Journal of PharmaSciTech
2012; 1(2): 6-11

Review Article

Improvement of Bioavailability of Poorly Soluble Drugs through Self Emulsifying Drug Delivery System

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Abstract

Self emulsifying drug delivery system (SEDDS) has received particular attention as a means of improvement of oral bioavailability poorly soluble and absorbed drugs. SEDDS are the mixture of oils, surfactants, and co-surfactants. This becomes emulsify when come in contact with aqueous solution of GIT under the condition of gentle stirring and digestive motility. SEDDS includes various dosage forms like capsule, tablets, beads, microspheres, nanospheres, etc. thus SEDDS could efficiently improve oral absorption of the sparingly soluble drugs by self-emulsification. 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 cyclodextrines complex formation, solid dispersions, 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. For lipophilic drugs, which have dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption.

Keywords: SEDDS, oil, surfactant, co-surfactant

Introduction

The oral route is the preferred route of chronic drug therapy. Numerous potent lipophilic drugs exhibit low oral bioavailability due to their poor aqueous solubility properties. The oral delivery of hydrophilic drugs presents a major challenge because of the low aqueous solubility of such compound. However, oral delivery of 50% of the drug compounds is hampered because of the high lipophilicity of the drug itself. Newly 40% of new drug candidates exhibit low solubility in water, which leads to poor oral bioavailability, high intra and inter-subject variability and lack of dose proportionality. The researchers have attention to minimize the toxic side effects of drug, to broaden their application, to expand mode of their administration and to solve absorption problems. Self-emulsifying drug delivery systems (SEDDS) is the one which can give the direction to the researchers to overcome the problem associated for drugs whose absorption is dissolution rate limiting.

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. Recently, SEDDS have been formulated using medium chain triglyceride oils and non-ionic surfactants, the latter being less toxic. Upon oral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility.1-2 Potential advantages of these systems include enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, and protection of drug(s) from the hostile environment in gut.3-4 SNEDDS5 and solid SEDDS6-7 has been observed. Attempts have been reported for transformation of SEDDS in solid dosage forms by addition of large amounts of solidifying excipients (adsorbents and polymers). But to obtain solids with suitable processing properties, the ratio of SEDDS to solidifying excipients must be very high,8 which seems to be practically non-feasible for drugs having limited solubility in oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for transformation of SEDDS in solid dosage forms will be significantly reduced if SEDDS is gelled. Colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which may serve the dual purpose of reducing the amount of solidifying excipients required and aiding in slowing drug release.

Advantage of SEDDS

1. Enhanced oral bioavailability enabling reduction in dose.

2. Selective targeting of drugs toward specific absorption window in GIT.

3. High drug payloads.

4. Control of delivery profiles.

5. Emulsion is sensitive and metastable dispersed forms while S(M)EDDS are physically stable formulation that are easy to manufacture.[9]

6. As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.

7. SEDDS help to wide distribution of the drug throughout the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.[10]

8. Potential advantages of these systems include enhanced oral bioavailability, more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut. Thus for lipophillic drug compounds that exhibit dissolution rate limited absorption, these system may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles.[11]

Limitation of SEDDS

conventional SEDDS, which are mostly prepared in a liquid form and orally administered in soft or hard gelatin capsules, can make some disadvantages such as high production costs, low drug incompatibility and stability, drugs leakage and precipitation, capsule ageing. Then incorporation of liquid SEDDS into a solid dosage form is compelling and desirable. Recently, a new drug delivery technology-solid SEDDS (S-SEDDS) which combine the advantages of SEDDS and those of solid dosage forms, have been investigated.

Formultaion consideration of SEDDS

When developing lipid based formulations the following parameters are believed to be important:

·The solubility of drug in the formulation as such and upon dispersion.

·The rate of digestion (for formulation susceptible to digestion) and possibly.

·The solubilization capacity of the digested formulation.

Oils:

Long and medium-chain triglyceride oils with different degrees of saturation have been used for the design of SEDDS. Oil can facilitate self-emulsification and increase the fraction of lipophilic drug transportation via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semi-synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.[12-14]

Surfactant:

Non-ionic surfactants are used in formulation of SEDDSs includes Tween, Labrasol, Labrafac CM 10, and Cremophore. The usual surfactant concentration is between the ranges of 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactant having a high hydrophilic lipophilic balance (HLB) and hydrophilicity 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.[15]

Co-solvents:

Co-solvents used in SEDDS helps to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the microemulsion systems.[16] The co-solvents used in SEDDS includes diethylene glycol monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate; tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc.

