



SELF EMULSIFYING DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Oral route still remains the favorite route of drug administration in many diseases and till today it is the first way investigated in the development of new dosage forms. Approximately 40 per cent of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with implications of low bioavailability, high intra and inter-subject variability, and lack of dose proportionality. Bioavailability problem of lipophilic drugs can be solved by formation of Self Emulsifying Drug Delivery System (SEDDS). SEDDS are isotropic mixtures of oil, surfactant, co-surfactant and drug with a unique ability to form fine oil in water microemulsion upon mild agitation following dilution with aqueous phase. 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.

Keywords: Self emulsifying drug delivery system (SEDDS), oil, surfactant, cosolvents.

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.¹ Self-emulsifying drug delivery systems (SEDDS) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDS are isotropic mixtures of oils and surfactants; sometimes it contains cosolvents, and it can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. SEDDS 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 gelatin capsules and form fine, relatively stable oil-in-water emulsions upon aqueous dilution. This article presents an overview of SEDDS 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 SEDDS typically produce emulsions with a droplet size between 100–300 nm while self-micro-emulsifying drug delivery systems (SMEDDS) form transparent micro emulsions with a droplet size of less than 50 nm.⁴

POTENTIAL ADVANTAGES OF THESE SYSTEMS INCLUDE⁵

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

APPLICATION

Improvement in Solubility and bioavailability⁵

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 C_{max} 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 hydrolytic 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 degrading environment and the drug.¹⁷ Supersaturable SEDDS contain a reduced amount of a surfactant and a water-soluble cellulosic polymer (or other polymers) to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. The S-SEDDS formulations can result in enhanced oral absorption as compared with the related self-emulsifying drug delivery systems (SEDDS) formulation and the reduced

surfactant levels may minimize gastrointestinal surfactant side effects.⁵

BIOPHARMACEUTICAL ASPECTS

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed and the interested reader is directed to these references for further details. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability *via* a number of potential mechanisms, including²².

1. Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution
2. Increases in effective luminal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micelle structures and a further increase in solubilization capacity.
3. Stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly *via* a reduction in first-pass metabolism.
4. Changes in the biochemical barrier function of the GI tract. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the glycoprotein efflux pump, and may also reduce the extent of enterocyte -based metabolism.
5. Changes in the physical barrier function of the GI tract. Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs.

EXCIPIENTS USED IN SEDDS

The self-emulsifying process depends on⁶

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

Oils⁷

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because 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. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride.

Surfactant

Nonionic surfactants with high hydrophilic-lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30–60% w/w of the

formulation in order to form a stable SEDDS. 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 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.

Cosolvents

Cosolvents like diethylene-glycol-monoethyl ether (transcutol), 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 of the cosurfactant in the microemulsion systems.

Example of surfactants, co-surfactant, and co-solvent used in commercial formulations⁵

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)
- Polyoxyethylated 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

MECHANISM OF SELF EMULSIFICATION

Self-emulsification occurs when the entropy change that favors 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 1.

$$DG = S N p r 2 s \dots\dots \text{(Equation 1)}$$

Where, DG= free energy associated with the process, N= number of droplets, r= radius of droplets, s= 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 reduce the interfacial energy as well as providing a barrier to prevent coalescence²¹ (Fig. 1)

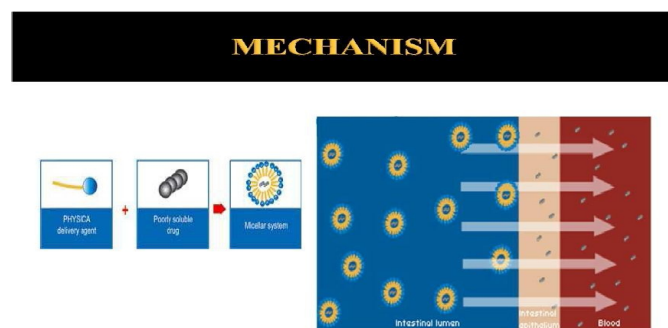


Fig. 1- Showing the mechanism of emulsification

TECHNIQUES FOR SEDDS

1. Spray Cooling

The molten droplets are sprayed into cooling chamber, which will congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms tablets or direct filling into hard shell capsules. Many types of equipment are available to atomize the liquid mixture and to generate droplets: rotary, pressure, two-fluid or ultrasonic atomizers⁸.

