Review Article

BIOAVAILABILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS: SELF EMULSIFYING DRUG DELIVERY SYSTEM - A NOVEL APPROACH

V.Ravichandiran, K.Masilamani*, S.Sathesh kumar, V.Lavakumar
School of Pharmaceutical Sciences, Vels University, Old Pallavaram, Chennai, India.
*Corresponding author's E-mail: masilamani33@gmail.com

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ABSTRACT

Self emulsifying drug delivery system (SEDDS) has gained attention in the area of pharmaceutical research as a means of enhancing the oral bioavailability of poorly soluble drugs. Due to low bioavailability, many drugs are not suitable for oral delivery or dose is increased. SEDDS provide a possible way to deliver the drug with increased bioavailability. SEDDS are liquid to semi-solid in nature, but it has certain drawbacks like formulation development, storage, stability, etc. During the formulation certain parameters to be considered such as surfactant concentration, oil/surfactant ratio, droplet size etc. Despite of few disadvantages, this system has promising benefits such as improvement in dosage regimen, controlled release, stability and reproducibility. The present review explains the biopharmaceutical aspects, mechanism, formulation, evaluation, applications and future trends of SEDDS.

Keywords: Self emulsifying drug delivery system, Bioavailability, Poorly soluble drugs, Surfactant, Oral delivery.

1. INTRODUCTION

Most of the drugs are frequently administered by oral route. More than 40% of new chemical entities are poorly soluble which may be difficult to deliver the drug through oral route. The difficulties include low bioavailability, high intra and inter subject variability and a possible increased dose. To solve these difficulties, various strategies are used including the use of surfactants, lipids, permeation enhancers, micronization, nanonization, salt formation and solid dispersions.[1,2]

There are number of formulation strategies that can be used to improve the bioavailability of poorly soluble drugs, either by increasing the dissolution rate or by presenting the drug in solution and maintaining the drug in solution in the intestinal lumen. SEDDS 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. SEDDS forms fine o/w emulsions upon mild agitation followed by dilution in aqueous media such as GI fluids. SEDDS spread readily in gastrointestinal tract and the digestive motility of stomach and the intestine provides agitation by so that emulsions are formed.[3]

SEDDS are the formulations which are easy to manufacture. Thus, for lipophilic drugs substances SEDDS may produce an improvement in rate and extent of absorption which may produce increase in bioavailability. The GI irritation caused by a drug can be avoided or reduced by SEDDS by formation of oil droplets thereby reducing the contact time of the drug with GI. The SEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SEDDS formulation contains drug, vegetable oil, surfactant and co-solvent. It may contain antioxidant if required.[4,5] Certain polymers such as natural polymers (guar gum, latex), synthetic polymers (polyvinyl pyrrolidine, polyvinyl chloride) can also be incorporated into SEDDS to achieve controlled or sustained release.

1.1. Advantages:[6,7]

- Enhanced oral bioavailability
- Reduction in dose
- Protection of drugs from hostile environment in the gut.
- Targeting of drugs
- Controlled drug delivery
- Reduced variability including food effects.
- Reproducibility can be achieved.
- Patient compliance.

1.2. Disadvantages:[8,9]

- No accurate predictive *in vitro* models for assessment of the formulations.
- Low stability and portability.
- Large quantity of surfactants in the formulations can induce GI irritation.

2. BIOPHARMACEUTICAL ASPECTS

Bioavailability for poorly soluble drugs may increase in the presence of lipids or food. The mechanism is not clearly understood but possible mechanism includes

- Lipids alter/reduce the gastric transit and it causes slow delivery of drugs to the absorption site and increasing the time of dissolution.[10,11]

➢ Lipids increases the secretion of bile salts and endogenous biliary lipids including phospholipids and cholesterol which leads to the formation of micelles subsequently causing solubilisation capacity of the GIT

➢ Lipids may enhance the extent of lymphatic transport and increase bioavailability for highly lipophilic drugs, lipids. [12,13]

➢ Certain lipids and surfactants may suppress the activity of intestinal efflux transporters and may reduce the extent of enterocyte-based metabolism.[14]

➢ Lipids with surfactants possess permeation enhancing properties. [15]

3. SUITABLE DRUG CANDIDATES FOR SEDDS

Few points given below suggest the types of drugs suitable for SEDDS. It doesn't mean that all drugs in that type are suitable. Complete drug profile, pharmacokinetics, blood drug concentration required are to be considered by the research professional before developing the SEDDS.

