

SELF EMULSIFYING DRUG DELIVERY SYSTEM- A REVIEW**Akanksha Singh***

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ABSTRACT

As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water-soluble. It is a great challenge for pharmaceutical scientists to convert those molecules into orally administered formulations with sufficient bioavailability. Among the approaches to improve the oral bioavailability of these molecules, the use of self-emulsified drug delivery systems (SEDDS) has been shown to be reasonably successful in improving the oral bioavailability of poorly water-soluble and lipophilic drugs. Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can

be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. It can be orally administered in soft or hard gelatin capsules. These systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility. Many parameters like surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge plays a critical role in oral absorption of drug from SEDDS. This formulation enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation.

KEYWORDS: Self-emulsifying drug delivery systems, isotropic, emulsions and bioavailability.

INTRODUCTION^[1]

SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SEDDS 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 mm and the dispersion has a turbid appearance. 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.^[4-8] Recently, SEDDS have been formulated using medium chain tri-glyceride oils and non-ionic surfactants, the latter being less toxic. Upon per oral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility.^[2,4,9]

Table 1 application of SEDDS in relation to BCS classification^[10]

BCS class	Aqueous solubility	Membrane permeability	Hurdles overcome by SEDDS
1	High	high	Enzymatic degradation, gut wall efflux
2	Low	High	Solubilization, bioavailability
3	High	Low	Enzymatic degradation, gut wall efflux
4	Low	Low	Solubilization, enzymatic degradation

ADVANTAGES OF SEDDS^[11,12]

1. Quick Onset of Action.
2. Reduction in the Drug Dose.
3. Ease of Manufacture & Scale-up.
4. Improvement in oral bioavailability.
5. Inter-subject and Intra-subject variability and food effects.
6. Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.
7. No influence of lipid digestion process.
8. Increased drug loading capacity.

DISADVANTAGES OF SEDDS^[12]

1. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
2. This in vitro model needs further development and validation before its strength can be evaluated.

3. Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested in vivo in a suitable animal model.

4. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

EXCIPIENTS CLASSES

A) Lipid based excipients

The lipid based excipients encompasses vegetable oil and their derivatives.

1) Vegetable oils

Vegetable oils contain mixture of triglycerides (90 to 95% w/w) but also free fatty acids, phospholipids and non saponifiable product such as pigments and sterols or fat soluble vitamins like tocopherol and carotenoids that act as natural antioxidant.^[13]

2) Vegetable oil derivative

The main vegetable oil derivatives are hydrogenated vegetable oil, partial glyceride, polyoxyglyceride, ethoxylated glyceride and esters of edible fatty acid and various alcohols.^[13]

Partial glycerides are products of glycerolysis. The physical aspect, melt characteristics and the HLB of partial glycerides vary depending on the nature of the fatty acid present and the degree of esterification with glycerol to yield mono and diglycerides.^[14]

B) SURFACTANTS^[15,16]

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) 34. Safety is a major determining factor in choosing a surfactant. The four main groups of surfactants are defined as following-

- 1) Anionic surfactants
- 2) Cationic surfactant
- 3) Ampholytic surfactants
- 4) Nonionic surfactants

1) Anionic Surfactants:- where the hydrophilic group carries a negative charge such as carboxyl (RCOO^-), sulphonate (RSO_3^-) or sulphate (ROSO_3^-). Examples: Potassium laurate, sodium lauryl sulphate.

2) Cationic surfactants: - where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.

3) Ampholytic surfactants: - (also called zwitter ionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

4) Nonionic surfactants: - where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene. Examples: Sorbitan esters (Spans), poly -sorbates (Tweens).

C) COSOLVENTS^[17]: The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value.^[18]

At this value the interface would expand to form fine dispersed droplets and subsequently adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. However, the use of co-surfactant in self emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SEDDS, but also to solubilization of the drug in the SEDDS.

METHOD OF PREPARATION

A) Solidification techniques for transforming liquid/semisolid^[19]

Various solidification techniques are as listed below.

1) Capsule filling with liquid and semisolid self-emulsifying formulations

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process:

A) Heating of the semisolid excipient to at least 20°C above its melting point.

B) Incorporation of the active substances (with stirring).

C) Capsule filling with the melt cooling to room temperature. For liquid formulations, it involves a two-step process.

D) Filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro spray sealing.

2) Spray drying: Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets.

The droplets are introduced into a drying chamber, where the volatile phase (e.g. the water contained in an emulsion) evaporates into tablet pattern and the drying chamber design are selected according to the drying characteristic the product and powder specification.

3) Adsorption to solid carriers: Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid On to carriers by mixing in a blender.

4) Melt granulation: Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures.

5) Melt extrusion/extrusion spheronization: Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity.^[20] Extrusion is a procedure of product of uniform shape and density, by forcing it through a die under controlled temperature, product flow and pressure conditions.^[21]

CHARACTERIZATION OF SEDDS

Ternary phase diagram

Pseudo ternary diagrams are often constructed for development of SEDDS that help in determining the optimum concentration of different excipients necessary to obtain homogeneous pre-concentrates, self-emulsification ability and drug loading. In this method water is incorporated to the SMEDDS pre-concentrate in drop wise manner, with gentle stirring to allow equilibration. Addition of water leads to formation of a complex system ranging from gels to system containing lamellar, hexagonal phases to micro emulsions. The mixture is visually examined for transparency. The points from clear to turbid and turbid to clear are designated as emulsion and micro emulsion.^[22]

