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Abhijeet Ojha
DIT University, Faculty of Pharmacy, Mussoorie Diversion Road, Dehradun, India.

Mini Ojha
Govt. Polytechnic, Department of Pharmacy, Dwarahat, Almora, India.

N.V. Satheesh Madhav
DIT University, Faculty of Pharmacy, Mussoorie Diversion Road, Dehradun, India.

Corresponding Author
Abhijeet Ojha
Email:
abhi_pharm1@rediffmail.com

AN UPDATED REVIEW ON SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS)

Abhijeet Ojha, Mini Ojha & N.V. Satheesh Madhav

ABSTRACT

The oral route is the most common administration route for majority of drugs. But more than 40% of drugs exhibit poor aqueous solubility, resulting in low bioavailability, high intra and inter-subject variability, and a lack of dose proportionality by oral route. To improve the oral bioavailability of lipophilic drugs, self-emulsifying drug delivery systems (SEDDS) have emerged. SEDDS are isotropic mixtures of oil, surfactants, solvents and co-solvents.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 through the gastrointestinal tract for lipophilic drugs. SEDDS may be a promising strategy to improve the rate and extent of oral absorption. This article gives an overview of various formulation strategies, characterization and applications of SEDDS.

Keywords: Self emulsifying drug delivery systems (SEDDS), Hydrophobic drugs, Bioavailability enhancement, Lipid based drug delivery system, Surfactants.

INTRODUCTION

Low aqueous solubility is the major reason for poor oral absorption of many drugs. According to an FDA survey conducted between 1995 and 2002, only 9% of the new drug entities belong to BCS class-I category (high solubility-high permeability), majority of new drug candidates (approximately more than 40%) have poor aqueous solubility because of their low bioavailability. By using the methods like solid dispersion, cyclodextrin complexation and self-emulsification, the solubility and bioavailability of drugs can be improved [1].

SEDDS are isotropic mixtures of drug, lipids and surfactants, usually with one or more hydrophilic co-solvents or co-emulsifiers. On agitation followed by dilution with aqueous media, these systems can form fine emulsion. 'SEDDS' is a broad term, typically producing emulsions with a droplet size ranging from a few nanometers to several-microns. "Self micro- emulsifying drug delivery systems" (SMEDDS) indicates the formulations forming transparent micro emulsions with oil droplets ranging between 100 and 250 nm. "Self-nano-emulsifying drug delivery systems" (SNEDDS) is a recent term with the globule size ranging less than 100 nm. The self-emulsifying drug delivery systems can be prepared which, after oral administration in gelatin capsules, will emulsify within the gastric contents. Distribution of the emulsion within the GIT helps to avoid the irritancy[2].

According to Reiss, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion[3]. The free energy of a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by following equation:

$$\Delta G = \Sigma N i \pi r 2 \sigma$$

Where ΔG= Free energy associated with the process

N=Number of droplets

R=Radius

Σ= Interfacial energy.

Emulsification occurs spontaneously with SEDDS because the free energy required to form the emulsion is either low or positive or negative. It is necessary for the interfacial structure to show no resistance against surface shearing in order for emulsification to take place[4]. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/non-ionic surfactant) to water. This is followed by the solubilisation of water within the oil phase as a result of aqueous penetration through the interface. This will occur until the solubilisation limit is reached close to the interphase. Further aqueous penetration will lead to the formation of the dispersed phase. Thus, following gentle agitation of the self-emulsifying system, water will rapidly penetrate into the aqueous cores and lead to interface disruption and droplet formation.

COMPOSITION OF SEDDS

Oils

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, there by increasing absorption from the GI tract. Long-chain triglycerideand medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages. Novel semi synthetic medium-chain triglycerideoils have surfactant properties and are widely replacing the regular medium- chain triglyceride [5-6].

Surfactant

Nonionic surfactants with high hydrophilic-lipophilic balance (HLB) values are used in formulation of SEDDS (e.g. Tween, Labrasol, Labrafac CM 10,

Cremophoreetc). The usual surfactant strength ranges between 30–60%w/w of the formulation in order to form stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and helps to prolong the existence of drug molecules.

