



Review Article

SELF EMULSIFYING DRUG DELIVERY SYSTEM: A PROMISING APPROACH FOR BIOAVAILABILITY ENHANCEMENT

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ABSTRACT

About 40% of the drug candidates have poor water solubility due to their low bioavailability. Self-emulsifying drug delivery systems (SEDDs) are mixtures of oils, surfactants and co-surfactants, which efficiently improve dissolution and bioavailability of sparingly soluble drugs by rapid self-emulsification. SEDDs belongs to lipid formulations, and size ranges from 100nm (SEDDs) to less than 50nm (SMEDDs). Lipophilic drugs can be dissolved in such systems, enabling them to be administered as a unit dosage form for per-oral administration. When such system is released in the lumen of the gastrointestinal tract, it disperses to form a micro/nano emulsion with the aid of GI fluid. These leads to solubilisation of drug that can subsequently be absorbed by lymphatic pathways, by passing the hepatic first pass effect.

Keywords: Self emulsifying drug delivery system, Surfactant, Oil, Marketed formulation of SEDDs.

INTRODUCTION

About 40% of the drug candidates identified via combinatorial screening programmes are poorly water soluble. The aqueous solubility for poorly water soluble drugs is usually less than 100 µg/ml.¹ Especially poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent the technological challenge, as their poor bioavailability is solely caused by poor water solubility resulting in low drug absorption.² Different techniques have been reported in the literature to achieve better drug dissolution rates. For example, (a) reduce the particle size via micronization or nanonization to increase the surface area, (b) co-grinding, (c) formulation of inclusion complexes, (d) solubilisation by surfactants, (e) solid dispersions, (f) inclusion of the drug solution or liquid drug into soft gelatine capsules such as self-emulsifying drug delivery systems.³

Self-emulsifying drug delivery systems (SEDDs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs.⁴ Self-emulsifying drug delivery systems (SEDDs) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. Recently, SEDDS have been formulated using medium chain tri-glyceride oils and non-ionic surfactants, the later being less toxic.^{5,6} Upon peroral administration, self-emulsifying formulations distribute readily in the GI tract, and the digestive motility of the stomach and the intestines provides sufficient agitation enough for the spontaneous formation of emulsions. In the case of sparingly soluble drugs that exhibit dissolution rate limited absorption, the SEDDs offers a way to improve the rate and extent of

oral absorption and to produce more reproducible blood-time profiles.⁷

Potential advantages of these systems include:

1. Enhanced oral bioavailability enabling reduction in dose,
2. More consistent temporal profiles of drug absorption,
3. Selective targeting of drug(s) toward specific absorption window in GIT,
4. Protection of drug(s) from the hostile environment in gut.
5. Control of delivery profiles
6. Reduced variability including food effects
7. Protective of sensitive drug substances
8. High drug payloads
9. Liquid or solid dosage forms⁵

Composition of SEDDs:

The SEDDs is commonly composed of the following:

Drugs:

Generally, SEDDs are prepared for drugs possessing poor water-solubility. BCS class II drugs are usually employed in preparation of SEDDs. Examples of drugs which belong to BCS class II include itraconazole, nifedipine, vitamin E, simvastatin, danazol, ketoconazole, mefenamic acid, carbamazepine, glibenclamide, cyclosporine-A, ritonavir^{8,9} etc.

Surfactant:

Numerous compounds exhibiting surfactant properties might be working for the design of self-emulsifying systems, but the choice is limited at the same time as very few surfactants are orally suitable, because safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactant. The most extensively suggested ones being the non-ionic surfactants with a relatively high hydrophilic lipophilic balance (HLB).¹⁰ The role of surfactant is to enhance absorption of drug, because of induction of permeation changes in biological membrane. It is reported that a cationic emulsion show greater absorption than an anionic emulsion. To form stable SEDDs, 30-60% concentration of surfactant is used.⁸

Oils:

Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SEDDs. 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 emulsification markedly reduces their use in SEDDs. Recently medium chain triglycerides are replaced by novel semi synthetic medium chain triglycerides containing compound such as GELUCIRE, other suitable oil phases are digestible or non-digestible oils and fats such as olive oil, corn oil, soya bean oil, palm oil and animal fats.⁹

Table 1: Type of surfactants used with drugs in SEDDs

| Surfactant | Drug |
|--------------------|---------------------------------|
| Tween 80 | Ibuprofen ¹¹ |
| PEG-35 | Cyclosporine-A ¹² |
| Cremophore EL | Furosemide ¹³ |
| Cremophore RH 40 | Glibenclamide ¹⁴ |
| Tween 80, Tween 20 | Diclofenac sodium ¹⁵ |

Table 2: Type of surfactants used in marketed SEDDs:

| Surfactant | Marketed Product | Drug |
|-----------------|---------------------------------------|----------------|
| Cremophor RH 40 | Neoral soft gelatine capsule | Cyclosporine A |
| Span 20 | Kaletra tablet, soft gelatine capsule | Lopinavir |
| Gelucire 44/14 | Lipofen hard gelatine capsule | Fenofibrate |
| Polysorbate 80 | Targretin soft gelatin capsule | Bexarotene |

