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Review article

Self-micro emulsifying drug delivery systems (smedds): as a promising approach in enhancing bioavailability of poorly aqueous soluble drugs

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ABSTRACT

Oral delivery of hydrophobic drugs presents a foremost confront because of the low aqueous solubility of such compounds. Number of technologies has been developed till now to overcome poor solubility issues, out of which recently Self micro-emulsifying drug delivery systems (SMEDDS) have gained much attention. (SMEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can dissolve hydrophobic drugs facilitating them to be rendered as a unit dosage form from oral administration. These can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil-in-water (o/w) emulsions on releasing in GIT lumen with the aid of GI fluid. This leads to in situ solubilization of drugs that can consequently be absorbed by lymphatic pathways. The efficiency of oral absorption of the drug compound from the SMEDDS depends on several formulations related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SMEDDS will continue, and more drug compounds formulated as SMEDDS will reach the pharmaceutical market in the future. This article include an reports on diverse types of self micro-emulsifying formulations with emphasis on their formulation, characterization and in vitro analysis, with examples of currently marketed preparations.

Keywords: Self emulsifying oil formulations (SEOF), Lipophilic drugs, Oral bioavailability, Lipid formulations.

INTRODUCTION

Oral route is the easiest and most suitable way of non-insidious administration. Low cost effectiveness crafts immense popularity to Oral drug delivery systems in worldwide drug delivery market. Solubility is the major concern for a drug to get systematically and completely absorbed followed by its permeation. Nearly half of the new drug candidate's exhibits poor aqueous solubility which ultimately leads to low bioavailability since the rate limiting step for absorption of these drugs is their solubilization in the gastrointestinal tract. These drugs are categorized as class II in Biopharmaceutical Classification System (BCS) i.e drugs with poor aqueous solubility and high permeability. To overcome the issue of solubility several approaches have come up like micronization, solid dispersion, complexation with cyclodextrins, use of surfactants, permeation enhancers and nanoparticles. Presenting a drug as a solubilize within a colloidal dispersion may enhances the availability of a drug for its absorption. Over the past few years a major attention has been focused on lipid based formulations to enhance the bioavailability of poorly aqueous drugs the basis of which is the 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 formulations usually consists of drug dissolved in oils, partial glycerides, surfactants and co-surfactants. The self-dispersing lipid

Formulations (SLDFs) of one of the techniques to overcome the formulation difficulties of several hydrophobic drugs and to improve the oral bioavailability of poorly aqueous soluble drugs. The SDLF's are mainly of two types i.e., Self-Emulsifying Drug Delivery Systems (SEDDS) and Self Micro Emulsifying Drug Delivery Systems (SMEDDS) [1].

Lipid formulation classification system

The major intention of the lipid formulation classification system is the prompting facilitation of in vivo studies interpretation and subsequently to assist the identification of the most suitable formulation for specific drugs with reference to their physicochemical properties. Table no. 1 illustrates specific features of each lipid formulation.

Table 1: Composition, Characteristics, advantages and disadvantages of the various types of Lipid formulations

LFCS Type	Characteristics	Advantages	Disadvantages
Type I	Non-dispersing; requires digestion	GRAS status; simple; excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	SEDDS without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25–2_m)
Type IIIA	SEDDS/SMEDDS with water-soluble components	Clear or almost clear dispersion; drug absorption without digestion	Possible loss of solvent capacity on dispersion; less easily digested
Type IIIB	SMEDDS with water-soluble components and low oil content	Clear dispersion; drug absorption without digestion	Likely loss of solvent capacity on dispersion
Type IV	Oil-free formulation based on surfactants and cosolvents	Good solvent capacity for many drugs; disperses to micellar solution	Loss of solvent capacity on dispersion; may not be digestible

