been developed, which were at start primarily based on modifying the drug's physicochemical properties. 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. Lipid-based drug delivery systems have gained considerable interest after the commercial success of Sandimmune NeoralTM (Cyclosporine A), Novartis Pvt. Ltd. and Fortovase (Saquinavir), Roche Laboratories Inc. Self micro-emulsifying drug delivery systems are a class of lipid based drug delivery systems. Self micro emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, and co-surfactant and are a vital tool in solving low bioavailability issues of poorly soluble drugs. Lipophilic drugs can be dissolved in these systems, enabling them to be administered as a unit dosage form for per-oral administration. When such a system is released in the lumen of the gastrointestinal tract, it disperses to form a fine w/o microemulsion with the aid of GI fluid. This leads to in situ solubilization of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect. This article represents a complete review on self micro-emulsifying drug delivery system.

KEY WORDS: Self microemulsifying drug delivery system (SMEDDS), lipid based drug delivery systems, oral bioavailability, poorly water soluble drugs

INTRODUCTION

Oral route has always been preferred route for formulators and has dominated over other routes of administrations. However this preferred route is limited to those drugs molecule that are permeable across the gastric mucosa and are at least sparingly soluble. Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. A rate limiting step for the absorption of these drugs is often their solubilization in the gastrointestinal tract. These drugs are classified as class II drug by Biopharmaceutical classification system (BCS), drugs with poor aqueous solubility and high permeability. Different formulation approaches like micronization, solid dispersion, and complexation with cyclodextrins have come up¹. There are some approaches to improve the oral bioavailability of poorly water soluble drugs²; those approaches are use of surfactants, co-solvency, solid dispersions, salt formation, nano and micro suspension, cyclodextrin and lipid based drug delivery system.

Indeed, in some selected cases, these approaches have been successful. In recent years, much attention has focused on lipid-based formulations to improve the oral bioavailability of poorly water soluble drug compounds. In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils, surfactant dispersions, self emulsifying formulations, emulsions and liposomes with particular emphasis on self-emulsifying drug delivery systems (SEDDS)³.

Self micro emulsifying drug delivery systems (SMEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. The basic difference between self emulsifying drug delivery systems

(SEDDS) also called as self emulsifying oil formulation (SEOF) and SMEDDS is SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS⁴.

However, poor palatability due to lipidic composition leads to poor patient compliance and acceptability and due to their water content, micro emulsions cannot be encapsulated in soft gelatin and hard gelatin capsules⁵. A feasible substitute is Self Micro Emulsifying Drug Delivery System (SMEDDS), an anhydrous system of microemulsion. Self-micro emulsifying formulations are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsion when introduced into aqueous phase under conditions of gentle agitation. The digestive motility of the stomach and intestine provide the agitation necessary for self emulsification in vivo⁶. These systems advantageously present the drug in dissolved form and the small droplet size provide a large interfacial area for drug absorption^{7, 8}.

One of the primary challenges to any oral formulation design program is maintaining drug solubility within the gastrointestinal tract and, in particular, maximizing drug solubility within the prime absorptive site of the gut⁹. For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, SEDDS can offer an improvement in rate and extent of absorption, resulting in reproducible blood time profiles. Logically speaking, however, use of SEDDS can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs¹⁰. These systems can help in solving the under-mentioned problems of all the categories of BCS class drugs, as depicted in Table 1. Lipinski's rule of five has been widely proposed as a qualitative predictive model for oral absorption trends. In the discovery setting, the 'rule of five' predicts that poor absorption or poor permeation is more likely when there are more than five H-bond donors, there are more than ten H-

bond acceptors, the molecular weight >500 and the calculated log P > 5.

LIPID FORMULATION CLASSIFICATION SYSTEM

The Lipid Formulation Classification System was introduced as a working model in 2000, and an extra 'type' of formulation was added in 2006¹¹. The main purpose of the Lipid Formulation Classification System is to enable in vivo studies to be interpreted more readily and, subsequently, to facilitate the identification of thermo stable appropriate formulations for specific drugs (i.e. with reference to their physicochemical properties)⁸. Table 2 indicates the fundamental differences between types I, II, III and IV formulations.

Type I: Type I 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 emulsifiers¹². Generally, these systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase/ co-lipase in the GIT to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I lipid formulations therefore represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required payload (dose)¹.

Type II: Type II lipid formulations constitute SEDDS¹³. 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 materials) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface^{7, 14}. 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^{15, 16}.