Droplet size

Droplet size is important factor in self –emulsification performance because it determines the rate and extent of drug release as well as absorption. It is measured by dynamic light scattering techniques. This employs the fluctuation in scattered light intensity to measure the velocity of Brownian diffusion and consequently the dispersed droplets. Photon correlation spectroscopy, coulter nanosizer are mainly employed for the determination of the emulsion droplet size.^[23,24]

Zeta potential

This is used to identify the charge on the droplets. The charge on the oil droplets is due to in conventional SMEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1-3% will yield cationic SMEDDS. Zeta potential help to predict the stability and flocculation effect in emulsion systems. If zeta potential falls below a certain level, colloid will aggregate due to attractive forces. Conversely, a high zeta potential maintains a stable system.^[25]

Emulsification rate

The rate of self emulsification is usually determined by adding a dose of the SMEDDS pre-concentrate, preferably in a capsule, to a relevant amount of water or biorelevant media. Rate of dispersion is determined by visual observation.

FORMULATION OF SEDDS**The following points should be considered in the formulation of a SEDDS**

Selection of oils, surfactant and co-solvent based on the solubility of the drug. The preparation of SEDDS formulation by dissolving the drug in mixture of oil, surfactant, co-solvents. The addition of drug to SEDDS is critical because the drug interferes with the self emulsifying process to certain extent, which leads to a change in optimal oil- surfactant ratio so design of optimal SEDDS require pre-formulation solubility and phase diagram study. Recently synthesized drug that are being discovered are lipophilic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Because of their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate limiting step in their absorption and systemic availability.

More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophilic active moieties (BCS class II drugs), lipid based formulations are inviting increasing attention.^[26,27] Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs. The Self-Dispersing Lipid Formulations (SDLFs) is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/lipophilic drugs and to improve the oral bioavailability of poorly absorbed drugs.^[11,33] The SDLFs contain oil and surfactant mixture into which the drug is incorporated. They emulsify when mixed with aqueous environment. The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio and the temperature at which self-emulsification occurs. After self-dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. The SDLFs are of two kinds namely, Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion. Many researchers have reported applications of SEDDS for delivering and targeting lipophilic drugs, e.g.: Coenzyme Q10^[28], Vitamin E^[29], Halofantrine^[30] and Cyclosporine A.^[31]

THE EMULSIFICATION PROCESS

Self-emulsification is a phenomenon which has been widely exploited commercially in formulations of emulsifiable concentrates of herbicides and pesticides.^[32] Concentrates of crop sprays are to be diluted by the user, such as farmers or house-hold gardeners, allowing very hydrophobic compounds to be transported efficiently. In contrast, SMEDDS, using excipients acceptable for oral administration to humans, have not been widely exploited and knowledge about their physicochemical principles is therefore limited.

A) Mechanism of Self Emulsification^[33]: In emulsification process the free energy (ΔG) associated is given by the equation:

$$\Delta G = \Sigma N \pi r \sigma \text{ ----- (1)}$$

In which 'N' is Number of droplets with radius 'r' and ' σ ' is interfacial energy. It is apparent from equation that the spontaneous formation of the interface between the oil and water phases is energetically not favored. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. The emulsification

process may be associated with the ease with which water penetrates the oil-water interface with the formation of liquid crystalline phases resulting in swelling at the interface thereby resulting in greater ease of emulsification.^[34-36] However, for system containing co-surfactant, significant partitioning of components between the oil and aqueous phases may take place leading to a mechanism described as “diffusion and stranding”, where by the oil is solubilized, leading to migration in to the aqueous phase.

B) Dilution phases: Upon dilution of a SMEDDS formulation, the spontaneous curvature of the surfactant layer changes via a number of possible liquid crystalline phases. The droplet structure can pass from a reversed spherical droplet to a reversed rod-shaped droplet, hexagonal phase, lamellar phase, cubic phase and various other structures until, after appropriate dilution, a spherical droplet will be formed again dilution.

EVALUATION^[37-39]

A) 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 excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, 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.

1) Heating cooling cycle: Six cycles between refrigerator temperature (40°C) and 45°C with storage at each temperature of not less than 48 hr is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

2) Centrifugation: Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at temperature for not less than 48 hr is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

3) Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

B) Dispersibility test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to

500 mL of water at $37 \pm 0.50^\circ\text{C}$. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following.

Grading system

Grade A: Rapidly forming (within 1 min) nanoemulsion, 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 min.

Grade D: Dull, grayish 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.

C) 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 plate at ambient temperature and the increase in turbidity is measured 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).

D) 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 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. If system has low viscosity then it is o/w type of the system and if high viscosities then it are w/o type of the system.

E) Droplet Size Analysis Particle Size Measurements: The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm.

FUTURE TREND

In relation to formulation development of poorly soluble drugs in the future, there are now techniques being used to convert liquid/semi-solid SEDDS and SMEDDS formulations into powders and granules, which can then be further processed into conventional 'powder-fill' capsules or even compressed into tablets. Hot melt granulation is a technique for producing granules or pellets, and by using a waxy solubilising agent as a binding agent, up to 25% solubilising agent can be incorporated in a formulation. There is also increasing interest in using inert adsorbents, such as the Neusilin products for converting liquids into powders – which can then be processed into powder fill capsules or tablet. Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules.

The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract.

Table 2: MARKETED SEDDS FORMULATION^[39-42]

Brand name	Drug used	Dosage form	company
Neoral	Cyclosporine	SGC	Novartis
Norvir	Ritonavir	SGC	Abbot laboratories
Fortovase	Saquinavir	SGC	Hoffmann roche
Agenerase	Amprenavir	SGC	GSK
Convulex	Valporic acid	SGC	Pharmacia

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