



Review Article

ENHANCING THE SOLUBILITY OF BCS CLASS II AND IV DRUGS BY SEDDS APPROACH- a structured review

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ABSTRACT:

Purpose: The solubility of orally administered hydrophobic drugs is a major challenge for pharmaceutical formulators as nearly 35-40% of newly launched drugs possess low aqueous solubility which leads to poor dissolution and low bioavailability, resulting in high intra & inter subject variability & lack of dose proportionality.

Approach: Self-Emulsifying Drug Delivery System, (SEDDS) is gaining popularity for improving the solubility of lipophilic drugs. Therefore, various formulation strategies have been investigated to improve the solubility and the rate of dissolution to enhance the oral bioavailability of lipophilic drugs.

Finding: This review mainly discusses about the mechanism of SEDDS, excipient used in SEDDS, dosage forms, evaluation, applications, advantages and drawbacks

Conclusion: SEDDS 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.

Key words: *SEDDS, Hydrophobic drugs, Micro emulsion, Lipid based system.*

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Introduction

SEDDS (Self-Emulsifying Drug Delivery System) are defined as isotropic mixtures of natural, synthetic oils, surfactants or alternatively one or more hydrophilic solvents and co solvents and surfactants.^{1,2} SEDDS is one of the best choices for the formulators to overcome the problem of solubility and bioavailability of many hydrophobic drugs. Hence it has received meticulous attention as a means of enhancing oral bioavailability of poorly soluble drugs. SEDDS formulation disperse into fine emulsion droplets inside the lumen of the gut where drug remains in solution state avoiding the dissolution step that frequently limit the rate of

absorption of hydrophobic drugs from the crystalline form. The mechanism of 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 potential advantages of this system include enhance oral bioavailability, enabling reduction in dose, more consistent temporal profile of drug absorption, selective targeting of drug towards specific absorption window in gastro intestinal tract and protection of drug from the hostile environment in gut. SEDDS are physically stable formulations which have a high extent of absorption and more reproducible plasma concentration profile easy to manufacture. An additional advantage of SEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. Thus, SEDDS can be an efficient vehicle for class II to Class IV molecules of biopharmaceutical classification system drugs.³

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MECHANISM OF SELF-EMULSIFICATION

Self emulsification occurs, when the entropy (energy) change occurs. The free energy of 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 the equation.

$$\Delta G = 4\pi N r^2 \sigma$$

Where, ΔG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius r , σ is interfacial energy with time. The two phases of the emulsion will tend to separate, in order to reduce the interfacial area and subsequently, the free energy of the system. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets and hence, reduce the interfacial energy, as well as providing a barrier to coalescence. In case of self-emulsifying system, the free energy required to form the emulsion is either very low or positive or negative then, the emulsion process occurs spontaneously. Emulsification requires very little input energy, involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing. Emulsification can be associated with the ease by which water penetrates into the various liquid crystals or phases get formed on the surface of the droplet. The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the 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, which occurs until the solubilisation limit is reached close to the interface. Further, aqueous penetration will result in the formation of the dispersed liquid crystalline phase. As the aqueous penetration proceeds, eventually all materials close to the interface will be liquid crystal, the actual amount depending on the surfactant concentration in the binary mixture once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self-emulsification process causes interface disruption and droplet formation. The high solubility of these self-emulsified systems to coalescence is considered to be due to liquid crystal interface surrounding the oil droplets.^{4,5}

EXCIPENTS USED IN SEDDS

- A) **OILS** The oil represents one of the most important excipient in the SEDDS formulation not only because it can solubilise the required dose of the lipophilic drug or facilitate self emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self emulsifying formulations.
- B) **SURFACTANTS:** 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)

Safety is a major determining factor in choosing a surfactant. The four main groups of surfactants are defined as following-

- A) Anionic surfactants
- B) Cationic surfactant
- C) Ampholytic surfactants
- D) Non-ionic surfactants

A) **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.