SMEDDS preparation

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble co-surfactant/co-solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to formation between the oil and aqueous-continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface, this will occur until the solubilization limit is close to the interface.[17-19]

Mechanism of emulsification

Self-emulsifying process is related to the free energy, ΔG by the following equation: $\Delta G = \sum N \pi r^2 \sigma$

Here, N is the number of droplets with radius r and σ the interfacial energy.[20-21] It is apparent from the equation that the spontaneous formation of interface between the oil and water phase is energetically not favorable. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in

behavior to the spontaneity of emulsification, with liquid crystals formation, tending to form emulsion more readily, as indicated by the lower equilibration times.[22] Pouton has argued that the emulsification properties of the surfactant may be related to phase inversion behavior of the system.[23] For example, if one increases the temperature of the thermodynamic sense. Mustafa and Groves developed a method of quantitatively assessing the ease of emulsification by monitoring the turbidity of the oil-surfactant system in a water stream, using phosphated nonylphenoloxylate (PNE) and phosphated fatty alcohol ethoxylate (PFE) in n-hexane and suggested that the emulsification process may be associated with the ease with which water penetrates the oil-water interface, with formation of liquid crystalline phase resulting in swelling at the interface, thereby resulting in greater ease of emulsification. Consequently, the authors were able to relate the phase he oil in the water system stabilized by using non-ionic surfactants, the cloud point of the surfactant will be reached followed by phase inversion. The surfactant is highly mobile at the phase inversion temperature; hence the O/W interfacial energy is minimized, leading to a reduction in energy required to bring about emulsification. It was suggested that the specificity of surfactant combination required to allow spontaneous emulsification is associated with a minimization of phase inversion temperature, there by increasing the ease of emulsification.

Evaluation of SEDDS

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 (4ºC) and 45ºC 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 21ºC and +25ºC with storage at each temperature for not less than 48h 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.

Dispersibility test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus II. One milliliter of each formulation was added to 500 ml of water at 37±0.5ºC. 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.

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 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).

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.

Droplet Size Analysis

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 transmittance

Refractive index and percent tranmittance 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 (1.333). 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 (1.333) and formulation have percent transmittance > 99%, then formulation have transparent nature.

Electro conductivity Study

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

In Vitro Diffusion Study

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

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.

Applications of SEDDS

Different formulation approaches that have been sought to achieve sustained release, to increase the bioavailability and for protection against biodegradation are as follows:

Self-emulsifying Capsules

It is a capsules containing liquid or semisolid form of self emulsifying system. In the GIT, the capsules get dispersed to self emulsifying system uniformly in the fluid to micron size enhancing bioavailability. [21-24]

Self-emulsifying Tablets

Nazzel et al., (2002) developed self-nanoemulsified tablet dosage form of ubiquinone. The main objectives of this study were to study effect of formulation ingredients on the release rate of ubi- Quinone and to evaluate an optimized self-nano emulsified tablets formulation. The first prepared self-nanoemulsion system containing Ubiquinone was prepared as nano emulsion; this nanoemulsion was adsorbed by granular materials and then compressed to form tablets. The optimized formulation of coenzyme Q10 self-Nano emulsified tablet dissolution profile showed that 80-90% drug release took place in 45min.[25]

Attama et al., (2003) formulated the solid self-emulsifying systems in the delivery of diclofenac. This solid self-emulsifying system was developed using goat fat and Tween 65. The fatty material and surfactant were heated together to melt and added to weighted quantity of drug dissolved in the melt; this molten mass was then poured into plastic mould and cooled. These tablets will liquefy at body temperature without agitation and at gastrointestinal conditions agitation as peristaltic movement will lower the liquefaction time, resulting in faster emulsifi- cation with increased plasma concentration. Different formulation ratio shows varying dissolution profile at constant speed/agitation. These tablets showed good release profiles with acceptable tablet properties.[26]

Self-emulsifying Pellets

Tuleu and his coworkers (2004) presented comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented as in pellets and the liquid form was compared with an aqueous suspension of progesterone. The in vitro dissolution tests showed that nearly 100% of progesterone dissolved within 30 min and within 5 min from capsules containing progesterone dissolved in self-emulsifying system. From the aqueous suspension, 50% of the dose was released within 60min. They also showed that pellets administered orally to dogs were tested versus the same dose of progesterone dissolved in liquid SES in capsules or suspension of micronized progesterone. It says that SES pellets and SES solution had higher plasma levels of progesterone at each time point as compared to the aqueous suspension of progesterone.[27]

Franceschinis et al., (2005) developed a method of producing self-emulsifying pellets by wet granulation. Here they first developed a binder solution containing an oil (mono and diglycerides), polysorbate-80,and model drug nimusulide indifferent proportion. Second step was to prepare granules from microcrystalline cellulose and Lactose in a granulator. These binder solutions were sprayed on to the granules and pellets were formed by increasing the speed of the granulator. Pellets were able to generate significantly smaller droplets with respect to corresponding emulsions.[28]

