

Review Article

ISSN 2320-4818
JSIR 2014; 3(2): 273-281
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Received: 11-02-2014
Accepted: 31-03-2014

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An insight to self emulsifying drug delivery systems, their applications and importance in novel drug delivery

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Abstract

Since last couple of years Self-emulsifying drug delivery systems are becoming important tool in novel drug delivery. It is very useful in solving problems such as low bioavailability issues associated with poorly water soluble drugs. The bioavailability of lipophilic drugs (BCS-II and IV) can be enhanced by these systems. SEDDS is released in the lumen of the gastrointestinal tract (GIT) after administration and with the aid of GI fluid a fine emulsion (micro-/nano-emulsion) is formed. The increased surface area and amphoteric nature of SEDDS lead to increase in bioavailability. The hepatic first-pass effect can be bypassed by these systems because the drugs can subsequently be absorbed by lymphatic pathways. In this review we present a report on the formulation, characterization and dosage forms and applications of self-emulsifying formulations, with examples of currently marketed preparations.

Keywords: Self-emulsifying drug delivery systems, Poor solubility, Bioavailability, Oils, Surfactants, Co-surfactants.

Introduction

Almost 50% of the new drug compounds are poorly water soluble, and low bioavailability is found in oral delivery of these drugs.^{1, 2} Different formulation strategies such as the use of surfactants, lipids, permeation enhancers, micronization, salt formulation, cyclodextrin, nanoparticles and solid dispersions are now being used to overcome these problems. The absorption and availability of the drug can be enhanced by solubilizing the drug within a colloidal dispersion.³ Physically stable formulations such as lipid solutions, emulsions and emulsion pre-concentrates are more popular and suitable for encapsulation of poorly soluble drugs.⁴ Self-emulsifying drug delivery systems (SEDDS) are important formulations which are now being used to overcome these problems. SEDDS are isotropic mixtures containing drug, lipids and surfactants, and one or more co-surfactants.⁵ These systems can spontaneously form fine (oil in water) emulsion upon mild agitation when diluted with aqueous media. The emulsion formed from SEDDS having particle size from a few nanometers to several microns. The formulations forming transparent emulsions with oil droplets ranging from 100 to 250 nm are termed as 'Self-micro emulsifying drug delivery systems' (SMEDDS). 'Self-nano-emulsifying drug delivery systems' are recent term having the globule size range less than 100 nm.⁶ In oral absorption of drug from SEEDS many parameters like surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge plays a important role. The bioavailability of the drug is increased due to increase in the solubility of drug from this formulation. The gastric

irritation is also minimized in this formulation by using proper oil, surfactant and co-surfactants.⁷ In these formulations the dose of the drug is reduced due to the increased solubility and bioavailability.

Determining suitable drug compound for SEDDS

The main challenge in any oral formulation design program is to maintain the drug solubility within the gastrointestinal tract and specially maximizing drug

solubility within the primary absorptive site of the gut.⁸ SEDDS can improve the rate and extent of absorption of lipophilic drug compounds that exhibit dissolution-rate-limited absorption and it also results in reproducible blood time profiles. The SEDDS can be used for all four categories of biopharmaceutical classification system (BCS) class drugs but the BCS II and IV categories of drugs are more needful as well suitable for the SEDDS formulations.⁷ Figure 1 gives a representative diagram showing drug candidates eligible for SEDDS delivery.