Cosurfactant/Cosolvents

Co-surfactant/Co-solvents like Spans, capyrol 90, Capmul, lauroglycol, diethylene glycolmonoethyl ether (transcutol), propylene glycol, polyethyleneglycol, polyoxyethylene, propylene carbonate,tetrahydrofurfuryl alcohol polyethylene glycol ether(Glycofurol), etc., may help to dissolve large amounts ofhydrophilic surfactants or the hydrophobic drugs in the lipid base. These co-solvents sometimes play the role of co-surfactants in the micro-emulsion systems.

DOSAGE FORM DEVELOPMENT OF SOLID SEDDS

Self-emulsifying capsules

Poor water soluble drugs can be dissolved in SEDDS and encapsulated in hard or soft gelatin capsules to produce convenient single unit dosage forms. Administration of capsules containing conventional liquid SE formulations form micro emulsion droplets and subsequently disperses in the GI tract to reach the site of absorption. However, if irreversible phase separation of the micro emulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation. With the similar purpose, the super-saturable SEDDS were designed, using a small quantity of HPMC in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state *in- vivo*. This system contains a reduced amount of a surfactant, there by minimizing GI side effects[7].

Dry emulsions

Dry emulsions are powders from which emulsion is formed in an aqueous solution. Dry emulsion formulations are typically prepared from o/w emulsions containing a solid carrier (lactose or maltodextrin) in the aqueous phase by rotary evaporation, freeze-drying or spray drying. Dry emulsion technology solves the stability problems associated with conventional emulsions (phase separation, contamination by microorganism, etc.) during storage.

Self- emulsifying tablets

Self-emulsifying sustained/controlled release tablets are developed. Colloidal silicon dioxide (Aerosil 200) is selected as a gelling agent for the oil-based systems, which serves the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release. The newest advance in the research field of SE tablet is the SE osmotic pump tablet, where the elementary osmotic pump system acts as the carrier of SES.

SE controlled-release pellets

Serratoni et al. prepared SE controlled-release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-

insoluble polymer that reduced the rate of drug release. Combinations of coating and SES controlled the *in- vitro* drug release by providing a range of release rates and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution[8].

Self-emulsifying solid dispersions

These formulations consist of a dispersion of the drug in an inert excipient matrix, but some manufacturing difficulties and stability problems exist. SE excipients like Gelucire1 44/14, Gelucire1 50/02, Labrasol1,Transcutol1 and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used in this field. Gupta et al. prepared SE solid dispersion granules using the hot-melt granulation method. Gelucire1 50/13 was used as the dispersion carrier, whereas Neusilinee US2 was used as the surface adsorbent[9].

Self-emulsifying sustained-release microspheres

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) exhibits potent pharmacological actions including tumor suppressive, antibacterial, and antithrombotic activity. You et al. prepared solid SE sustained-release microspheres using the quasi-emulsion–solvent-diffusion method of the spherical crystallization technique. With ZTO as the oil phase, ZTO release behavior could be controlled by the altering the ratio of hydroxypropylmethylcellulose acetate succinate to Aerosil 200 in the formulation[10].

Self-emulsifying nanoparticles

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nano particles were thereafter filtered out and dried. A second technique is that of sonication emulsion-diffusion-evaporation [11].

Self-emulsifying Suppositories

Some investigators proved that S-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester[12].

Self-emulsifying implants

Some copolymers have a bio resorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain. Such copolymers show SE property without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses[13].

CHARACTERIZATION OF SEDDS

The various ways to characterize SEDDS are Visual assessment, Droplet Size Analysis, Zeta potential measurement, Thermodynamic stability studies, Dispersibility test, Turbidimetric evaluation, Viscosity determination, Refractive index and Percent transmittance, Electro conductivity study, *In- vitro* diffusion study and Drug content determination[14,15].

Visual assessment

This may provide important information about the self-emulsifying and micro

emulsifying property of the mixture and about the resulting dispersion.

Droplet size analysis

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 stable, isotropic dispersions called SMEDDS.