- Low bioavailability / poorly soluble drugs
- Drugs possessing hydrophobic nature
- Drugs which cause GIT irritation
- Drugs which require controlled delivery
- Drugs which require targeted delivery
- Drugs which cause high intra and inter subject variability

4. MECHANISM

The exact mechanism behind the self-emulsification is not clearly known. According to '*Reiss',* self-emulsification occurs when the entropy change that favours 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. It can be represented by following equation:

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

Where, G is the free energy, N is the number of droplets of radius r and σ indicates the interfacial energy. [16-18]

According to "Wakerly et al", the addition of a binary mixture to water, results in interface formation between the oil and aqueous continuous phases, followed by the solubilisation of water within the oil phase owing to aqueous penetration through the interface. This process will occur until the solubilisation limit is reached close to the interface.[19,20]

5. FORMULATION APPROACH[21-23]

In the formulation of SEDDS, the first prerequisite to be considered is selection of oil and surfactant. Compatibility studies are to be performed for the drug with additives.

The steps involved in the formulation of SEDDS

- ➢ Solubility of the drug is determined in various oils and surfactants
- ➢ Series of SEDDS systems containing drug in various oils and surfactants are prepared.
- ➢ In-vitro self-emulsification properties droplet size of these formulations is studied.
- ➢ Pseudo-ternary phase diagram is constructed, which helps in identification of efficient self-emulsification region.
- ➢ From the pseudo ternary diagram optimized formulation is selected
- ➢ Bioavailability of optimized formulation is compared with reference formulation

The efficiency of oral absorption and bioavailability of a drug entity from the SEDDS depends upon many factors as given below.

- ➢ Surfactant concentration
- ➢ Oil/surfactant ratio
- ➢ Polarity of emulsion
- ➢ Droplet size and charge
- ➢ Solubility of drug in formulation
- ➢ The temperature at which self-emulsification occurs.

5.1. Composition of SEDDS

The main component of the dosage form is the drug. Except the drug the remaining components are as follows:-

5.1.1. Oils

It is the most important ingredient in the formulation of SEDDS. Lipophilic drugs are soluble in oily phase. It can increase self-emulsification and thereby increasing absorption from the GI tract as per the mechanism of action already discussed. Long chain triglycerides and medium chain triglycerides oil with different degrees of saturation have been used in the design of SEDDS. Hydrolysed vegetable oils have also been used in SEDDS because of their physiological advantages.[9,14] Novel semisynthetic medium-chain triglyceride oils possess surfactant properties and therefore widely used instead of regular medium- chain triglyceride.

5.1.2. Surfactants

Surfactants are usually classified as anionic, cationic and non-ionic. Non-ionic with high HLB values are used in the formulation of SEDDS. Non-ionic surfactants are less toxic when compared to ionic. Examples include tween, labrasol, cremophor etc. Normally a range of 30% to 60% w/w of surfactant strength is required to acquire a stable SEDDS formulation. Surfactants are amphiphilic in nature and they can solubilize relatively high amounts of hydrophobic drug compounds. This can prevent

precipitation of the drug in the GI and may suitable for prolonged existence of drug molecules.[12, 24]

5.1.3. Co-solvents

Co-solvents like propylene glycol, poly ethylene glycol, polyoxyethylene, lauroglycol, propylene carbonate etc may help to dissolve large amount of hydrophilic surfactants or the hydrophobic drug in the lipid base.[12,25]

Table1: Examples of Oils, Surfactants and Co-solvents

OILS	SURFACTANTS	CO-SOLVENTS
Cotton seed oil Soya bean oil Corn oil Sunflower oil Castor oil Peanut oil Sesame oil Olive oil	Polysorbate 20 Polysorbate 80 Sorbitan monooleate Labrasol Polyoxy-35-castor oil Polyoxy-40-hydrogenated -castor oil	Ethanol Polyethylene glycol Lauroglycol Transcutol Capmul

6. TECHNIQUES OF SOLID SEDDS DEVELOPMENT

Solid SEDDS were developed mainly by adsorption to solid carriers, spray drying, melt extrusion, solid dispersion etc.