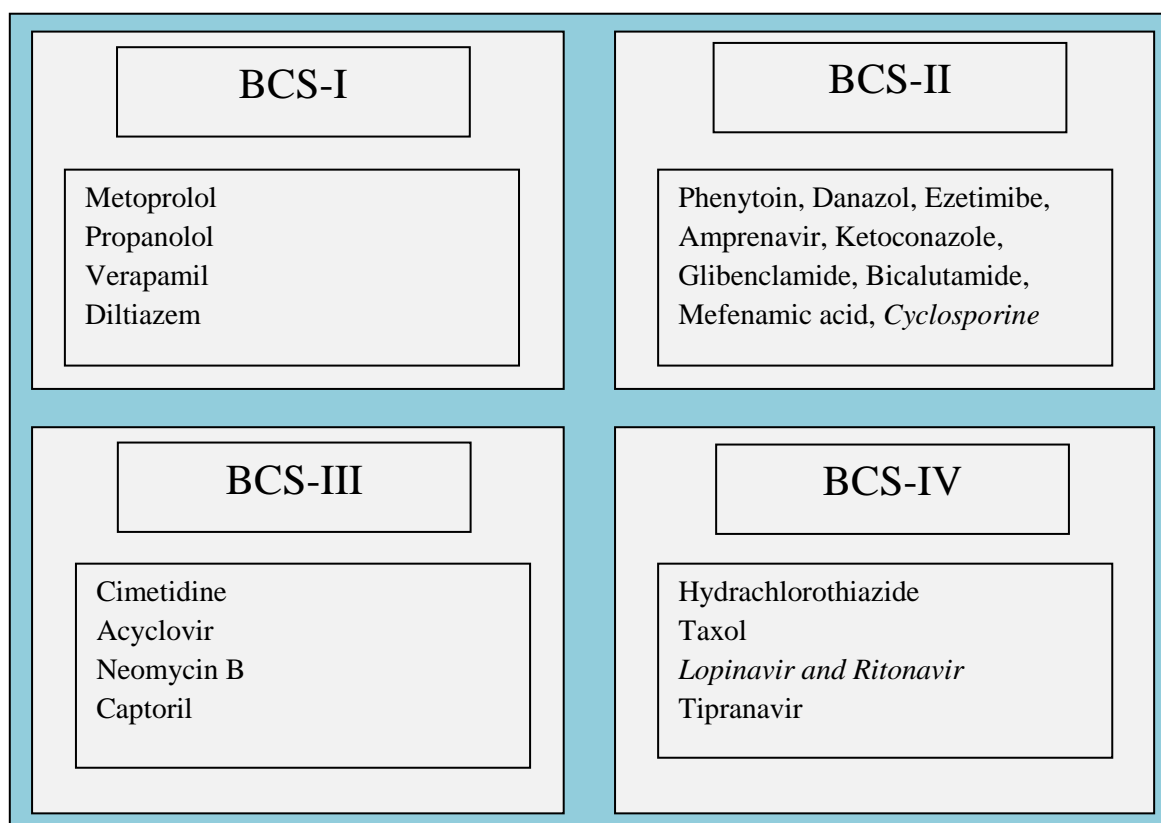


Figure 1: BCS classification of drugs and drug candidates suitable for SEDDS formulation development

Identifying the most appropriate formulations for specific drugs

A working model, Lipid Formulation Classification System was introduced in 2000⁴ to facilitate the identification of the most appropriate formulations for specific drugs (i.e. with reference to their physicochemical properties). To enable in vivo studies to be interpreted more readily and, subsequently, the Lipid Formulation Classification System is used.⁹

Merits and demerits of SEDDS

The SEDDS formulations have many advantages over conventional formulations but these also have some demerits which are discussed in table I.^{10,11}

Process of emulsification

In formulations of emulsifiable concentrates of herbicides and pesticides. The phenomenon of self-emulsification has been widely used and is also commercially available.¹² The user, such as farmers or house-hold gardeners dilute the concentrates of crop sprays to transport hydrophobic compounds efficiently. The orally acceptable excipients

used in formulation of SMEDDS have not been widely exploited and therefore their physicochemical properties are not known widely.

