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Self-Eumlsifying Drug Delivery System A Novel Approach for enhancement of Bioavalibility

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Abstract : Oral route is the easiest and most convenient route for drug administration. Oral drug delivery systems being the most cost-effective and leads the worldwide drug delivery market. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. This may lead to high inter- and intra subject variability, lack of dose proportionality and therapeutic failure. It is estimated that 40% of active substances are poorly water soluble (water insoluble in nature). For the improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations. Various technological strategies are reported in the literature including solid dispersions, cyclodextrines complex formation, or micronization, and different technologies of drug delivery systems. Including these approaches self-emulsifying drug delivery system (SEDDS) has gained more attention for enhancement of oral bio-availability with reduction in dose. SEDDS are isotropic mixtures of oil, surfactants, solvents and co-solvents/surfactants. 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. For lipophilic drugs, which have dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption.
This review article explains how self-emulsifying drug delivery systems can increase the solubility and bioavailability of poorly soluble drug.
Key words: Self emulsifying drug delivery system (SEDDS), oil, co-surfactant, surfactant, self-micro-emulsifying drug delivery systems (SMEDDS).

Introduction

Oral route is the easiest and most convenient route for non invasive administration. Oral drug delivery system is the most cost-effective and leads the worldwide drug delivery market. The oral route is a problematic route for those drug molecules which exhibit poor aqueous solubility. When a drug is administered by oral route the first step for it to get solubilized and then absorbed. Approximately 40% of new chemical drug moieties have poor aqueous solubility and it is a major challenge to modern drug delivery system. The rate limiting step for the absorption of these types of drugs is their solubilization in the gastrointestinal tract. The drugs with poor aqueous solubility and high permeability are classified as class II drug by Biopharmaceutical classification system (BCS). Different approaches like micronization, solid dispersion, and complexation with cyclodextrins are used for formulation development, but in some selected cases, these approaches have been successful but they offer many other disadvantages. [1]

Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are isotropic mixtures of oils and surfactants; sometimes it contains co-solvents, and it can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. SEDDSs emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation. SEDDS can be administered orally in soft or hard gelatine capsules and form fine, relatively stable oil-in-water emulsions

upon aqueous dilution. This article presents an overview of SEDDSs and their applications. [2]

Self-emulsifying formulations spread readily in the gastrointestinal tract (GIT), and the GI motility of the stomach and the intestine provide the necessary agitation for self emulsification. These systems have the advantage that the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. [3] SEDDSs typically produce emulsions with a droplet size between 100–300 nm while self-micro-emulsifying drug delivery systems (SMEDDSs) form transparent micro-emulsions with a droplet size of less than 50 nm. SEDDSs are physically stable formulations that are easy to manufacture, but when compared with emulsions, which are sensitive and metastable dispersed forms. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles[4]. The process of self-emulsification proceeds through formation of liquid crystals (LC) and gel phases. Release of drug from SEDDS is highly dependent on LC(liquid crystal) formed at the interface, since it is likely to affect the angle of curvature of the droplet formed and the resistance offered for partitioning of drug into aqueous media.[5]

Why SEDDS are Needed

SEDDS are promising approach for oral delivery of poorly water-soluble compounds. It can be achieved by pre-dissolving the compound in a suitable solvent and fill the formulation into capsules. The oral drug delivery of hydrophobic drugs can be made possible by SEDDS. 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, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favour the drug remaining in the lipid droplets.[6]

Potential Advantages of these Systems Include [7]

1. Protection of sensitive drug substances
2. More consistent drug absorption,
3. Selective targeting of drug(s) toward specific absorption window in GIT,
4. Protection of drug(s) from the gut environment.
5. Control of delivery profiles
6. Reduced variability including food effects
7. Enhanced oral bioavailability enabling reduction in dose
8. High drug loading efficiency
9. For both liquid and solid dosage forms

Composition of SEDDSS

The self-emulsifying process depends on: [8]

- The nature of the oil and surfactant
- The concentration of surfactant
- The temperature at which self-emulsification occurs.

