

REVIEW ARTICLE

ENHANCEMENT OF ORAL BIOAVAILABILITY OF LIPOPHILIC DRUGS FROM SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)*GUPTA ROOP N¹, GUPTA RAKESH AND RATHORE GARVENDRA SINGH**

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ABSTRACT

Approximately 40 per cent of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with implications of low bioavailability, high intra and inter-subject variability, and lack of dose proportionality. Bioavailability problem of lipophilic drugs can be solved by formation of Self-Micro Emulsifying Drug Delivery System (SMEDDS). SMEDDS appears to be a unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs. 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 vivo. This review describes SMEDDS as one of the important approaches to overcome the formulation difficulties of potent lipophilic drugs.

.KEY WORDS: Oral delivery, Bioavailability, Lipophilic drugs, Self-Micro Emulsifying Drug delivery system.

INTRODUCTION

Most of the New Chemical Entities (NCE) that are being discovered are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Because of their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophilic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs.

Various formulation strategies reported in the literature includes, incorporation of drug in oils^[1], solid dispersions^[2], emulsions^[3], liposomes^[4], use of cyclodextrins^[5], coprecipitates^[6], micronization^[7,8], nanoparticles^[9], permeation enhancers^[10] and lipid solutions. The Self-Dispersing Lipid Formulations (SDLFs) is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/lipophilic drugs and to improve the oral bioavailability of poorly absorbed drugs. The SDLFs contain oil and a surfactant mixture into which the drug is incorporated. They emulsify when mixed with aqueous environment. The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant

concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs^[11,12,13]. After self-dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. Bioavailability enhancement results from the finely dispersed state of the drug containing lipid globules. The large surface area enhances the dissolution. The emulsion globules are further solubilized in the gastrointestinal tract by bile fluids. The presence of surfactant causes enhanced absorption due to membrane induced permeation changes. The droplets formed are either positively charged or negatively charged. As the mucosal lining is negatively charged it was observed that positively charged particles penetrated deeper into the ileum^[14]. A cationic emulsion has greater bioavailability than an anionic emulsion^[15,16]. The SEDDS are of two kinds namely, Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion. Therefore, they are not dependent on bile secretion for absorption. The emulsified form itself is readily absorbable. This ensures a rapid transport of poorly soluble drugs into the blood.

Many researchers have reported applications of SEDDS for delivering and targeting lipophilic drugs, e.g., coenzyme Q10^[17], vitamin E^[18], halofantrine^[19] and cyclosporin A^[20]. Potential advantages of these systems include enhanced oral bioavailability (enabling dose reduction), more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut^[21,22]. For selecting a suitable self-emulsifying vehicle, drug solubility in various components, identification of emulsifying regions and resultant droplet size distribution need careful monitoring, since these are drug-specific systems^[17].

Microemulsions (drop size 10-100nm) have received considerable attention for their potential as drug delivery vehicle due to advantages like excellent thermodynamic stability, longer shelf life, high drug solubilisation capacity, improvement in oral bioavailability and protection against enzymatic hydrolysis^[23]. 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 capsules^[24]. A feasible substitute is Self-Micro Emulsifying Drug Delivery System (SMEDDS) -an anhydrous system of micro-emulsion. 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 vivo^[25]. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for drug absorption^[26,27].

SMEDDS can also be formulated to give sustained release dosage form, by adding inert polymeric matrix, which is not ionizable at physiological pH, and dispersed in the self-micro emulsifying system before ingestion. The polymer matrix (after ingestion) in contact with GI fluid forms a gelled polymer making it possible to release the micro emulsified active agent in a continuous and sustained manner by diffusion^[28].

The lipophilic (poorly water soluble) drugs such as Nifedipine, Griseofulvin, Cyclosporin, Digoxin, Itraconazole Carbamazepine, Piroxicam, Fluconazole, Indomethacin, Steroids, Ibuprofen, Diazepam, Finasteroids, Difunisal, etc. are formulated in SMEDDS to improve efficacy and safety^[29].

FORMULATION CONSIDERATION

Studies have 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^[11,12,13]. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self-micro emulsifying systems. The formulated Self-Micro Emulsifying Drug Delivery Systems is specific to that particular drug only. Various major components of SMEDDS are:

Oils: Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SMEDDS. Unmodified edible oils provide the most 'natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-micro emulsification markedly reduces their use in SMEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SMEDDS owing to their biocompatibility^[30]. Recently medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound such as GELUCIRE (Gattefosse Corporation, Westwood, N.J.). These excipients form good emulsification systems because of higher fluidity, better solubilising potential and self-micro emulsification ability. Other suitable oil phases are digestible or non-digestible oils and fats such as olive oil, corn oil, soyabean oil, palm oil and animal fats^[29].