Zeta potential measurement

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

Thermodynamic stability studies

These studies include heating cooling cycle, centrifugation and freeze thaw cycle. Six heating cooling cycles between 4^0C and 45^0C for not less than 48 h are performed. Those formulations, which are stable at these temperatures, are subjected to centrifugation test. The formulations are centrifuged at 3500 rpm for 30 min and stored between 21^0C and 25^0C for not less than 48 h. Those formulations that do not show any phase separation are taken for the freeze thaw stress test. Three freeze thaw cycles are performed for the formulations. Those formulations that pass this test show good stability with no phase separation, creaming, or cracking.

Dispersibility test

The efficiency of self-emulsification of oral nano emulsion or microemulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation is added to 500 mL of water at 37 ± 0.5 0C. A standard stainless steel dissolution paddle rotating at 50 rpm provides gentle agitation. The *in-vitro* performance of the formulations is visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 minute) nano emulsion, having a clear or bluish appearance.
Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
Grade C: Fine milky emulsion is formed within 2 minutes.
Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify.
Grade E: Formulation, with poor emulsification with large oil globules present on the surface.

Turbidimetric evaluation

Nephelo-turbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of self-emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter.

Viscosity determination

The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it can be easily pourable into capsules and such system should not be toot hick to create a problem. The rheological properties of the micro emulsion is evaluated by Brookfield

viscometer. This viscosity determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and vice-versa.

Refractive index and Percent transmittance

Refractive index and percent transmittance proves the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and compared with water (1.333)**.** The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water(1.333)and formulation has percent transmittance > 99 percent, then formulation has transparent nature.

Electro conductivity study

The SEDD system contains ionic or non-ionic surfactant, oil, and water. So, this test is used to measure the electro-conductive nature of system. The electro-conductivity of resultant system is measured by electro-conductometer.

***In- vitro* diffusion study**

In-vitro diffusion studies are performed to study the release behavior of formulation from liquid crystalline phase around the droplet using dialysis technique.

Drug content determination

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the extract is analyzed by suitable analytical method against the standard solution of drug.

APPLICATIONS OF SEDDS

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. SEDDS present drugs in a small droplet size and well-proportioned distribution, and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDS 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. The application of SEDDS for delivery of various drugs has been depicted in Table 1[16-20].

Table 1: Pharmaceutical applications of SEDDS

S.No.	Drug	Lipid	Surfactant	Improvement
1	Simvastatin	Lauroglycol:Captex (1:1)	Cremophor EL: Capmul MCM	Hypo lipidemic activity is increased
2	Griseofulvin	Myvacet	Capmul GMO-50	Increase in solubility
3	Ketoprofen	Captex 200	Tween 80	Droplet size of the emulsion increases and slows the drug diffusion
4	Vinpocetin	Labrafac: Oleic acid (40:10)	Cremophor EL	Improved bioavailability
5	Nimodipine	Gelucire 44/14	Labrasol	Improved *in-vitro*&*in- vivo* performance of nimodipine
6	Fenofibrate	LabrafacCM10	Tween 80	Improvement in drug release
7	Celecoxib	Capmul PG8	Tween 20	Improvement in bioavailability
8	Tacrolimus	Capmul MCM C8	Cremophor EL	Enhanced pharmacological activity
9	Puerarin	Oleic acid	Tween 80	Significant increase in bioavailability
10	Silymarin	Glyceryl monooleate	Polysorbate 20: HCO- 50 (1:1)	Improved bioavailability

CONCLUSION

SEDDS can be used in industry to fasten the oral bioavailability of the lipophilic drugs. Since the absorption of BCS class II drugs oral absorption is increased by SEDDS, it is one of the methods for increasing oral bioavailability of drugs. Since the development of SEDDS is hypothetical therefore, the *in-vitro* models used for the determination of oral bioavailability enhancement have to be designed. Care has to be exercised to maintain the quality and stability of drugs inside lipid systems. Any incompatibility between the components of capsules shells and the lipid systems will have to be evaluated. Despite of these challenges there is great prospect in the use of lipid formulation. Conductance of human bioavailability studies should be the priority for future research and more emphasis should be given towards the studies on the mechanisms of action of SEDDS formulations. *In-vitro* procedures for finding the dynamic changes occurring with the drug in the gut and the status of

solubilization state of the drug *in-vivo* shall have to be monitored, and then SEDDS can show the great future ahead in the field of drug delivery.

CONFLICT OF INTEREST

Nil

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