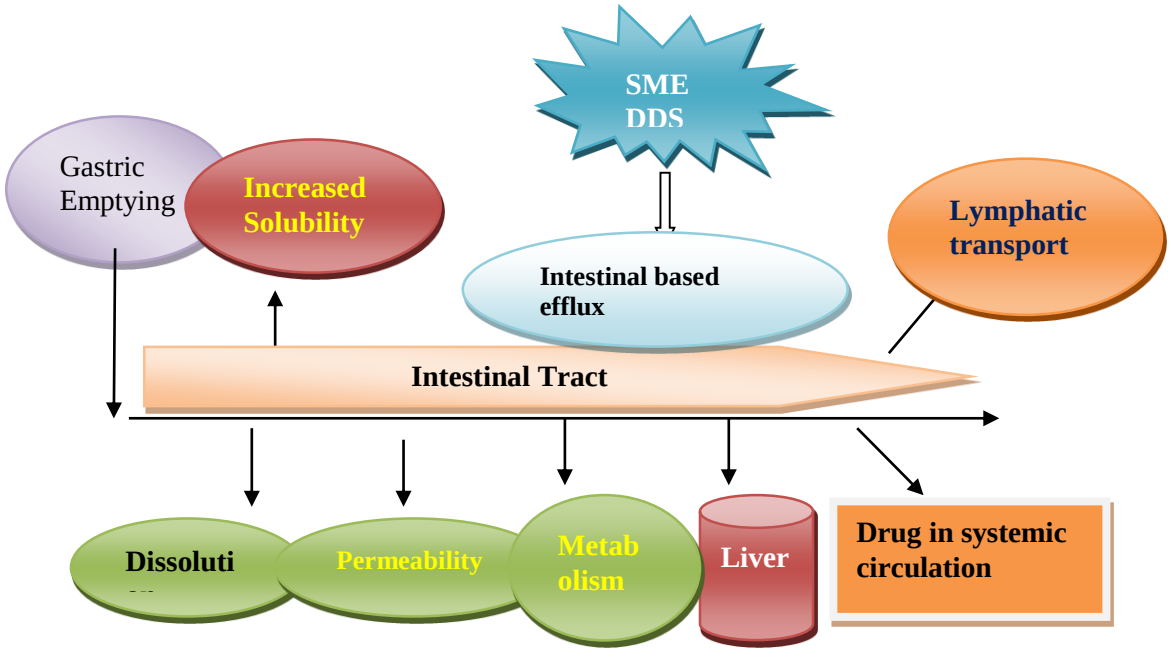
Type I formulations consists of formulations solubilized drug in triglycerides and/or mixed glycerides or in an oil-in-water emulsion stabilized by little concentration of emulsifiers such as 1% (w/v) polysorbate 60 and 1.2% (w/v) Lecithin. Generally these systems shows poor initial aqueous dispersion and requires digestion by pancreatic lipase/co-lipase in the GIT to produce more amphilphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I formulations are therefore are a good option for drugs having sufficient solubility in oils.

Type II formulations are referred to as SEDDS. SEDDS are isotropic mixtures of lipids, surfactants (HLB<12), co-surfactant and the drug which form oil- in water emulsion under gentle agitation subsequent dilution with aqueous phases. Self-emulsification is usually obtained at surfactants contents above 25% (w/w). However at higher surfactant concentration (greater than 50-60% (w/w), the progress of emulsification may be hindered by the formation of viscous crystalline gels at the oil/water interface [2].

Type III formulations are generally referred as self-micro-emulsifying drug delivery systems (SMEDDS). It consists of oils, hydrophilic surfactants (HLB>12) and co solvents. Type III formulations are further divided into Type IIIA and Type IIIB formulations. Later comprises of higher amount of hydrophilic surfactants and co-solvents and lesser lipid content, as compared to Type IIIA. Type IIIB formulations cause greater risk of drug precipitation on dispersions given their high content of hydrophilic surfactants and co-solvents. An example of marketed TypeIII formulation is Neoral® (Novartis) cyclosporine formulation.

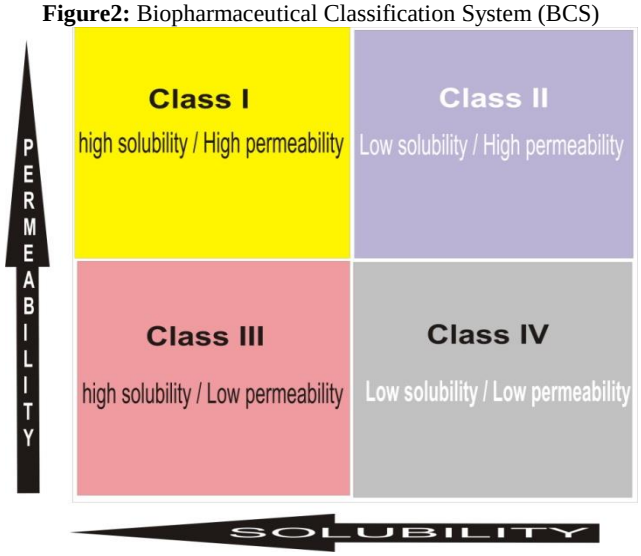
Type IV systems are basically pure surfactants or mixtures of surfactants and co-solvents. Formulation of poorly water soluble drugs in pure co-solvents is likely to result in precipitation of the drug.