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

C) **Ampholytic surfactants:** - (also called zwitterionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

D) **Non-ionic 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) CO-SOLVENTS : 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. 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 solubilisation of the drug in the SEDDS.^{5,6}

DOSAGE FORM OF SEDDS:

(1) Oral delivery:

- ❖ Self emulsifying capsule: After administration of capsules containing conventional liquids SEDDS formulations, microemulsion droplets form and subsequently disperse in the GIT to reach site of absorption. If irreversible phase separation of microemulsion occurs an improvement of drugs absorption can't be expected. For handling this problem, sodium dodecyl sulphate was added into the SEDDS formulation
- ❖ Self emulsifying sustained / controlled release: Combination of lipids and surfactant has presented great potential preparing SE tablets. SE tablets are of great utility in obviating adverse effect. Inclusion of Indomethacin (or other hydrophobic NSAID) for example, into SE tablets may increase its penetration efficacy through GI mucosal membrane, potentially reducing GI bleeding.
- ❖ Self emulsifying sustained / controlled release pellets: Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage form, such as flexibility of manufacture, reducing intra subject and inter subject variability of plasma profile and minimizing GI irritation without lowering drug bioavailability.

❖ Self emulsifying solid dispersions: Solid dispersions could increase the dissolution rate and bioavailability of poorly water soluble drugs but still some manufacturing difficulties and stability problems existed.

(2) Topical Delivery: Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drugs and related toxicity effects.

(3) Oculars and Pulmonary delivery: For the treatment of eye disease, drugs are essentially delivered topically o/w microemulsion have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

(4) Parenteral delivery: Parenteral administration of drugs with limited solubility is a major problem in industry because of the extremely low amount of drug actually delivered as target site.^{7,8}

Evaluation

(1) 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 gelatine capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

❖ Heating cooling cycle: Six cycles between refrigerator temperature (4°C) and 45°C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

❖ Centrifugation: Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 48 h 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.

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

(2) Dispersibility test:

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One millilitre of each formulation was added to 500 ml of water at 37 ± 0.5 °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: Finemilky emulsion that formed within 2 min.

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.

(3) Turbidimetric Evaluation:

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Selfemulsifying 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 turbid meter. 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).

(4) Viscosity Determination:

The SEDDS system is generally administered in soft gelatine 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 deter-

mination conform whether the system is w/o or o/w. If the system has low viscosity then it is o/w type of system and if it high viscosities then it is w/o type of the system.

(5) 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. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water.

Refractive Index and Percent

(6) Transmittance:

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water. 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 and formulation have percent transmittance > 99 percent, then formulation have transparent nature.

(7) Electro conductivity Study:

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

(8) In Vitro Dissolution Study:

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

(9) Drug content:

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.^{9,10}

APPLICATIONS

SEDDS formulation is composed of lipids, surfactants, and cosolvents. The system has the ability to form an oil-in water emulsion. When dispersed by an aqueous phase under gentle agitation, the drugs present in SEDDS showcase itself in a small droplet size and well proportioned distribution, and increase the dissolution and permeability, furthermore the 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.

Below Table shows Applications of Self emulsifying Drug Delivery Systems

Type of delivery system	drug	Oil	Surfactant	Co-surfactant	Improvement
SEDDS (Gelled)	Ketoprofen	Caplex	Tween	Capmul MCM	Silicon-di-oxide was used as gelling agent. As the concentration of silicon-di-oxide increases, it causes an increase in droplet size of emulsion and slows the drug diffusion
SEDDS	Carvedilol	Labrasol	Labrafil M	Transcutol	It improves the oral bioavailability of the drug up to 413% when compared to conventional tablet
SMEDDS	Simvastatin	Caproyl	Cremophore	Carbitol	The release rate of drug from SMEDDS Was higher than the conventional tablet
Self-emulsifying tablet	Diclofenac sodium	Goat fat	Tween 65	-----	The tablet containing higher Tween 65 :goat fat content ratios give better release rate
Self-emulsifying pellets	Methyl and Perabens	Capric & caprylic acids	Tween 80	-----	Self emulsifying formulation improves the rate of drug release from the pellets by applying water insoluble polymer

