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SELF-EMULSIFYING DRUG DELIVERY SYSTEM: A NOVEL APPROACH FOR ENHANCEMENT OF BIOAVAILABILITY

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ABSTRACT

Oral route is the easiest and most convenient route for drug administration. Oral drug delivery systems being the most cost-effective and leads the worldwide drug delivery market. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. This may lead to high inter- and intra subject variability, lack of dose proportionality and therapeutic failure. It is estimated that 40% of active substances are poorly water soluble (water insoluble in nature). For the improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations. Various technological strategies are reported in the literature including solid dispersions, cyclodextrines complex formation, or micronization, and different technologies of drug delivery systems. Including these approaches self-emulsifying drug delivery system (SEDDS) has gained more attention for enhancement of oral bio-availability with reduction in dose. SEDDS are isotropic mixtures of oil, surfactants, solvents and co-solvents/surfactants. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or micro-emulsions upon mild agitation following dilution by an aqueous phase. For lipophilic drugs, which have dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption.

This review article explains how self-emulsifying drug delivery systems can increase the solubility and bioavailability of poorly soluble drug.

Key words: Self emulsifying drug delivery system (SEDDS), Oil, Co-surfactant, Surfactant, Self-micro-emulsifying drug delivery systems (SMEDDS).

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INTRODUCTION

Oral route is the easiest and most convenient route for non invasive administration. Oral drug delivery system is the most cost-effective and leads the worldwide drug delivery market. The oral route is a problematic route for those drug molecules which exhibit poor aqueous solubility. When a drug is administered by oral route the first step for it to get solubilised and then absorbed. Approximately 40% of new chemical drug moieties have poor aqueous

solubility and it is a major challenge to modern drug delivery system. The rate limiting step for the absorption of these types of drugs is their solubilisation in the gastrointestinal tract. The drugs with poor aqueous solubility and high permeability are classified as Class II drug by Biopharmaceutical Classification System (BCS). Different approaches like micronisation, solid dispersion and complexation with cyclodextrins are used for formulation development, but in some selected cases, these approaches have been successful but they offer many other disadvantages^[1]. Self emulsifying drug delivery system (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are isotropic mixtures of oils and surfactants; sometimes it contains co-solvents and it can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. SEDDSs emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation. SEDDS can be administered orally in soft or hard gelatin capsules and form fine, relatively stable oil-in-water emulsions upon aqueous dilution. This article presents an overview of SEDDSs and their applications^[2].

SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SMEDDS requires the use of a co-surfactant to generate a micro emulsion. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm- 5 μm and the dispersion has a turbid appearance. SMEDDSs, however, have a smaller lipid droplet size (<200 nm) and the dispersion has an optically clear- to- translucent appearance. Both systems are associated with the generation of large surface area dispersions that provide optimum conditions for the increased absorption of poorly soluble drugs. The choice of whether a SEDDS or a SMEDDS is the preferred formulation option often depends on the interplay between the intrinsic properties of the drug compound and its solubility and dissolution profile during in vitro screening with a number of excipients^[3].

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 1.

$$DG = S N p r 2s$$

(Equation 1)

Where, DG= free energy associated with the process, N= number of droplets, r= radius of droplets, s= 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 reduce the interfacial energy as well as providing a barrier to prevent coalescence^[4].

DIFFERENCE AND SIMILARITIES BETWEEN SEDDS AND SMEDDS

SEDDS	SMEDDS
DIFFERENCE	
Can be a simple binary formulation with the drug And a lipidic excipient able to self-emulsify in Contact with GIF	Are composed of the drug compound, surfactant, and oil.
OR	
A system comprising drug, surfactant, oil.	
Lipid droplet size in the dispersion ranges From 200nm-5μm providing large surface area absorption. The dispersion has a turbid appearance.	Lipid droplet size in the dispersion is <200nm.
SEDDS system is not thermodynamically Stable in water or physiological condition.	SMEDDS system is thermodynamically Stable.
SIMILARITIES	
Form fine oil-in-water dispersion in contact with GIF	

COMPOSITION OF SEDDS

The self-emulsifying process depends on:^[5]

- The nature of the oil and surfactant
- The concentration of surfactant

▪ The temperature at which self emulsification occurs

Oils: Oils are the most important excipient because oil can solubilise the lipophilic drug in a specific amount and it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Both long chain triglyceride and medium chain triglyceride oils with different degrees of saturation have been used for the formulation of SEDDSs. Modified or hydrolyzed vegetable or edible oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semi synthetic medium chain triglyceride oils have surfactant properties and are widely replacing the regular medium chain triglyceride^[6].