Figure 1: SMEDDS improving the bioavailability of drugs through oral absorption



SMEDDS are isotropic and thermodynamically transparent stable solutions consisting of an oil, surfactant, co-surfactant and drug mixtures which form water in oil micro-emulsions when mixed with aqueous phase under mild stirring. Through these systems enhancement in drug solubilization takes place followed by improvement in release and absorption properties due to already dissolved form of the drug in the formulation and the resulting small droplet size providing a large interfacial surface area for drug absorption. Apart from improved drug dissolution one more factor contributed to SMEDDS in enhancing bioavailability is that the lymphatic transport is responsible for a portion of a complete drug uptake as well. Fig. no 1 illustrates the absorption of self-micro-emulsifying formulation from oral mucosa to gastrointestinal tract dosage forms, this system works on the grounds of recognition that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption. Fig. no. 2 depicts BCS [3].

Figure2: Biopharmaceutical Classification System (BCS)



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 (equilibrium solubility at 37°C).

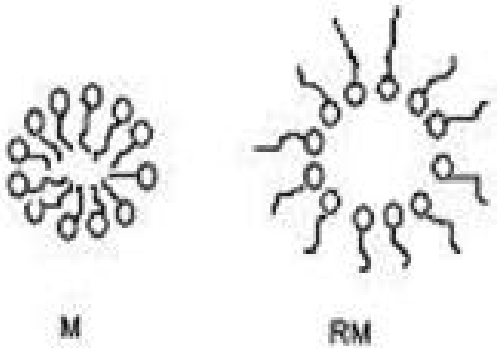
Permeability

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

Microemulsion

The Strategy of micro-emulsion was first established by Hoar and Schulman in 1943. Micro-emulsions are thermodynamically stable, transparent, dispersions of oil and water stabilized by an interfacial film of surfactant molecules. Micro-emulsions are frequently identified by equilibrium phase studies as systems which are optically transparent to the eye, however contains a extensive mass of both oil and water Fig. no. 3. Micro-emulsions are prepared by mixing a suitable quantity of aqueous solution with organic phase containing the surfactant solution. Major role of these system includes enhancement in oral bioavailability, fortification against enzymatic hydrolysis and decreased toxicity. The only problem with micro-emulsion is poor palatability and moreover due to their water content, microemulsion cannot be encapsulated in soft and hard gelatin capsules. Hence SMEDDS is a great necessity for delivery of hydrophobic drugs

Figure 3: The structure of micelles. M= Micelles for o/w micro-emulsion, RM= Reverse micelles for w/o micro-emulsion



SMEDDS

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 SEDDS. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles. SMEDDS formulation is in theory, comparatively simple. The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SMEDDS formulation contains oils, surfactants and if required an antioxidants. Often co-

surfactants and co-solvents are added to improve the formulation characteristics [4].

Advantages of SMEDDS

Enhanced oral bioavailability

Dissolution rate dependant absorption is a major factor that limits the bioavailability of numerous poorly water soluble drugs. The ability of SMEDDS to present the drug to GIT in solubilised and micro emulsified form (globule size between 1-100 nm) and subsequent increase in specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability. E.g. In case of halofantrine approximately 6-8 fold increase in bioavailability of drug was reported in comparison to tablet formulation.

Ease of manufacture and scale-up

Ease of manufacture and scaleup is one of the most important advantage that makes SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposome's, nanoparticles, etc., dealing with improvement of bio-availability. SMEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of industry in the SMEDDS.

Reduction in inter-subject and intra-subject variability and food effects

There are several drugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a boon for such drugs. Several research papers specifying that, the performance of SMEDDS is independent of food and, SMEDDS offer reproducibility of plasma profile are available.