6.1. Adsorption to solid carriers[26-29]

It is a simple and convenient process, where the emulsifying system is incorporated into a powder material known as solid carriers. Solid carriers are the substances which possess adsorption property which aids in development of SEDDS.

The ideal characteristics of solid carriers include

- Inertness
- Compatibility with drug and other additives
- Good adsorption property
- Free flowing property and
- Economic

In this technique liquid or semisolid formulations are converted to free flowing powders by adsorption to solid carriers. The resulting free flowing powder may be filled directly into capsules or mixed with suitable excipients and compressed into tablets. A remarkable advantage of this technique is that it can produce précised content uniformity. Solid carriers may be inorganic substances like silica, silicates, magnesium trisilicate, magnesium hydroxide, crospovidone, or may be cross-linked polymers like cross-linked sodium carboxy methyl cellulose, cross-linked polymethyl methacrylate or may be nanoparticle adsorbents like porous silicon dioxide, charcoal. Cross-linked polymers may be useful in sustaining the drug delivery. Aerosil is widely used as a carrier for drugs like ketoprofen, ezetimibe, etc.

6.2. Spray drying[30-32]

Spray drying is defined as a process by which a liquid solution is sprayed as fine droplets into a hot air chamber where the volatile portion evaporates leaving dried solid particles. This method involves preparation of formulation containing oil, surfactant, solid carrier, drug, etc. The prepared formulation is sprayed into a drying chamber. The volatile portion evaporates leaving small solid dried particles. These small solid dried particles are free flowing which makes it suitable for capsule filling or compression into tablets.

6.3. Melt extrusion[33-35]

Extrusion is a process of converting a substance with plastic properties into a product of uniform shape and density by forcing it through a die cavity under controlled temperature and pressure. This process holds valuable advantages such as high drug loading, solvent-free, as well as content uniformity. The size of the spheroids depends on the extruder aperture size. This method is suitable to prepare self emulsifying pellets of diazepam and progesterone which provides an increased bioavailability.

6.4. Melt granulation[36-38]

Melt granulation is a process in which granulation is obtained through the addition of a binder that melts at relatively low temperatures. The melted binder acts as a solvent which makes the powder into granules which is required for granulation step. The granules are converted to spheronized pellets by subsequent mixing under controlled conditions. The notable advantage of this technique includes no use of solvent. Generally, low HLB substances are suitable for sustained release and high HLB substances are suitable for immediate release.

7. CHARACTERIZATION OF SEDDS

7.1. Drug content

By using suitable solvent the drug is extracted from the formulation and then estimated by specified method.

7.2. Visual evaluation

Visual evaluation may provide some primary information about the self-emulsifying and micro emulsifying property of the SEDDS.

7.3. Turbidity measurement[39]

Nepheloturbidimeter is commonly used for turbidity measurement for SEDDS. Self emulsifying dosage form is added to fixed quantity of suitable buffer medium (0.1 N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at suitable temperature and the turbidity is measured.

7.4. Droplet size

The droplet size of the SEDDS should be controlled and monitored properly because it relates to the drug release and stability of the product. The size of the droplet can be measured by using any one of the techniques such as photon correlation spectroscopy, microscopy or coulter nanosizer. The size range between 10 to 5000 nm can be measured easily by using nanosizer. Usually 1ml solution

of SEDDS is mixed with 100 ml of 0.1N HCl buffer and then particle size is measured by using suitable technique.

7.5. Viscosity Determination

As the system is normally filled in soft or hard gelatin capsules, it should be easily pourable into capsules and it should not be too much viscous which may affect the filling process. Viscosity can be measured by using Brookfield viscometer or any other viscometer which suits for SEDDS.[40]

7.6. Zeta potential measurement

Zeta potential is used to identify the charge of the droplets. Due to presence of fatty acids the charge on oil droplet is negative. This test gives information about the stability and ionization of the product. [41, 42]

7.7. Emulsification time

According to H. Shen et al., based on self emulsification time, dispersibility, appearance and flowability the formulations were graded as given below:

Grade A: Rapidly forming (within 1 min.) emulsion having a clear/bluish appearance.