Table I: Description of merits and demerits of SEDDS formulations

Advantages	Disadvantages
1) Peptides that are prone to enzymatic hydrolysis in GIT can be delivered in this formulation.	1) <i>In vitro</i> - <i>in vivo</i> correlations are responsible for further development, therefore development of different prototype lipid based formulations and their <i>in vivo</i> testing in a suitable animal model are necessary.
2) These formulations reduce the dose of the drug by increasing solubility and bioavailability of the drug.	2) This system has different drawbacks such as chemical instabilities of drugs, high concentration of surfactants in formulation (approximately 30-60%) which causes irritation in GIT.
3) Drug loading capacity is higher in SEDDS, than other lipid/oil based formulation.	3) Before evaluating the strength of SEDDS <i>in vitro</i> model, development and validation are needed.
4) The SEDDS offer ease in manufacture & scale-up.	4) Since these formulations depend on digestion prior to release of the drug, traditional <i>in vitro</i> dissolution methods do not work, for SEDDS.
5) The oral bioavailability of the drug is improved in SEDDS.	
6) Onset of action of SEDDS is quick.	
7) Lipid digestion process has no influence on SEDDS.	

Self-emulsification mechanism

The free energy (ΔG) associated in emulsification process is given by the equation:

$$\Delta G = \Sigma N i \pi r i$$

Where, N=Number of droplets, r=radius of droplets, i=interfacial energy.¹³

It is clear from the equation that the interface formation between the oil and water phases is energetically not favored. In the thermodynamic sense the SEDDS have not shown to emulsify spontaneously. The process of emulsification is established when water penetrates into the oil-water interface and it leads in the formation of liquid crystalline phases. It results in swelling at the

interface and emulsification ease is increased.¹⁴⁻¹⁶ For system containing co- surfactant, the components may partitioned between the oil and aqueous phases and it leads to a mechanism described as diffusion and stranding, where by the oil is solubilised, promoting migration in to the aqueous phase. Figure 2 presents a diagrammatic illustration of mechanism of SEDDS.

Phases of dilution

The number of possible liquid crystalline phase's changes by the natural deviation of the curve of the surfactant layer upon dilution of a SMEDDS formulation. After appropriate dilution, spherical droplets is formed again after different droplet structure formation like rod-shaped droplet, hexagonal phase, lamellar phase, cubic phase from spherical droplet.

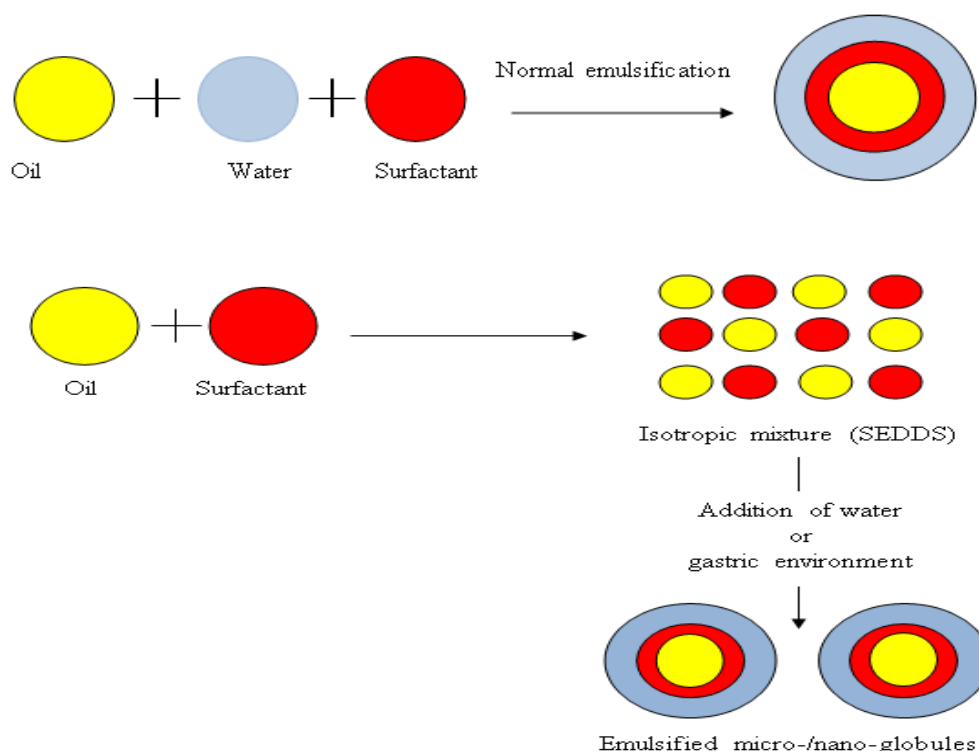


Figure 2: diagrammatic representation of mechanism of self-emulsification

SEDDS formulation

A clear dispersion is formed rapidly from SEDDS and it should remain stable on dilution.