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

One unique property that makes SMEDDS superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis. The intestinal hydrolysis of prodrug by cholinesterase can be protected if polysorbate 20 is emulsifier in micro emulsion formulation. These systems are formed spontaneously without aid of energy or heating thus suitable for thermo labile drugs such as peptides.

No influence of lipid digestion process

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

Increased drug loading capacity: SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<log P>4) are typically low in natural lipids and much greater in amphilphilic surfactants, co surfactants and co-solvents.

Suitable drug candidate selection for SMEDDS

Upholding drug solubility within the gastrointestinal tract and, in particular, maximizing drug solubility within the major absorptive site of the gut is one of the prime challenges to any formulation design system. SMEDDS offers a potential platform in enhancing the oral bioavailability of poorly aqueous soluble drugs especially those belonging to BCS class II and class IV , candidates of class II are poorly water soluble with high permeability but once dissolved they absorbed over the GIT membrane and class IV compounds are drugs with poor solubility and poor permeability respectively.

Selection procedure of suitable drug candidate for SMEDDS depends majorly on under mentioned criteria [5].

Lipophilicity

The drug candidate should have sufficient solubility in pharmaceutically acceptable lipid excipients i.e in the United States, the Food and Drug Administration (FDA) has published listings in the Code of Federal Regulations for Generally Recommended as Safe (GRAS) substances that are generally recognized as safe its Packaging/ Generally Recognized as Safe GRAS/default.htm). Over the years, the Agency has also maintained a list entitled 'Inactive Ingredient Guide' for excipients that have been approved

Incorporated in marketed products. This guide is helpful in that it provides the database of allowed excipients with the maximum dosage level by route of administration or dosage form for each excipients.

Food effects

Meals rich in fatty acids in stomach instead of empty stomach favors the absorption of drug from the lipid based formulation because the absorption of lipophilic drug usually exhibit dissolution-rate-limited. To explain the inclination for oral absorption Lipinski's rule of five has been widely used as a qualitative predictive model. The rule of five explains poor absorption or poor permeation in terms of situation where there more than five H-bond donors, there are more than ten H-bond acceptors, the molecular weight >500 and the calculated log p >5. Both BCS and Lipinski's rule of five are useful, mainly at the primary screening stage but they have limitations. It is considered that the rule of five is only applicable to those compounds which are not substrates for active transporters, and with increasing evidence suggesting that for some efflux or uptake transporters, this limitation might be notable [6].

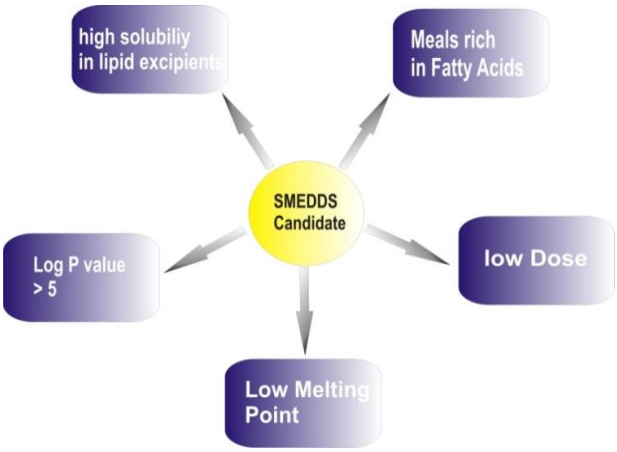
Log P Value

This can be consider as the prime characteristics for dipodic system higher log P (>4) values are desirous. For e.g., cinnarizine, atorvastatin, etc a lipophilic drug, having log P values greater than 5 is

strong candidate for SMEDDS.

Melting point and Dose: Low melting point and dose are desirable for development of lipoids systems, drugs having high melting point and low log P values (around 2) are not suitable candidates for SMEDDS. Fig. no. 4 illustrates major criteria's for selecting suitable drug candidate for SMEDDS.

Figure 4: Criteria's for suitable drug candidate selection for SMEDDS



Screening of excipients for smedds

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids and hydrophobic and hydrophilic surfactants to water-soluble co-solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures that disperse to give fine colloidal emulsions. The following points should be considered in the formulation of a SMEDDS: (i) the solubility of the drug in different oil, surfactants and co-solvents and (ii) the selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram. The backbone of SMEDDS formulation comprises lipids, surfactants and co-solvents. The right concentration of the above three decides the self-emulsification and particle size of the oil phase in the emulsion formed. These ingredients are discussed below.