Surfactant: Non-ionic surfactants with high hydrophilic-lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). Emulsifiers derived from natural sources are expected to be safer the synthetic once. The usual surfactant strength ranges between 30-60% w/w of the formulation in order to form a

stable SEDDS. A large quantity of surfactant may irritate the GIT and it can be proved that the Non-ionic surfactants are to be less toxic as compared to ionic surfactants. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilise relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules^[7].

Co solvents: Co-solvents like ethanol, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role as co-surfactant in the micro-emulsion systems. Although alcohol free self emulsifying microemulsions have also been described in the literature. Various examples of surfactant, co-solvents and oil are given in Table 1.

Table: 1 Example of Surfactants, Co-Surfactant and Co-Solvent Used in Commercial Formulations^[14]

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, Polypropylene 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

FORMULATION OF SEDDS

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble cosolvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions^[8].

The following should be considered in the formulation of a SEDDS:

- The solubility of the drug in different oil, surfactants and co solvents.
- The selection of oil, surfactant and co solvent based on the solubility of the drug and the preparation of the phase diagram.

The preparation of SEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co-solvent^[9].

The addition of a drug to a SEDDS is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil-surfactant ratio. So, the design of an optimal SEDDS requires preformulation-solubility and phase-diagram studies. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent^[10].

CHARACTERIZATION OF SEDDS

The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

Visual assessment: This may provide important information about the self-emulsifying and micro emulsifying property of the mixture and about the resulting dispersion^[11].

Turbidity Measurement: This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time^[12].

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. The reduction of the droplet size to values below 50 μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions.

Zeta potential measurement: This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.

Determination of emulsification time: Self-emulsification time, dispersibility, appearance and flow ability was observed.

BIOPHARMACEUTICAL ASPECTS

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been

comprehensively reviewed and the interested reader is directed to these references for further details.

Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms, including^[13]:

1. Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution
2. 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. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micelle structures and a further increase in solubilisation capacity.
3. Stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism.
4. Changes in the biochemical barrier function of the GI tract. 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 may also reduce the extent of enterocyte-based metabolism.
5. Changes in the physical barrier function of the GI tract. Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs.

APPLICATION

SEDDS formulation is composed of lipids, surfactants, and co-solvents. The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation. SEDDSs present drugs in a small droplet size

Table 2. Application of Self Emulsifying Drug Delivery Systems

Type of Delivery System	Drug	Oil	Surfactant	Co solvent	Improvement
SEDDS (Gelled)	Ketoprofen	Capex 200	Tween 80	Capmul MCM	Silicon dioxide was use for gelling. As the concentration of Silicon dioxide. Increase in the droplet size of emulsion and slows the drug diffusion. ^[15]
SEDDS	Carvediol	labrasol	Labrafil M	Transcutol P	It improves the oral bioavailability of carvedilol up to 41.3%when compare to conventional tablet. ^[16]
SMEDDS	Simvastatin	caproyl 90	Cremophore EL	Cabitol	The release rate of Simvastatin from SMEDDS was higher than conventional tablet. The oral bio availability of SMEDDS is about 1.5- fold higher than conventional tablet. ^[17]
Self Emulsifying Tablet	Diclofenac sodium	Goat fat	Tween 65	-	SEDDS tablets were formulated by pour molding using plastic mould. the tablet containing higher tween 65: goat fat content ratios give release rate. ^[18]

and well-proportioned distribution and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic by pass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the pre-systemic clearance in the GI mucosa and hepatic first-pass metabolism. Table 2 shows the SEDDSs prepared for oral delivery of lipophilic drugs in recent years.

CONCLUSION

From the above review we can conclude that Self-emulsifying drug delivery systems are approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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