The hydrophobic agent remains solubilised until the time that is relevant for its absorption.¹⁷ The efficient release of the drug compounds from SEDDS is determined by two main factors: small particle size and polarity of resulting oil droplets.¹⁸ In o/w micro emulsions, the drug compound incorporated within the oil droplets reaches the capillaries because the impact of polarity of oil droplets is not considered.

It is very difficult to determine the morphology of the materials and, most importantly, the polymorphism properties of the drug within the wax that is why isotropic liquids are preferable to waxy pastes. In general, the simple effective formulation should be used and the minimum number of excipients should be used.¹⁹

Excipients used in SEDDS formulation

Oils

Oil is the most important excipient in SEDDS formulation because it solubilises the required dose of the lipophilic drug. It also facilitates self-emulsification. The fraction of lipophilic drug transportation via the intestinal lymphatic

system is increased and also absorption from the GIT is increased depending on the molecular nature of the triglyceride. In formulation of SEDDS, the long and medium chain triglyceride (LCT and MCT) are used with different degrees of saturation.^{11, 20-24}

Surfactants

Many compounds which are having surfactant properties may be used for the formulation of self-emulsifying systems, but only those surfactants which are orally acceptable are used. The non-ionic surfactants are mostly recommended because they have a relatively high hydrophilic-lipophilic balance (HLB). In selection of surfactants, safety is a major issue. There are four types of surfactants available such as anionic surfactants, e.g.: potassium laurate, sodium lauryl sulphate, cationic surfactant, e.g.: quaternary ammonium halide, amphoteric surfactants, e.g.: sulfobetaines and nonionic surfactants, e.g.: sorbitan esters (spans), poly-sorbates (tweens).²⁵⁻²⁷

Co-Solvents

The optimum SEDDS formulation requires generally high concentrations (generally more than 30-50% w/w) of surfactants; therefore, the incorporation of co-surfactant is done to reduce the concentration of surfactant. The interfacial tension is reduced to a very small even transient

negative value by the use of co-surfactant together with the surfactant. At this value the fine dispersed droplets are formed due to expansion of the interface, resulting into more absorption of surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. For many non-ionic surfactants, the use of co-surfactant in self-emulsifying systems is not necessary. For the formation of SEDDS and also for solubilization of the drug in the SEDDS, the proper selection of surfactant and co-surfactant is very important.^{28, 29}

Dosage forms of SEDDS

Different dosage forms of SEDDS can be formulated. For oral delivery of SEDDS, self-emulsifying capsule, sustained / controlled release tablets, sustained / controlled release pellets, solid dispersions are available. And topical delivery, oculars and pulmonary delivery, parenteral delivery are also available for SEDDS.

Method of preparation

The formulation is generally prepared by mixing lipids, surfactants, co-surfactants and drug. If it needs to be formulated into semisolid or solid dosage form then it will mixed with the solid carriers. The methods are used for the preparation of solid SEDDS such as spray drying methods, adsorption to solid carriers, melt granulation, and melt extrusion/extrusion spheronization. Spray drying method is generally used to convert liquid formulation into solid formulation. Solubilisation of the mixture is done before spray drying. Solubilised liquid formulation is then atomized into a spray of droplets. Droplets are then introduced into a drying chamber, where the volatile phase is evaporated. The design of the drying chamber is selected according to the drying characteristic the product and powder specification. Then the dried powder is prepared into tablet. Melt granulation technique is generally used for the formulation of SEDDS tablet.