Surfactant: The choice of surfactants is limited as very few surfactants are orally acceptable. Non-ionic surfactants with high HLB value are used in formulation of SMEDDS including: Ethoxylated polyglycolysed glycerides, Tween 80, LABRFAC CM10-a mixture of saturated compounds containing 8 carbon polyglycolysed glycosides (HLB =10, Gattefosse Corporation, Westwood, N.J.) and other long chain alkyl sulfonate sulfate surfactants, such as sodium dodecyl benzene sulfonate, sodium lauryl sulfate and dialkyl sulfo succinate and quaternary ammonium salts, fatty alcohols such as lauryl, cetyl and stearyl, glyceryl esters, fatty acid esters and

polyoxyethylene derivatives are also, employed. Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SMEDDS use despite their limited ability to self-emulsify. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents. The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate formation of o/w droplets and /or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/self-micro emulsifying performance. The usual surfactant concentration in SMEDDS required forming and maintaining a microemulsion state in the GI tract ranged from 30 to 60 % w/w of the formulation^[29]. The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased / inhibited p-glycoprotein drug efflux^[27]. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. The effect of formulation and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case.

Co-surfactant: In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion^[29,31].

Co-solvent: Organic solvents are suitable for oral administration. Examples are ethanol, propylene glycol, and polyethylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid base^[30]. Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents act as co-solvents. Triacetin is suitable since it is miscible in the oil lipid

phases and it can be used to solubilize a hydrophobic drug [29].

Consistency builder: Additional material can be added to alter the consistency of the emulsions; such materials include tragacanth, cetyl alcohol, stearic acids and /or beeswax [32].

Polymers: Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionizable at physiological pH and being capable of forming matrix are used. Examples are hydroxy propyl methyl cellulose, ethyl cellulose, etc. [28].

FACTORS AFFECTING SMEDDS

1. 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. The drugs exhibit limited solubility in water and lipids are most difficult to deliver by SMEDDS.

2. The ability of SMEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oily phase. If the surfactant or co-surfactant is contributing to a greater extent for drug solubilization, then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of surfactant or co-surfactant.

3. Equilibrium solubility measurement can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in solubilizing and colloidal stabilizing environment of the gut. Studies reveals that such formulations can take up to 5 days to reach equilibrium and that the drug can remain in a super saturated state up to 24 hours after the initial emulsification event [25].

4. The polarity of lipid phase is one of the factors that govern the release from the micro-emulsion. HLB, chain length and degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces involved.

The high polarity will promote rapid rate of release of the drug into the aqueous phase. Sang-Cheol Chi *et al.* [33], who 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 oily phase with highest polarity.

FORMULATION

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-microemulsifying excipient includes various steps as described below [29]:

- 1) Preparation of phase diagram [34].
- 2) Solubilizing a poorly water-soluble drug and/or pharmaceutical ingredient, in a mixture of surfactant, co-surfactant and solvent. Now mix the oil phase suitably prepared, if necessary, by heating or other preparatory means, to the solubilized drug formulation and thoroughly mixed.
- 3) The emulsion can then be added to a suitable dosage form such as soft or hard-filled gelatin capsules and allowed to cool.

MECHANISM OF SMEDDS

Different approaches have been reported in the literature. No single theory explains all aspects of microemulsion formation. Schulman *et al.* [35] considered that the spontaneous formation of microemulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant. Thermodynamic theory of formation of microemulsion explains that emulsification occurs, when the entropy change that favour dispersion is greater than the energy required to increase the surface area of the dispersion [36] and the free energy (ΔG) is negative. The free energy in the microemulsion formation, is a direct function of the energy required to create a new surface between the two phases and can be described by the equation:

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

where, ΔG is the free energy associated with the process (ignoring the free energy of the mixing), N is the number

of droplets of radius r and σ represents the interfacial energy.

With time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. Therefore, the emulsion resulting from aqueous dilution are stabilized by conventional emulsifying agents, which forms a mono layer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to prevent coalescence.