Serratoni et al., (2007) presented controlled drug release from self-emulsifying pellets. The prepared self-emulsifying system formed by mixing oil-surfactant within solubilized drug in appropriate concentrations, because higher quantity of drug incorporated into SES, could be precipitated when diluted with water. This SES was added into damp mass of microcrystalline cellulose and lactose monohydrate, water was then added to the prepared wet mass for extrusion-speronization to form pellets. These pellets were coated by hydrophilic polymers namely ethyl cellulose then coated by aqueous solution of hydroxyl-propyl-methyl cellulose in a fluid bed coater. The ability of this formulation to enhance dissolution of the model drug, where diss -olution results for the uncoated pellets containing methyl or propyl parabens with and without addition of self-emulsifying system were compared.[29] Ahmed abdalla and Karsten Mader investigated preparation and characterization of selfemulsifying Pellets formulation. They formulated three self emulsifying systems separately by melting Cithrol GMS (mono

and diglycerides) and solutol HS 15, to this was added drug, dye and spin probe. Then added water to the molten lipid blend until creamy mass was formed, then added dry MCC into it to form suitable mass for extrusion. The dye was added for assessment of self-emulsification and spin probe was added or the release kinetics and micro environ- ment of pellets, during release process, which were assessed using electron spin resonance spectro copy. The dissolution profile showed complete release of drug as diazepam from the non-self-emulsifying GMS/MCC pellets. It had 3-fold duration of action. Nearly 90% of the drug was released after an hour while only 55% was released from GMS/MCC pellets. Pellets composed of MCC/GMS were only capable of rele- asing diazepam until the saturation solubility reached.[30]

Iosio et al., (2008) prepared bi-layered self-emulsifying pellets, SEP formed by coextrusion speroniz ation with two cohesive layers, in that, type 1 pellets had formulation A (a matrix made of lactose and MCC loaded with SES dispersion) in the inner part and formulation B (a inert matrix containing in lactose, MCC, and water) in the outer and type 2 having formulation B in inner core and formulation. A externally SEP were formulated in two steps, first prepared oil-surfactant mixture then added to water to form self-emulsifying system and this mixture was then loaded into MCC and lactose to form suitable extrusion speronization mass for pellets. Pellets of type I plus 2% of croscarmellose sodium 90% of vinpocetine as a model drug within 30 min, pellets of type II were release in 20 min and from the physical mixture only 25% of drug were released after 60 min.[31]

Self-emulsifying Beads

Self-emulsifying system canbe formulated as a solid dosage form by using less excipients. Patil and Paradkar discovered that deposition of SES into micro porous polystyrene beads was done by solvent evaporation. Porous polystyrene beads with complex internal void structures were typically produced by copolymerizing styrene and m-divinylbenzene. It is inert and stable over a wide range of pH, temperature and humidity. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES loaded PPB.[32]

Self-emulsifying Microspheres

You et al., 2005 formulated solid self sustained release micro-spheres using the Quasi-emulsion solvent diffusion method for spherical crystallization technique. Zedoary turmeric Oil release behavior could be controlled by the ratio of hydroxypropyl methyl-cellulose acetate succinate to Aerosil 200 in the formulation.The plasma concentration time profiles achieved after oral Administration of such microspheres into rabbits, with a bioavailability of 135.6% with respect to the Conven- tional liquid SEDDS.[33]

Self-emulsifying Nanoparticles

Nanoparticle technology can be applied to the formulation of self emulsifying nanoparticle. One of the solvent was injection, in this method prepared molten lipid mass contained lipid, surfact- ant and drug. This lipid molten mass was injected drop wise into a non solvent system. This is filtered and dried to get nanoparticles. By these method 100 nm size particles with 70-75 % drug loading efficiency was obtained.[34]

Second technique is sonication emulsion diffusion evaporation by this method co-load 5-fluroura -cil and antisense EGFR (epidermal growth factor receptor) plasmids into biodegradable PLGA /O-CMC nanoparticles. The mixture of PLGA (poly-lactide co-glycolide) and O- CMC (O-carbo -xmethyl-chitosan) had a SE effect, with no additional surfactant required.[35]

Trickler et al., (2005) developed a novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX). These chitosan-GMO nano particles, with bioadhesive properties increased cellular association and were prepared by multiple emulsion (o/w/o) solvent evaporation methods.[36]

Biopharmaceutical aspects

It is important to note that lipids affect the oral bioavailability of drugs by changing biopharmaceutical properties, such as increasing dissolution rate and solubility in the intestinal fluid, protecting the drug from chemical as well as enzymatic degradation in the oil droplets and the formation of lipoprotein promoting lymphatic transport of highly lipophilic drugs. Drugs processed by intestinal lymph are generally transported to the systemic circulation in association with the lipid core of lipoproteins.

Conclusion

Self-emulsifying drug delivery system is a promising alternative to improve solubility/dissolution, absorption and bioavailability for poorly water soluble drug. SEDDS has the flexibility to develop into different solid dosage form. In future, the extensive research is necessary to solve problems associated with the delivery of poorly soluble drug in future.

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