Oils:. Oils are the most important excipient because oils can solubilize the lipophilic drug in a specific amount and it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. [10] Both long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used for the formulation of SEDDSs. Modified or hydrolyzed vegetable or edible oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages.[9] Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.[10]

Surfactant: Non-ionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). Emulsifiers derived from natural sources are expected to be safer the synthetic once. The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. A large quantity of surfactant may irritate the GIT and it can be proved that the Non-ionic surfactants are to be less toxic as comp aired to ionic surfactants. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or 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 for prolonged existence of drug molecules.[11]

Cosolvents: Co-solvents like ethanol, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role as co-surfactant in the micro-emulsion systems.[12] Although alcohol free self emulsifying micro emulsions have also been described in the literature.

Various examples of surfactant, co-solvents and oil are given in **table 1.**

Formulation of SEDDSS:

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble cosolvents, 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.[13]. The following should be considered in the formulation of a SEDDS:

- The solubility of the drug in different oil, surfactants and cosolvents.
- The selection of oil, surfactant and cosolvent based on the solubility of the drug and the preparation of the phase diagram.[14]
- The preparation of SEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co-solvent.

The addition of a drug to a 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 an optimal SEDDS requires preformulation-solubility and phase-diagram studies. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent [15].

Mechanism of Self-Emulsification:

The process by which self-emulsification takes place is not yet well understood. However, 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. In addition, 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 equation

$$\Delta G = \sum_i N_i \pi r_i^2 \sigma$$

Where, **G** 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. 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 systems.[16]

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.. Emulsification requiring 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. [17] In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously)

Evaluation:

Thermodynamic Stability Studies:

The physical stability of a lipid –based formulation is also important to its performance, which can produce adverse effect in the form of precipitation of the drug in the excipient matrix. In addition, the poor physical stability of the formulation can lead to phase separation of the excipient, which affects not only formulation performance, as well as visual appearance of formulation. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

For thermodynamic stability studies we have performed three main steps, they are-

1. Heating cooling cycle: Six cycles between refrigerator temperature (4^0C) and 45^0C 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.

2. Centrifugation: Passed formulations are centrifuged thaw cycles between 21 ^{0}C and +25 ^{0}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.

3. Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking. [18]

Dispersibility Test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed by using a standard USP XXII dissolution apparatus 2 for dispersibility test. One millilitre of each formulation was added in 500 mL of water at 37 ± 1 ^{0}C. A standard stainless steel dissolution paddle is used with rotating speed of 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) 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 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 nano-emulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation. [18]

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) [19, 20]

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 systems should not be too thick. 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 the system has low viscosity then it is o/w type of the system and if a high viscosity then it is w/o type of the system. [19, 20]

Droplet Size Analysis and 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. [19, 20]

Refractive Index and Percent Transmittance
Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by putting a drop of solution on slide and it comparing it with water (1.333)**.** The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer by using distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature.

Electro Conductivity Study
The SEDD system contains ionic or non-ionic surfactant, oil, and water.This test is performed for measurement of the electro conductive nature of system. The electro conductivity of resultant system is measured by electro conductometer. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids. [21]

in vitro Diffusion Study
In vitro diffusion studies are carried out to study the drug release behaviour of formulation from liquid crystalline phase around the droplet using dialysis technique. [19]

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.[7]

Factors which affect SEDDS [28]
Polarity of the Lipophillic Phase: The polarity of the lipid phase is one of the main factors that govern the drug release from the micro-emulsions. The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces formed. The high polarity will promote a rapid rate of release of the drug into the aqueous phase. This is confirmed by the observations of Sang-Cheol Chi, who observed that the rate of release of idebenone from SEDDS is dependant upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oil phase with highest polarity.