Type III: Type III lipid-based formulations, commonly referred to as self-microemulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further segregated (somewhat arbitrarily) into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. 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 content¹.

Type IV: In order to capture the recent trend towards formulations which contain predominantly hydrophilic surfactants and cosolvents, this category was recently added¹¹. Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug payloads when compared to formulations containing simple glycerides lipids and also produce very fine dispersions when introduced in aqueous media. Little is known however, as to the solubilisation capacity of these systems in vivo and in particular whether they are equally capable of maintaining poorly water soluble drug in solution during passage along the GIT when compared with formulations comprising

natural oils (Type II and Type III). An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase) which contains TPGS as a surfactant and PEG 400 and propylene glycol as co-solvents¹⁷.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

The introduction of the Biopharmaceutical Classification System (BCS) in 1995 was the result of continuous efforts on mathematical analysis for the elucidation of the kinetics and dynamics of the drug process in the gastrointestinal (GI) tract. Since the BCS was introduced, it has been used as a regulatory tool for the replacement of certain bioequivalence (BE) studies with accurate in vitro dissolution tests. This step certainly reduces timelines in the drug development process, both directly and indirectly, and reduces unnecessary drug exposure in healthy volunteers, which is the normal study population in BE studies¹⁸.

BCS is a scientific framework for classifying substances according to their aqueous solubility and their intestinal permeability. The BCS also takes account of the dissolution of the drug product and hence covers the three main factors which govern the rate and extent of drug absorption from immediate release (IR) solid oral dosage forms (e.g. tablets, capsules):

- dissolution rate
- solubility
- permeability

Characteristics of drugs of various BCS classes

According to the BCS, drug substances can be classified as belonging to one of four classes:

Class 1: high solubility and high permeability

Class I drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step. Bioavailability and dissolution is very rapid. So bioavailability and bioequivalence studies are unnecessary for such products. IVIVC (in-vitro in-vivo correlation) can not be expected. Thus compounds are highly suitable for design the SR (sustain release) and CR (controlled release) formulations¹⁹. Examples include Ketoprofen, Naproxen, Carbamazepine, Propranolol, Metoprolol, Diltiazem, Verapamil etc.

Class 2: low solubility and high permeability

Class II drugs have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. These drugs exhibit variable bioavailability and need the enhancement in dissolution for increasing the bioavailability. These compounds are suitable for design the SR and CR formulations. In vitro- In vivo correlation (IVIVC) is usually expected for class II drugs¹⁹.

Examples include Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine, Felodipine, Nifedipine, Nisoldipine etc.

Class 3: high solubility and low permeability

Drug permeability is the rate-limiting step for drug absorption, but the drug is solvated very quickly. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. If the formulation does not change the permeability or

gastrointestinal duration time, then Class I criteria can be applied¹⁸.

Examples include Cimetidine, Ranitidine, Acyclovir, Neomycin B, Atenolol, and Captopril.

Class 4: low solubility and low permeability

The drugs of this class are problematic for effective oral administration. These compounds have poor bioavailability. They are usually not well absorbed through the intestinal mucosa, and a high variability is expected. Fortunately, extreme examples of Class IV compounds are the exception rather than the rule, and these are rarely developed and marketed. Nevertheless, several Class IV drugs do exist¹⁸.

Examples include Hydrochlorothiazide, Taxol, and Furosemide etc.

SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)

Self microemulsifying drug delivery systems (SMEDDS) are isotropic mixtures of oil, hydrophilic surfactant and/or a co-surfactant, and a solubilized drug. They can be encapsulated in hard or soft gelatin capsules. These formulations spontaneously form a fine oil-in-water nanoemulsion upon dilution with water. In the GI tract, they are readily dispersed, where the motility of the stomach and small intestine provides the gentle agitation necessary for emulsification. This property of SMEDDS makes them a natural choice for delivery of hydrophobic drugs that have adequate solubility in oil-surfactant blends. SMEDDS improves the rate and extent of absorption of hydrophobic drugs, whose absorption is considered to be dissolution rate-limited. Upon aqueous dilution the drug remains in the oil droplets or as a micellar solution since the surfactant concentration is very high in such formulations²⁰. Some examples of marketed Pharmaceutical self emulsifying formulations are as shown in table 3.