Capsule filling with liquid and semisolid self-emulsifying formulations is also done. For semisolid formulations it is a four step process. In first step we provide heat to the semisolid excipients to at least 20°C or above its melting point. In second step active substances are incorporated in it with stirring. The next step involves capsule filling with the melt cooling to room temperature. The last step which is used for liquid formulations involves capsules filling with the formulation, then the body and cap of the capsule is sealed either by banding or by micro spray sealing.

Evaluation of SEDDS

Thermodynamic stability studies

The performance of a lipid based formulation is very important and it depends upon its physical stability and it can be affected by precipitation of the drug in the excipients matrix. The physical stability can cause separation of the phase of excipients, affecting formulation performance and visual appearance resulting in poor formulation. The incompatibilities between the gelatin capsules shell and the formulation cause deformation or brittleness and also lead to delayed disintegration, or incomplete release of drug.³⁰

Heating cooling cycle

Six cycles is performed for studying heating cooling cycle by storing each formulation at refrigerator temperature (40°C) and 45°C respectively for not less than 48 h. The formulations which are stable at these temperatures, are subjected to centrifugation test.³⁰

Centrifugation

The formulations which passed the heating cooling cycle are centrifuged between 21 °C and 25 °C with storage at temperature for not less than 48 h. This is done for 30 min at 3500 rpm. The freeze thaw stress test is performed for the formulations which does not show any phase separation.

Freeze thaw cycle

Three freeze thaw cycle are performed for the formulations. Those formulations passed this test show good stability with no creaming, cracking or phase separation.³⁰

Turbidity measurement

Turbidity measurement determines efficiency of self-emulsification by determining the reproducible time after which the dispersion reaches the equilibrium.³¹ Turbidity meters, such as the Hach turbidity meter and the Orbeco-Helle turbidity meter are used for the measurements of turbidity.^{32, 33} The dissolution apparatus is connected to the turbidity meter.³⁴ The apparatus is placed under continuous stirring (50 rpm) on magnetic plate at ambient temperature and a fixed quantity of Self-emulsifying system is added to a defined quantity of suitable medium (0.1N hydrochloric acid).³⁰ After every 15 sec the optical clarity of the formulations taken to determine clarity of nano-or micro-

emulsion formed and emulsification time using a turbidimeter.³⁴ The rate of change of turbidity (rate of emulsification) cannot be monitored because the time required for complete emulsification is too short.³⁰

Droplet size analysis

It is very important factor in self-emulsification performance. The rate and extent of drug release, as well as the stability of the emulsion is determined by droplet size. Microscopic techniques or Coulter Nanosizer, Photon correlation spectroscopy are mainly used for the determination of the droplet size of the emulsion.^{35, 36}

Measurement of zeta potential

The charge of the droplets is determined by zeta potential measurement. The charge on an oil droplet is negative in conventional SEDDS, because of the presence of free fatty acids.³⁷ Cationic lipid, such as oleylamine (at a concentration range 1-3%) incorporation will yield cationic SEDDS. Zeta potential helps in predicting the flocculation effect and stability in emulsion systems. Colloid will aggregate due to attractive forces if the zeta potential falls below a certain level.

Electron microscopic studies

Studies of surface characteristics of such dispersed systems are done by Freeze-fracture electron microscopy.³⁸ In this, samples were characterized with a TEM/SEM/AFM microscope. The self-emulsifying properties of a mixture of mono- and diglycerides of cupric and caprylic acids, and Tween 80 systems are examined by particle size analysis and low-frequency dielectric spectroscopy.

Viscosity determination

Soft gelatin or hard gelatin capsules are generally used for the administration of the SEDDS system. Therefore the SEDDS can be easily pourable into capsules and such system should not too thick to create a problem. Viscometer is used for the evaluation of the rheological properties of the micro emulsion. The nature of the system i.e. w/o or o/w is confirmed by the viscosities determination.³⁰

Applications

Improvement in Solubility and bioavailability

If SEDDS is used to incorporate the drug, the solubility increases because it circumvents the dissolution step in of BCS Class-II drug (Low solubility/high permeability).