2. Spray Drying

Spray drying is defined as a process by which a liquid solution is sprayed into a hot air chamber to evaporate the volatile fraction.⁹

3. Supercritical Fluid Based Method⁷

Lipids may be used in supercritical fluid based methods either for coating of drug particles, or for producing solid dispersions. For environmental reasons, the preferred supercritical fluid of choice is supercritical carbon dioxide. Examples include controlled release applications using glyceryltrimyristate (DynasanTM 114) and stearylpoloxyglycerides (Gelucire® 50/02).

4. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

SLN and NLC are two types of submicron size particles (50–1000 nm) composed of physiologically tolerated lipid components. SLN are produced by high-pressure homogenization of the solid matrix and drug with an aqueous solution of the glyceryldibehenate as solid lipid matrix and poloxamers 188 or polysorbates 80 as surfactants¹⁰.

5. Melt Granulation

Melt granulation or pelletization is a one step process allowing the transformation of a powder mix containing the drug into granules or spheronized pellets¹¹. The melted binder forms liquid bridges with the powder particles that shape into small agglomerates (granules) which can, by further mixing under controlled conditions transform to spheronized pellets. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder during melt granulation¹².

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EVALUATION

Thermodynamic Stability Studies

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

1. Heating cooling cycle: Six cycles between refrigerator temperature (40°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.

2. 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 3500rpm for 30 min. Those formulations that do 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 cracking¹³.

Dispersibility Test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed by using a standard USPXXII dissolution apparatus 2 for dispersibility test. One millilitre of each formulation was added in 500mL of water at 37 ± 1°C. A standard stainless steel dissolution paddle is used with rotating speed of 50rpm 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 2min

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

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 recommended for SEDDS formulation¹³.

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 SEDDS, the charge on an oil droplet is negative due to presence of free fatty acids.¹⁴

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.¹⁵

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.¹⁶

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 be too thick to create a problem. The rheological properties of the micro emulsion

are evaluated by Brookfield viscometer. These 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 is w/o type of the system.^{18,19}

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)^{18,19}.

LIMITATION OF SEDDS

One of the obstacles for the development of self-emulsifying drug delivery systems (SEDDS) and other lipid-based formulations is the lack of good predicative *in vitro* models for assessment of the formulations. Traditional dissolution methods do 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 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. Future studies will address the development of the *in vitro* model.⁷

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). Most importantly, Solid- SEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration and GI irritation is avoidable and controlled and sustained release of drug of drug release is achievable.

Table 1: Examples of pharmaceutical products formulated as self emulsifying systems

Drug name	Compound	Dosage form	Company
Neoral	Cyclosporine	Soft gelatin capsule	Novartis
Norvir	Ritonavir	Soft gelatin capsule	Abbott laboratories
Fortovase	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche Inc.
Agenerase	Amprenavir	Soft gelatin capsule	Glaxosmithkline
Solufen	Ibuprofen	Hard gelatin capsule	Sanofi- Aventis
Lipirex	Fenofibrate	Hard gelatin capsule	Sanofi- Aventis

Examples of some marketed products in which it has been used^{23,24,25}

1. Targretin soft gelatin capsule
2. Gengraf hard gelatin capsule
3. Ritonavir soft gelatin capsule
4. Ritonavir oral solution

5. Sandimmune soft gelatin capsules
6. Sandimmune oral solution
7. Agenerase Soft gelatin capsule
8. Agenerase oral solution
9. Nerol soft gelatin Capsule
10. Nerol Oral Solution
11. Lamprene soft gelatin capsule
12. Fortavase soft gelatin capsule
13. Rocaltrol soft gelatin capsule,
14. Hectrol soft gelatin capsule
15. Rocatrol oral solution
16. Avodat soft gelatin capsule
17. Depakene capsule
18. Norvir soft gelatin capsule
19. Marinol soft gelatin capsule
20. Accutane soft gelatin capsule
21. Vesanoid soft gelatin capsule
22. Accutane soft gelatin capsule
23. Vesanoid soft gelatin capsule
24. Accutane soft gelatin capsule
25. Prometrium soft gelatin capsule
26. Vesanoid soft gelatin capsule

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