Table 3: Type of oil used with drug in SEDDs

| Oil | Drug |
|-----------------|---------------------------------|
| Palm kernel oil | Ibuprofen ¹¹ |
| Castor oil | Cyclosporin-A ¹² |
| Captex 500 | Furosemide ¹³ |
| Capmul MCM C8 | Glibenclamide ¹⁴ |
| Lemon oil | Diclofenac Sodium ¹⁵ |

Table 4: Type of oil used in marketed preparation:

| Oil | Marketed product | Drug |
|----------------|---------------------------------|----------------|
| Corn oil | Sandimmune soft gelatin capsule | Cyclosporine A |
| Peppermint oil | Kaletra oral solutions | Lopinavir |
| Sesame oil | Marinol soft gelatin capsule | Dronabinol |
| Peanut oil | Prometrium soft gelatin capsule | Progesterone |

Co-solvents:

Usually an effective self emulsifying formulation requires a high concentration of surfactant. Accordingly, co-solvents such as ethanol, propylene glycol and polyethylene glycol are required to facilitate the dissolution of large quantities of hydrophilic surfactant. These co-solvents sometimes play the role of the co-surfactant in the micro-emulsion system. On the other hand, alcohol and other volatile co-solvents have the drawback of evaporating into the shell of soft or hard gelatin capsules, leading to precipitation of the drug.¹⁶

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.⁹ Examples are hydroxyl propyl methyl cellulose, ethyl cellulose, etc.

Mechanism of self-emulsification:

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 and can be described by the equation:

$$DG = S N_i \text{ pri } 2S (1)$$

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.¹⁷

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 co-solvents, 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. The following should be considered in the formulation of SEDDs:

1. The solubility of the drug in different oil, surfactants and co-solvents.
2. The selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram.
3. The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and co-solvent.
4. The addition of a drug to 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 optimal SEDDs requires pre-formulation solubility and phase-diagram studies. In the case of prolonged SEDDs, formulation is made by adding the polymer or gelling agent.¹⁰

Evaluation parameters:**Thermodynamic stability studies:**

The physical stability of a lipid -based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipients matrix. In addition, poor formulation physical stability can lead to phase separation of the excipients, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.⁵

The following cycles are carried out for these studies:

1. Heating cooling cycle: - Six cycles of cooling and heating between refrigerator temperature (4°C) and elevated temperature (45°C) with exposure at each temperature for not less than 48 hours are carried. Those formulations, which are stable, are then subjected to centrifugation test.

2. Centrifugation: - Formulations which pass the heating cooling cycle are centrifuged at 3500 rpm for 30 min. Those formulations that doesn't show any phase separation are taken for the freeze thaw stress test.
3. Freeze thaw stress cycle:- Three freeze thaw cycles b/w -21° C & 25° C with storage at each temperature for not less than 48 hours. Those formulations which pass this test show good stability with no phase separation, cracking or creaming.²⁰

Dispersibility test:

The efficiency of self-emulsification of oral nano or micro emulsion is carried out using a standard USP XXII dissolution apparatus II and the *in vitro* performance of the formulations is visually assessed using the following grading system

Grade A: Rapidly forming (within 1 min) 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 that formed within 2 minutes

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

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.¹⁸

Zeta potential measurement:

Zeta potential for micro emulsion can be determined using a suitable Zeta sizer²³. This is used to identify the charge of the droplets. In conventional SEDDS, the charge on an oil droplet is negative because of the presence of free fatty acids.¹⁹

Turbidimetric evaluation:

Nepheloturbidimetric 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 hot plate at appropriate temperature, and the increase in turbidity is measured, by using a turbidimeter. However, since the time required for complete emulsification

is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification).

Self emulsification time:

The self emulsification time is determined by using USP dissolution apparatus II at 50 rpm, where 0.5 g of SEDDS formulations is introduced into 250 ml of 0.1N HCL or 0.5% SLS solution. The time for emulsification at room temperature is indicated as self emulsification time for the formulation.²⁰

Viscosity determination:

The SEDDS system is generally administered in soft gelatin or hard gelatine capsules. so, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w.²¹

***In vitro* dissolution profile:**

Dissolution profiles of the self-emulsified formulations can be determined using USP dissolution apparatus II. The amount of drug released in the dissolution medium can determine by UV spectrophotometer. The dissolution experiment was carried out in triplicate.²²

Bioavailability study:

Based on the self emulsification properties, particle size data and stability of micro emulsion the formulation is selected for bioavailability studies. The *in vivo* study is performed to quantify the drug after administration of the formulation. Pharmacokinetic parameters of the maximum plasma concentration (C_{max}) and the corresponding time (t_{max}) for the drug following oral administration are calculated. The relative Bioavailability of SEDDS formulation to the conventional tablet is calculated using the following Equation Relative Bioavailability.

(%) = (AUC test/AUC reference) X (Dose reference/Dose test).²³

Conclusion:

SEDDs seem to be novel system and hence its use can be followed in industry to fasten the oral bioavailability of the lipophilic drugs. Since the absorption of BCS class II drugs oral absorption is increased by applying SEDDS, so it can be used as one of the methods for increasing oral bioavailability of drugs.

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