Ketoprofen, a non steroidal anti-inflammatory drug (NSAID) is moderately hydrophobic (log P 0.979). For sustained release formulation it is a drug of choice and during chronic therapy it has high potential for gastric irritation. Ketoprofen shows incomplete release from sustained release formulations because of its low solubility. The SEDDS formulation of this drug enhanced bioavailability due to increase in the solubility and it also minimizes the gastric irritation. The release of Ketoprofen in SEDDS is sustained due to incorporation of gelling agent. The lipid matrix interacts readily with water in SEDDS, leading to the formation of a fine particulate oil in-water (o/w) emulsion. The drug is delivered to the gastrointestinal mucosa by the emulsion droplets, in the dissolved state readily accessible for absorption. Therefore SEDDS shows increase in AUC i.e. bioavailability and C_{max} of many drugs.

Protection against biodegradation

The self-emulsifying drug delivery system is able to reduce degradation as well as improve absorption may be especially useful for drugs which have both low solubility and degradation in the GI tract and low oral bioavailability. Because of acidic PH, enzymatic degradation or hydrolyte in stomach, many drugs are degraded in physiological system. These degradation processes can be well protected when drug is presented in the form of SEDDS, as liquid crystalline phase in SEDDS might act as barrier between degradation environment and the drug. For example Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because in an acid environment, it is readily hydrolyzed to salicylic acid. By the Galacticles Oral Lipid Matrix, the oral bioavailability of un- degraded acetylsalicylic acid is improved by 73%.

Controlling the release of drug

Sustained release, bioavailability enhancement and decreased gastric irritation of Ketoprofen achieved by different formulation approaches which include preparation of matrix pellets of nano-crystalline Ketoprofen, sustained release Ketoprofen micro particles and floating oral Ketoprofen systems and transdermal systems of Ketoprofen. Processing, stability, and economic problems are the drawbacks of preparation and stabilization of nano-crystalline or improved solubility forms of drug. When Ketoprofen is presented in SEDDS formulation, this problem can be successfully overcome. The SEDDS formulation of this drug enhanced bioavailability due to increase in the solubility and it also

minimizes the gastric irritation. The release of Ketoprofen in SEDDS is sustained due to incorporation of gelling agent. The lipid matrix interacts readily with water in SEDDS, leading to the formation of a fine particulate Oil in-water (o/w) emulsion.

Marketed formulations of SEDDS

Many pharmaceutical companies are formulating SEDDS formulations. These are also available in market. The SEDDS formulations available in market are listed in table II.

Table II: Some representative products as SEDDS in market

Active moiety	Trade name	Company name	Use/applications
Tretinoin	Vesanoid	Roche	Used in the treatment of acute promyelocytic leukemia.
Isotretinoin	Accutane	Roche	Used to treat cystic acne.
Cyclosporine	Panimumbioral	Panacea Biotec	Used to reduce the activity of the immune system.
Cyclosporin A	Gengraf	Abbott	Used as a powerful immunosuppressant.
Cyclosporin A	Sandimmune	Novartis	Used as a powerful immunosuppressant.
Lopinavir and Ritonavir	Kaletra	Abbott	Used for the treatment of HIV infection.
Sanquinavir	Fortovase	Roche	It is an antiretroviral drug used in HIV therapy.
Tipranavir	Aptivus	BoehringerIngelheim	Used to treat HIV infection.
Amprenavir	Agenerase	GSK	Used to treat HIV infection.

Conclusion

In general, the liquid/semi-solid SEDDS formulations are now being converted into powders and granules which can then be further processed into conventional 'powder-fill' capsules or even compressed into tablets by using different techniques such as hot melt granulation. The inert adsorbents, such as the Neusilin products for converting liquids into powders are also used, and then it is processed into powder fill capsules or tablet. Oral bioavailability of poorly water-soluble compounds is increased by using this formulation. So in future the SEDDS may be used as a vital tool in reducing the dose size in the formulation.

Acknowledgement

All authors thankfully acknowledge, School of medical and allied sciences, Galgotias university for providing infrastructure for completing this review.

Conflict of interest

All authors in present review paper have no conflict of interest.

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