❖ **Improvement in Solubility and bioavailability:** If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in of Class-? drug (Low solubility/high permeability). Ketoprofen, a moderately hydrophobic nonsteroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also because of its low solubility, Ketoprofen shows incomplete release from sustained release formulations. This formulation enhanced bioavailability due to increase the solubility of

drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of Ketoprofen. In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate Oil in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore, increase in AUC i.e. bioavailability and Cmax is observed with many drugs when presented in SEDDS.

❖ **Protection against Biodegradation:**
The ability of self emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic PH in stomach, enzymatic degradation or hydrolyte Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might act as a barrier between degrading environment and the drug.

Ex: - Acetylsalicylic acid a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an acid environment. The oral bioavailability of undegraded acetylsalicylic acid is improved by 73% by the Galacticles Oral Lipid Matrix

❖ **Controlling the release of drug:**
Different formulation approaches that have been sought to achieve sustained release, increase the bioavailability, and decrease the gastric irritation of Ketoprofen include preparation of matrix pellets of nanocrystalline Ketoprofen, sustained release Ketoprofen-micro particles and floating oral Ketoprofen systems and transdermal systems of Ketoprofen. Preparation and stabilization of nano-crystalline or improved solubility forms of drug may pose processing, stability, and economic problems. This problem can be successfully overcome when Ketoprofen is presented in SEDDS formulation. This formulation enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of Ketoprofen.^[10,11]

ADVANTAGES OF SEEDS:

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

DISADVANTAGES OF SEDDS^{11,12}

- Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- This in vitro model needs further development and validation before its strength can be evaluated.
- 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.
- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

FUTURE TRENDS IN SEDDS DEVELOPMENT:

The fact that almost 50% or more than of the new drugs are hydrophobic by nature implies that SEDDS studies should continue, where more SEDDS formulations should be released at the pharmaceutical market. Formulating these compounds using lipid based systems is one of the growing interest and suitable drug delivery strategies are applied to this class of molecules. Recent advances in these formulation technologies have led to the successful commercialization of lipid-based formulations. Still there is low uptake of lipid-based formulations due to the large empirical development strategies, which include only few commercially successful drug products in the market. There are a number of issues in relation to lipid-based systems which require further investigation including; an understanding of physicochemical properties of lipids and how lipids reduce the variability in plasma

profile, lipid drug interactions and formulation classification systems, a better understanding of the versatility of lipid systems and standard methodologies by which the best formulation can be selected for each drug.¹²

CONCLUSION

Lipid-based formulations are a key technology to formulating lipophilic compounds and represent an alternative for improving the oral absorption. SEDDS are usually explored to improve the bioavailability of hydrophobic drugs. Currently, several formulations have been developed to produce modified emulsified formulations as alternatives to conventional SEDDS. The vast amount of research on the use of SEDDS for enhancing the bioavailability of hydrophobic drugs has paved the way for the development of novel commercial drugs. SEDDS formulations are a promising pharmaceutical form for the oral administration of hydrophobic drugs to improve their solubility as well as their bioavailability profile.^{13,14,15}

GLOSSARY:

SEDDS : Self-emulsifying Drug Delivery System is a formulation approach which is used to increase the solubility of hydrophobic drugs and to make a stable emulsion.

Hydrophobic Drugs: These are the heterogeneous drug molecules that exhibit poor solubility in water but that are typically, but certainly not always, soluble in various organic solvents.

Micro emulsions: Dispersion made of water, oil, and surfactant(s) that is an isotropic and thermodynamically stable system with dispersed domain diameter varying approximately from 1 to 100 nm, usually 10 to 50 nm.

Lipid based systems: It's a system that has an impact on solubility, permeability, absorption, distribution, and metabolism; to produce physically and chemically stable formulations that offer safe and effective means to deliver drugs to the intended site of absorption/action.

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