BIOAVAILABILITY ENHANCEMENT OF DRUGS FROM SMEDDS

The fate of SMEDDS following oral administration and mechanisms for improved bioavailability are shown in **Fig.1**. On coming in contact with aqueous gastric components, after oral administration, SMEDDS gets spontaneously emulsified, which is further emulsified by the bile salt resulting in the formation of small oil droplets of approximately $0.5 \mu\text{m}$ size. In order to understand the mechanism by which subsequent drug absorption occurs from emulsion system, it is necessary to consider the in vivo behavior of constituent components. There are several reports indicating enhanced drug absorption from emulsified dosage form and SMEDDS.

Various modes of enhanced drug absorption can be hypothesized as follows:

Drugs may be absorbed through lymphatics via chylomicron synthesis of the fatty components of the digestible oil phase of emulsion. Lipophilic drugs, which preferably remain in the oil droplet, may in fact be absorbed via bile salt micelles along with metabolites of the lipid carrier ^[37,38].

Bates and Sequeria suggested that inhibition of gastric motility caused by the presence of the lipid phase of emulsion might allow more time for dissolution and absorption of drug from lipid phase ^[39].

Increased mucosal permeability via incorporation of lipids from mixed micelles ^[36] and enhanced mesenteric lymph

flow may be responsible for the enhanced drug absorption ^[40].

A hydrophilic drug is less likely to be absorbed through the lymphatics (chylomicron) and instead may diffuse directly in to the portal supply. Hence, in this case, increased dissolution from the large surface area afforded by emulsion may be a contributing factor to enhanced absorption of drugs ^[25,41].

A relatively less focused consideration is the presence of surfactant in formulation, which may also play a role in increasing the absorption of the drug ^[25].

SMEDDS: POTENTIAL STRIKED

Cyclosporine (Sandimmune Neoral) a microemulsion with self-emulsifying properties, is reported to improve oral bioavailability and reduce inter and intra subject variability in cyclosporine pharmacokinetics as compared to its earlier version Sandimmun. The microemulsion had better absorption profile than the conventional formulation. Moreover, lower dose of cyclosporine microemulsion are required to obtain C_{max} value, similar to that obtained with conventional cyclosporine ^[42].

Gattefosse Corporation, France, has patented SMEDDS formulation of indomethacin which offered two fold increase in bioavailability in rats compared to conventional formulations ^[43].

A poorly water-soluble drug used in treating liver disease, biphenyl dimethyl dicarboxylate (BDD) showed ten fold increase in bioavailability when given orally as SMEDDS ^[44].

Charman et.al reported improvement in pharmacokinetic parameters of Halofantrine (highly lipophilic anti-malarial drug) and reduction in inter-subject variability when administered as SMEDDS ^[25].

K Itoh et al observed improvement in biopharmaceutical properties of N-4472, an investigational lipophilic drug having lipolytic activity in SMEDDS formulation ^[45,46].