Advantages of SMEDDS

- Enhanced oral bioavailability enabling reduction in dose²¹.
- More consistent temporal profiles of drug absorption¹⁶.
- Selective targeting of drug(s) towards specific absorption window in GIT¹⁶.
- Protection of drug(s) from the hostile environment in gut²².
- Reduced variability including food effects²³.
- Protection of sensitive drug substances²⁴.
- Liquid or solid dosage forms²⁴.
- In SMEDDS, 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 SMEDDS¹⁶.
- Fine oil droplets empty rapidly from the stomach and promote wide distribution of drug throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall²².
- Ease of manufacture and scale up is one of the most important advantage that make SMEDDS unique when compared to other drug delivery system like solid dispersion, liposomes, nanoparticles etc.²⁴.
- SMEDDS has potential to deliver peptides that are processed to enzymatic hydrolysis in GIT²⁴.

- When polymer is incorporated in composition of SMEDDS it gives prolonged release of medicament²⁴.
- SMEDDS formulation is composed of lipids, surfactants and co-solvents. The system has the ability to form an oil-on-water emulsion when dispersed by an aqueous phase under gentle agitation. SMEDDS present drugs in a small droplet size and well-proportioned distribution an increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered to the lymphatic system, can bypass first pass metabolism. Thus SMEDDS protect drugs against hydrolysis by enzymes in the GI tract and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism²⁴.

Excipients used in SMEDDS

Self-emulsification has been shown to be specific to: the nature of the oil/surfactant pair; the surfactant concentration and oil/surfactant ratio; and the temperature at which self emulsification occurs. In support of these facts, it has also been demonstrated that only very specific pharmaceutical excipient combinations could lead to efficient self emulsifying systems³.

Oils: The oil represents one of the most important excipients in the self emulsifying formulations not only because it can solubilized marked amounts of the lipophilic drug or facilitate self emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride^{15, 25-27}. Both long and medium chain triglyceride 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 excipients choice for the development of SEDDS 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^{16, 28, 29}. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semisynthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SEOFs¹⁶.

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. 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 polyglycolized 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 surfactants²⁸. 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 lumen²⁹. Usually the surfactant concentration ranges between 30 and 60% w/w in order to form stable SMEDDS. 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 solubilized relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS³⁰.

Co-solvents: The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants. Organic solvents such as, ethanol, propylene glycol (PG), and polyethylene glycol (PEG) are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. These solvents can even act as co-surfactants in microemulsion systems. On the other hand, alcohols and other volatile co-solvents have the disadvantage of evaporating into the shells of the soft gelatin, or hard, sealed gelatin capsules in conventional SEDDS leading to drug precipitation. Thus, alcohol-free formulations have been designed¹⁶, but their lipophilic drug dissolution ability may be limited.

Mechanism of self-emulsification

The mechanism by which self-emulsification occurs is not yet well understood. Nevertheless, it has been suggested that self-emulsification takes place when the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion^{3,31}. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases and can be described by the equation:

$$DG = SN_i \text{pr}_2S$$

Where DG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r and S represents the interfacial energy. The two phases of emulsion tend to separate with time to reduce the interfacial area and, subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence^{16, 32}.

FORMULATION DEVELOPMENT OF SMEDDS

The method of making self microemulsion drug delivery system for increasing the bioavailability of a drug and/or pharmaceutical ingredient by emulsifying the drug with the self micro emulsifying excipient includes various steps as described below:

Construction of 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 system¹. A Titration method is employed to construct phase diagram. Mixture of oil with surfactant is prepared at different ratios (e.g. 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10) into different vials. A small amount of water in 5 % (w/w) increments is added into the vials. Following each water addition the mixture in vials is centrifuged for 2 to 3 minute and is incubated at 25°C for 48 hrs with gentle shaking. The resulting mixture is evaluated by visual and microscopy observation. For phase diagram the micro emulsion is the region of clear and isotropic solution. Coarse emulsion is the region of cloudy dispersion²⁴.

Preparation of formulation

Briefly, accurately weighed drug is placed in a glass vial, and oil, surfactant, and co-surfactant are added. Then the components are mixed by gentle stirring and vortex mixing and are heated at 40 °C on a magnetic stirrer, until drug is perfectly dissolved³³.

EVALUATION OF SMEDDS

Thermodynamic stability studies

Freeze thawing is employed to evaluate the stability of formulations. The formulations are subjected to 3 to 4 freeze-thaw cycles, which include freezing at – 4 °C for 24 hours followed by thawing at 40 °C for 24 hours. Centrifugation is performed at 3000 rpm for 5 minutes. The formulations are then observed for phase separation. Only formulations that are stable to phase separation are selected for further studies³³.