Lipids. Lipid is a vital ingredient of the SMEDDS formulation. It can not only solubilize large amount of lipophilic drugs or facilitate self-emulsification but also enhance the fraction of lipophilic drug transported via intestinal lymphatic system, thereby increasing its absorption from the GIT. Natural edible oils, comprising medium-chain triglycerides, are not frequently preferred in this regard owing to their poor ability to dissolve large amounts of lipophilic drugs. Modified ligand medium-chain triglyceride oils, with varying degrees of saturation or hydrolysis, have been used widely for the design of SEDDS. These semi-synthetic derivatives form good emulsification systems when used with a large number of solubility enhancing surfactants approved for oral administration.

Surfactants

A surfactant is obligatory to provide the essential emulsifying characteristics to SMEDDS. Surfactants, being amphilphilic in nature, invariably dissolve (or solubilize) high amounts of hydrophobic drug compounds. The two issues that govern the selection of a surfactant encompass its hydrophilic–lipophilic balance (HLB) and safety. The HLB of a surfactant provides vital information on its potential utility in formulation of SMEDDS. For attaining high emulsifying performance, the emulsifier involved in formulation of SMEDDS should have high HLB and high hydrophilicity for immediate formation of o/w droplets and rapid spreading of formulation in aqueous media in this context. It would keep drug solubilize for a prolonged period of time at the site of absorption for effective absorption, so precipitation of drug compound within GI lumen is prevented. A range of industrial nonionic surfactants were screened for their ability to form SMEDDS with medium-chain and long-chain triglycerides has been used by utilizing subjective visual assessment [7].

Co-solvents

Usually, the formulation of an effective SMEDDS requires high concentrations of surfactant. Accordingly, co-solvents such as ethanol, propylene glycol and polyethylene glycol are required to enable the dissolution of large quantities of hydrophilic surfactant. The lipid mixture with higher surfactant and co-surfactant: oil ratios leads to the formation of SMEDDS. Alcohol and other volatile co-solvents have the disadvantage of evaporating into the shell of soft or hard gelatin capsules, leading to precipitation of drug. Table. 1 depicts some common excipients used in formulation of SMEDDS.

Table 2: (Examples of typical excipients used in SMEDDS)

Lipid ingredients	Corn oil, Mono,di,tri-glycerides, DL-alpha-Tocopherol, Fractionated triglyceride of palm seed oil(medium-chain triglyceride), Medium chain mono-and di-glycerides, Corn oil Olive oil, Oleic acid, Soyabean oil, Peanut oil, Beeswax, Hydrogenated vegetable oils
Surfactants/co-surfactants	Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), Sorbitan monooleate (Span 80), Polyoxy-40- hydrogenated castor oil (Cremophor RH40), Polyoxyethylated glycerides (Labrafil M 2125 Cs), Polyoxyethylated oleic glycerides (Labrafil M1944 Cs)
Co-solvents	Ethanol, Glycerin, Polypylene glycol, Polyethylene glycol

Lipid ingredients

Corn oil, Mono,di,tri-glycerides, DL-alpha-Tocopherol, Fractionated triglyceride of palm seed oil(medium-chain triglyceride), Medium chain mono-and di-glycerides, Corn oil Olive oil, Oleic acid, Soyabean oil, Peanut oil, Beeswax, Hydrogenated vegetable oils

Surfactants/co-surfactants

Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), Sorbitan monooleate (Span 80), Polyoxy-40- hydrogenated castor oil (Cremophor RH40), Polyoxyethylated glycerides (Labrafil M 2125 Cs), Polyoxyethylated oleic glycerides (Labrafil M1944 Cs)

Co-solvents Ethanol, Glycerin, Polypylene glycol, Polyethylene glycol

Mechanism of self-emulsification

Self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. 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 = SNi pri2S

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.