1. Nitrendipine, a calcium channel blocker with poor bioavailability showed three-fold increase in peak plasma

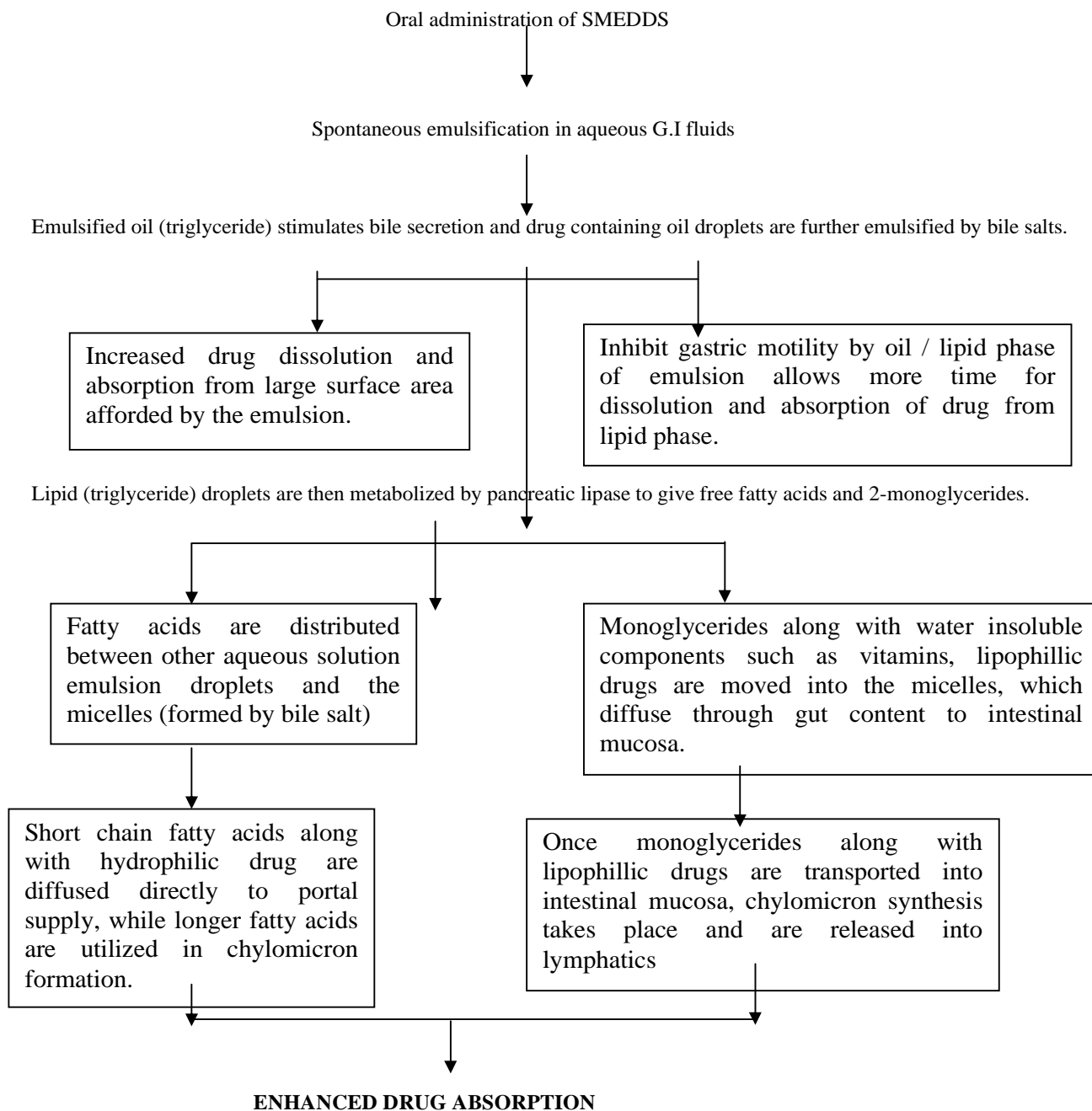


Figure.1. Fate of SMEDDS following oral administration and mechanisms proposed for bioavailability enhancement of drugs.

concentration in rats when given as SMEDDS formulation [47].

Nazzal et al observed improvement in pharmacokinetics and two-fold increase in bioavailability of Ubiquinone, a lipophilic drug used as an anti-anginal agent and as antioxidant when given as SMEDDS [48].

The bioavailabilities of Calcein and RGD peptide were shown to be significantly increased when administered as microemulsion pre-concentrate [49].

EVALUATION OF SMEDDS

1. Visual assessment may provide important information about the self-emulsifying property of the SMEDDS and about the resulting dispersion [26,50,51]. Estimation of the

efficiency of the self-emulsification can be done by evaluating the rate of emulsification and particle size distribution [52]. Turbidity measurement to identify efficient self-emulsifying can be done to establish whether the dispersion has reached equilibrium rapidly and in reproducible time [26].

2. Droplet polarity and droplet size are important emulsion characteristics. Polarity of oil droplets is governed by the HLB value of oil, chain length and degree of unsaturation of the fatty acids, the molecular weight of the hydrophilic portion and concentration of the emulsifier. A combination of small droplets and their appropriate polarity (lower partition coefficient o/w of the drug) permit acceptable rate of release of the drug. Polarity of the oil droplets is also estimated by the oil/water partition coefficient of the lipophilic drug [27].

3. Size of the emulsion droplet is very important factor in self-emulsification / dispersion performance, since it determine the rate and extent of drug release and absorption [26,51]. The Coulter nano-sizer, which automatically performs photon correlation analysis on scattered light, can be used to provide comparative measure of mean particle size for such system. This instrument detects dynamic changes in laser light scattering intensity, which occurs when particle oscillates due to Brownian movement. This technique is used when particle size range is less than 3 μ m, size range for SMEDDS is 10 to 200 nm [26].

4. For sustained release characteristic, dissolution study is carried out for SEMDDS. Drugs known to be insoluble at acidic pH can be made fully available when it is incorporated in SMEDDS [28].

CONCLUSION

Self-Micro Emulsifying Drug Delivery Systems appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs. More efforts are needed to predict solubility state of the drug in vivo, interaction of lipid content with components of capsule shell and basic mechanism of transport of drug from SMEDDS.

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