Nature and Dose of the Drug
Drugs which are administered at very high dose are not suitable for SEDDS unless they have extremely good solubility in at least one of the components of SEDDS, preferably lipophillic phase. The drugs which have limited or less solubility in water and lipids are most difficult to deliver by SEDDS. The ability of SEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. As mentioned above if surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallisation could be slow in the solubilising and

colloidal stabilizing environment of the gut. Pouton's study reveal that such formulations can take up to five days to reach equilibrium and that the drug can remain in a super-saturated state for up to 24 hours after the initial emulsification event. It could thus be argued that such products are not likely to cause precipitation of the drug in the gut before the drug is absorbed, and indeed that super-saturation could actually enhance absorption by increasing the thermodynamic activity of the drug. There is a clear need for practical methods to predict the fate of drugs after the dispersion of lipid systems in the gastro-intestinal tract.

Drawback of SEDDS: [7]

The main drawback for the development of self emulsifying drug delivery systems (SEDDS) and other lipid-based formulations is the lack of good *in vitro* models for assessment of the formulations for SEDDS .The traditional dissolution methods does not work, because these formulations potentially are dependent on digestion prior to release of the drug. To mimic this, an *in vitro* model simulating the digestive processes of the duodenum has been developed. This *in vitro* model needs further development and validation is carried out before its strength can be evaluated. Further development will be carried out on the basis of *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. Future studies will address the development of the *in vitro* model.

Application:[7]

Improvement in Solubility and Bioavailability:

If drug is formulated in SEDDS, then it increases the solubility because it circumvents the dissolution step in case of Class-Π drug (Low solubility/high permeability).

Ketoprofen, a moderately hydrophobic non steroidal anti-inflammatory drug (NSAID), it is a drug of choice for sustained release formulation but it has produce the gastric irritation during chronic therapy. Along with this due to its low solubility, ketoprofen shows incomplete release from sustained release formulations. It is reported that the complete drug release from sustained release formulations containing ketoprofen in nano crystalline form. [22]

Different formulation approaches that have been achieved sustained release, decrease the gastric irritation, and increase the bioavailability, of ketoprofen include preparation of matrix pellets of nano-crystalline ketoprofen,[22] sustained release ketoprofen microparticles [23]and formulations[23], floating oral ketoprofen systems[24], and transdermal systems of ketoprofen.[25] 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. 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. These drugs are listed in **table 2 .**

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, hydrolytic degradation, or
enzymatic degradation etc. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as barrier between degradating environment and the drug

Conclusion

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

Table: 1 Example of surfactants, co-surfactant, and co-solvent used in commercial formulations[7]

Excipient Name (commercial name)
Surfactants/co-surfactants
Polysorbate 20 (Tween 20)
Polysorbate 80 (Tween 80)
Sorbitan monooleate (Span 80)
Polyoxy-40- hydrogenated castor oil (Cremophor RH40)
Polyoxyethylated glycerides (Labrafil M 2125 Cs)
Polyoxyethlated oleic glycerides (Labrafil M1944 Cs)
Co-solvents
Ethanol
Glycerin
Polypylene glycol
Polyethylene glycol
Lipid ingredients
Corn oil mono,di,,tri-glycerides
DL-alpha-Tocopherol
Fractionated triglyceride of palm seed oil(medium-chain triglyceride)
Medium chain mono-and di-glycerides
Corn oil
Olive oil
Oleic acid
Sesame oil
Soyabean oil
Peanut oil
Beeswax
Hydrogenated soyabean oil
Hydrogenated vegetable oils

Table: 2 Example of bioavailability enhancement of poorly soluble drug after administration of SEDDS and SMEDDS formulations

Sr.No.	Compound	Observation after Study	Reference
1	Halofantrine	Trend to higher BA from LCT SMEDDS	10
2	Ontazolast	BA increase of at least 10- fold from all lipid based formulations	33
3	Vitamin	E BA 3- fold higher from SEDDS	29
4	Coenzyme Q10	BA 2- fold higher from SEDDS	30
5	Progesterone	BA 9- fold higher from SEDDS	31
6	Tocotrienols	BA 2-3 fold higher from SEDDS	32
7	Silymarin	BA approximately 2-and 50- fold higher from SMEDDS	34

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