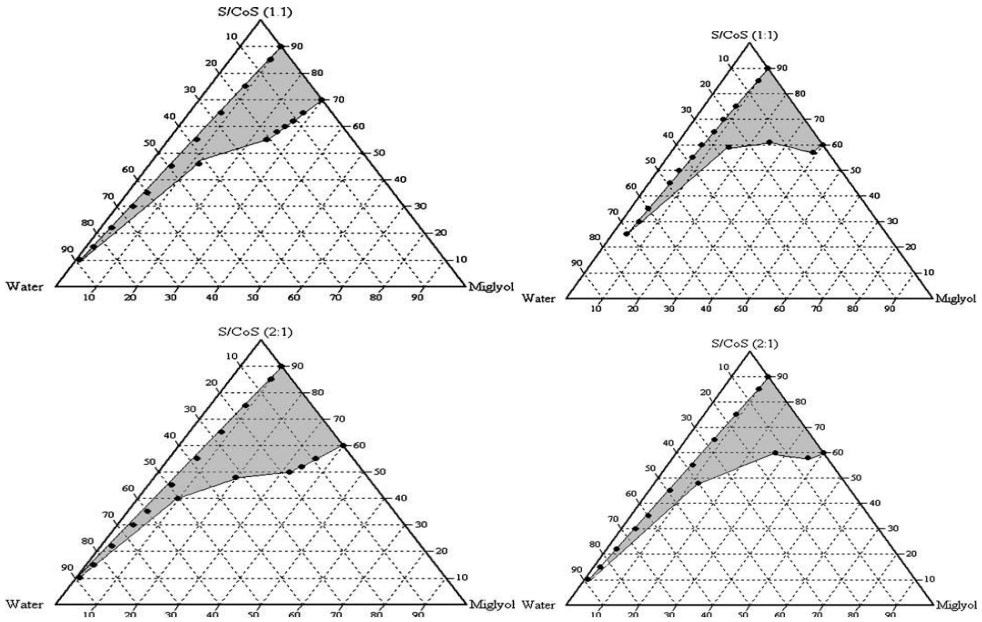
Formulation of SMEDDS

General methodology of preparation of SMEDDS initiates with determination of solubility (by using shake flask method and determination through HPLC) of selected drug candidate in different oil, surfactant and co-solvents followed by selection of oil, surfactant, co-surfactant and co-solvent on the basis of above mentioned determination results, preparation of phase diagram for optimum combination of drug and excipients and then formulations were prepared by initially mixing oil with surfactant at 50-60°C. Drug compounds were dissolved into the mixture of surfactant and oil by constant stirring and kep at 50°C until a clear solution was obtained. All the mixtures stayed clear at room temperature [8].

Construction of pseudo ternary phase diagram

Pseudo-ternary phase diagrams are useful tools to determine the composition of an aqueous phase, oil phase and surfactant: co-surfactant phase that will yield a micro emulsion (ME), Liquid crystal (LC) and coarse emulsion (EM). Each corner of diagram typically represents 100% of the particular component. It is constructed to define the extent and nature of micro-emulsion region. The different phases are mix in different proportion to construct the phase diagram and identify the micro-emulsion region. Since four chemical species were incorporated in micro-emulsion, one of the components (co-surfactant) is in fixed ratio with surfactant. Each of the three components of the system is titrated with the aqueous phase until a phase changes between micro-emulsion and two phase of mixture were observed. Further addition of water it from the LC were detected under gentle stirring. By continuing the addition of water LC disappeared. However, unlike the first situation the mixture was somewhat cloudy and opaque which form the coarse emulsion. After optimization of the micro-emulsion region we draw the phase diagram with the help of software like Triplot 4.1.2 chemix.

Figure 5: (a) Pseudoternary phase diagram with following components : oil (Miglyol), surfactant–cosurfactant (Labrasol–Cremophor EL 1:1 and 2:1), and water. The gray area indicates the micro-emulsion region, (b) Pseudoternary phase diagram with following components: oil (Miglyol), surfactant–cosurfactant (Labrasol–Tween 80 1:1 and 2:1), and water. The gray area indicates the micro-emulsion region



(a) (b)

Factors affecting SMEDDS

Nature and dose of the 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 lipophillic phase. The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately 2) 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. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in the solubilizing and colloidal stabilizing environment of the gut. Pouton's study reveal that such formulations can take up to five days to reach equilibrium and that the drug can remain in a super-saturated state for up to 24 hours after the initial emulsification event. It could thus be argued that such products are not likely to cause precipitation of the drug in the gut before the drug is absorbed, and indeed that super-saturation could actually enhance absorption by increasing the thermodynamic activity of the drug. There is a clear need for practical methods to predict the fate of drugs after the dispersion of lipid systems in the gastro-intestinal tract. Polarity of the lipophilic phase: The polarity of the lipid phase is one of the factors that govern the drug release from the micro-emulsions. The polarity of the droplet is governed by the HLB, the chain length and degree of un-saturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces formed. The high polarity will promote a rapid rate of release of the drug into the aqueous phase. This is confirmed by the observations of Sang-Cheol Chi, 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 oil phase with highest polarity.