Self emulsification and precipitation assessment

The efficiency of self-emulsification is assessed using a dissolution apparatus. One millilitre of SMEDDS formulation is added drop wise to 200 ml of either 0.1 N HCl or purified water at 37°C. Gentle agitation is provided by a standard stainless steel dissolution paddle rotating at 60 rpm. The lipid-based formulations are assessed visually according to the rate of emulsification and the final appearance of the emulsion³⁴.

Precipitation is evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations are then categorized as clear (transparent or transparent with bluish tinge), nonclear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours)³³.

Droplet size measurement

This is a crucial factor in self micro emulsification performance because it determines the rate and extent of drug release as well as the stability of the micro emulsion³². The droplet size of the micro emulsion is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) which can measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle after external standardization with spherical polystyrene beads. The nano metric size range of the particle is retained even after 100 times dilution with water, which proves the system's compatibility with excess water²⁴.

Zeta potential

The charge of the oil droplets of SMEDDS is another property that should be assessed³⁵. 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 SMEDDS. Thus, such systems have a positive n-potential value of about 35-45 mV³⁵. This positive n-potential value is preserved following the incorporation of the drug compounds.

DISADVANTAGE 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 formulation. Traditional dissolution methods do not work because these formulations potentially are dependent on digestion prior to release of the drug³⁶. To mimic this, 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-in vivo correlations and therefore different prototype lipid based formulations need to be developed and tested in vivo in a suitable animal model^{24, 36}.

FACTOROS INFLUENCING FORMULATION OF SMEDDS

Dose of drug

Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase^{1,24}. The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately 2) are most difficult to deliver by SMEDDS¹.

Solubility of drug

The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. 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.

Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut¹.

Polarity of lipid phase

The polarity of the lipid phase is another factor that influences the drug release from the microemulsions. The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. Polarity indicates the affinity of drug towards solvent, oil or water and type of forces involved. The high polarity promotes rapid release of the drug into the aqueous phase³⁷. It was observed that the rate of release of idebenone from SMEDDS is dependent upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oil phase with highest polarity³⁸.

Table 1: problems associated with BCS class drugs

Class I	Enzymatic degradation, gut wall efflux
Class II	Solubilization and bioavailability
Class III	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	Solubilization, enzymatic degradation, gut wall efflux and bioavailability

Table 2: The Lipid Formulation Classification System: characteristic features, pros and cons of the four essential types of 'lipid' formulations

Type I	Oils without surfactants (e.g. tri-, di- and monoglycerides)	Non dispersing, requires digestion	GRAS status; simple; excellent, capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water-insoluble surfactants	SEDSS formed without water soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w emulsion (0.25-2 µm)
Type III	Oils, surfactants and cosolvents (both water-insoluble and water-soluble excipients)	SEDSS/SMEDDS formed with water-soluble components	Clear or almost clear dispersion; drug absorption without digestion	Possible loss of solvent capacity on dispersion, less easily digested
Type IV	Water-soluble surfactants and cosolvents (no oils)	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Loss of solvent capacity on dispersion, may not be digestible

Table 3: Examples of marketed self emulsifying formulation

Neoral®	Cyclosporine A/I	Soft gelatin capsule	Novartis	Immune suppressant
Norvir®	Ritonovir	Soft gelatin capsule	Abbott Laboratories	HIV Antiviral
Fortovase®	Sequinavir	Soft gelatin capsule	Hoffmann-La Roche inc.	HIV Antiviral
Agenerase®	Amprenavir	Soft gelatin capsule	Glaxo Smithkline	HIV Antiviral
Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Lipirex®	Fenofibrate	Hard gelatin capsules	Genus	Antihyperlipoproteinemic
Sandimmune®	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immune suppressant
Targretin®	Bexarotene	Soft gelatin capsule	Ligand	Antineoplastic
Rocaltrol®	Calcitriol	Soft gelatin capsule	Roche	Calcium regulator
Gengraf®	Cyclosporine A/III	Hard gelatin capsules	Abbott Laboratories	Immune suppressant

DISCUSSION

SMEDDS is a promising drug delivery system for the enhancement and improvement of the bioavailability of lipophilic drugs. SMEDDS appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs. Self emulsifying drug delivery system has improved solubility/dissolution, absorption and bioavailability for poorly water soluble drug. The present study will definitely drag the attention to understand the individual role of individual lipid and surfactants used for the formulation of SMEDDS as lipid based formulations. Also this study explore the possibilities of loading a wide variety of hydrophobic drugs and plant actives as their scale up is convenient as well as economical too.

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