Grade B: Rapidly forming emulsion having slightly less clear /bluish white appearance.

Grade C: Fine milky emulsion (within 2 min)

Grade D: Dull white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min.).

Grade E: Formulation, which exhibits poor emulsification with large oil globules present on the surface.

Grade C could be recommended for SEDDS formulation.[43,44]

7.8. Thermodynamic stability studies

The thermodynamic stability of SEDDS can be performed by the following steps:

- **Heating cooling cycles:** SEDDS formulations are stored at 4°C and 45°C for not less than 48 hrs. Those which are stable at these temperatures are subjected to the centrifugation test.
- **Centrifugation:** Passed formulations are centrifuged between 21°C and ±25°C at 3500 rpm for 30 min with storage at each temperature not less than 48 hrs. Those formulations that does not show any phase separation are taken for the freeze thaw stress test. [8,45]
- **Freeze thaw cycle:** Three freeze thaw cycles were done for formulations. Those formulations passed this test showed good stability with no phase separation, creaming or cracking. [8,21]

8. DOSAGE FORMS FROM SELF EMULSIFYING SYSTEM:

8.1. SE capsules[46, 47]

In SE capsules liquid or semisolid can be filled in either hard or soft gelatin capsules. In the GIT, the capsules will disperse in the fluid to micron size, thereby enhancing the bioavailability. Solid medicament can also be dispensed as SE capsules. This system contains reduced amount of surfactant, thereby minimising the GI side effects. Phenytoin, metronidazole, atorvastatin drug molecules are available as SE capsules.

8.2. SE sustained/controlled release tablets[48]

SE tablets are mainly prepared as they are stable than the available dosage forms. Sustained action can be produced by using polymeric approach. The latest research in SE tablets is self emulsifying OROS, in which elementary osmotic pump serves as the carrier for the drug. Self emulsifying OROS have some advantages like providing stable plasma concentration and controllable release rate, and increased bioavailability. Solid self emulsifying tablet of diclofenac were prepared by using goat fat and tween 65. Carvedilol prepared as SEDDS tablets is used for treatment of hypertension and cardiac heart failure with controlled release.

8.3. SE pellets[49, 50]

Pellets possess many advantages over conventional solid dosage forms such as flexibility of manufacture, reducing the inter-subject and intra-subject variability of plasma profiles and reducing GI irritations. Combination of coating and SES could control in vitro drug release by providing a range of release rates. Sustained release matrix pellets can be successfully prepared with glyceryl palmito stearate and glyceryl benzoate. Examples are self emulsifying progesterone pellets and nitrendipine pellets

8.4. SE beads[42,50]

The deposition of SES into micro porous polystyrene may lead to SE beads. They are stable over wide range of pH, temperature and humidity. In vitro drug release and loading efficiency can be evaluated by bead size and pore architecture of beads.

8.5. SE microspheres

SE microspheres produce increased bioavailability and can be filled in capsules.

8.6. SE nanoparticles

SE nanoparticles can be prepared by solvent injection technique. Indomethacin nanoparticles were prepared to enhance its dissolution thereby increase in bioavailability.[51]

8.7. SE suppositories

Glycyrrhizin administered as vaginal or rectal suppositories can produce satisfactory therapeutic levels for chronic hepatic diseases.

9. CONCLUSION

A drug, although possessing pharmacological activity can't be dispensed as such. To fulfill the needs and to exhibit full pharmacological activity of a drug, it requires to be dispensed in suitable drug delivery system. Especially for poorly soluble drugs, special care to be taken to develop drug delivery systems. SEDDS are newer and provides proper enhancement of bioavailability for poorly soluble drugs. Solid, liquid and semi-solid substances can be filled and dispensed as SEDDS. The techniques and additives used to formulate SEDDS are economic and easy which makes this system more popular. There are also some difficulties in SEDDS like GI irritation due to surfactant and development of *in vitro* models which correlates to *in vivo* models. Future research should involve human bioavailability studies and other required studies to make full utilization of this system properly.

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