Characterization of SMEDDS

Turbidity measurement

This identifies efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. These measurements are carried out on turbidity meters, most commonly the Hach turbidity meter and the Orbeco-Helle turbidity meter. This apparatus is connected to a dissolution apparatus and optical clarity of formulation is taken every 15 s to determine clarity of nano or micro emulsion formed and emulsification time. Turbidity can also be observed in terms of spectroscopic characterization of optical clarity (i.e. absorbance of suitably diluted aqueous dispersion at 400 nm).

Droplet size

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size [9].

Electron microscopic studies

Freeze-fracture electron microscopy has been used to study surface characteristics of such dispersed systems. Because of the high lability of the samples and the possibility of artifacts, electron microscopy is considered a somewhat misleading technique. Particle size analysis and low-frequency dielectric spectroscopy have been used to examine the self-emulsifying properties of Imwitor 742 (a mixture of mono- and diglycerides of capric and caprylic aciss) and Tween 80 systems.

Zeta potential measurement

This is used to identify the charge of the droplets. In conventional SMEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids.

Determination of emulsification time

In this quantification the efficiency of emulsification of various compositions of the Tween 85 and medium-chain triglyceride systems using a rotating paddle to promote emulsification in a crude nephelometer. This enabled an estimation of the time taken for emulsification. Once emulsification was complete, samples were taken for particle sizing by photon correlation spectroscopy, and self-emulsified systems were compared with homogenized systems. The process of self-emulsification was observed using light microscopy. It was clear that the mechanism of emulsification involved erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size.

Cryo-TEM studies

For Cryo-Transmission Electron Microscopy (TEM), samples were prepared in a controlled environment verification system. A small amount of sample is put on carbon film supported by a copper grid and blotted by filter paper to obtain thin liquid film on the grid. The grid is quenched in liquid ethane at _1808C and transferred to liquid nitrogen at _1968C. The samples were characterized with a TEM microscope.

Liquefaction time

This test is designed to estimate the time required by solid SEDDS to melt in vivo in the absence of agitation to simulated GI conditions. One dosage form is covered in a transparent polyethylene film and tied to the bulb of a thermometer by means of a thread. The thermometer with attached tablets is placed in a round bottom flask containing 250 ml of simulated gastric fluid without pepsin maintained at 37±18°C. The time taken for liquefaction is subsequently noted.

Small-angle neutron scattering

Small-angle neutron scattering can be used to obtain information on the size and shape of the droplets. The term 'droplet' is used to describe micelles, mixed micelles and oil-swollen micelles

Throughout the present work. Small-angle neutron scattering experiments use the interference effect of wavelets scattered from different materials in a sample (different scattering-length densities).

Future prospects and concluding remarks

SMEDDS are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs is now possible by SMEDDS, which have been shown to improve oral bioavailability substantially. The efficiency of the SMEDDS formulation is case specific in most instances thus composition of the SMEDDS formulation should be determined very carefully. Since a relatively high concentration of surfactants is generally employed in the SMEDDS formulation, toxicity of the surfactant being used should be taken into account. In fact, a compromise must be reached between the toxicity and self-emulsification ability of the surfactant that is considered for use. The size and charge of the oil droplet in the emulsion formed are two other important factors that affect GI absorption efficiency. Versatility of SMEDDS could be proved if issues like method to predict solubilization state of the drug in vivo, interaction of lipid systems with components of capsule shell and basic mechanism of transport of SMEDDS through GIT are adequately addressed. Despite the proven ability of these systems relatively few lipid based product have been commercialized. The reasons underlying the lack of application of these technologies is not clear, but likely reflects the limited knowledge of the formulation parameters that are responsible for good in vivo performance and the fact that relatively few in vivo studies in human have been reported in literature when compared with conventional dosage forms. Perhaps more importantly the lack of effective in vitro tests that are predictive of in vivo performance has significantly hindered successful development of these self-emulsifying drug delivery systems [10].

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