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New Strategy for Solubilization of poorly soluble drug- SEDDS

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Abstract

Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils, surfactants, and cosurfactants, which are emulsified in aqueous media under conditions of gentle stirring and digestive motility that would be encountered in the gastrointestinal tract. We found that SEDDS could efficiently improve oral absorption of the sparingly soluble drugs by rapid self-emulsification and subsequently dispersion in the absorption sites.

Keywords: SEDDS, poorly-soluble, self emulsifying, co-solvents, SMEDDS

Introduction

In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Upto 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which leads to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality. To overcome these problems, various formulations strategies are exploited including the use of surfactant, lipid permeation enhancers, micronisation, salt formation, cyclodextrins, nanoparticles and solid dispersions. Recently much attention has been paid to lipid based formulations with particular emphasis on self emulsifying drug delivery system (SEDDS), to improve the oral bioavailability of lipophilic drugs [1]. However, 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, drug leakage and precipitation, capsule-ageing [2] Then incorporation of liquid SEDDS into a solid dosage form is compelling and desirable.

Recently, a new drug delivery technologies solid SEDDS (S-SEDDS) which combine the advantages of SEDDS and those of solid dosage forms, have been investigated. [2]

SEDDS or self-emulsifying oil formulations (SEOP) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents and co-solvents/surfactants. [3-8]

Advantages of SEDDS over Conventional DDS (1)

1. Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these system can form fine oil in water (o/w) emulsion or microemulsion (S(M)EDDS). Fine oil droplets would pass rapidly wide distribution of the drug through 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.
2. Emulsion are sensitive and metastable dispersed forms while S(M)EDDS are physically stable formulation that are easy to manufacture.
3. As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.
4. 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 lipophilic 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. [8]

Composition of SEDDSs

The self-emulsifying process is depends on: [9]

1. The nature of the oil-surfactant pair
2. The surfactant concentration
3. The temperature at which self-emulsification occurs.

Oils. 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. [11] 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 [10]. Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride. [11]

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 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 . [12]

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.

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 mix of oil, surfactant and cosolvent. 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

- According to Reiss, 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:

$$DG = S N_i p r_i 2s$$

Where, DG 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. 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 reduces the interfacial energy, as well as providing a barrier to prevent coalescence[16]

Characterization of SEDDSs

The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

Visual assessment. This may provide important information about the self-emulsifying and microemulsifying property of the mixture and about the resulting dispersion. [17-19]

Turbidity Measurement. This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.

Droplet Size. This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. [12, 20] Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size. [12, 21, 22] The reduction of the droplet size to values below 50 μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions. [12]

Zeta potential measurement. This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.[3] Determination of emulsification time. Self-emulsification time, dispersibility, appearance and flowability was observed and scored according to techniques described in H. Shen et al. used for the grading of formulations.

Biopharmaceutical aspects [10]

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 [23, 24]. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms including [25]

- a) Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution.
- b) 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 solubilisation 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 micellar structures and a further increase in solubilisation capacity.[25]
- c) 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.[26, 27, 28]
- d) 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 p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism [29,30,31]

e) 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.

Application of SEDDS

1. Supersaturable SEDDS (S-SEDDS)

The high surfactant level typically present in SEDDS formulations can lead to GI side-effects and a new class of supersaturable formulations, including supersaturable SEDDS (S-SEDDS) formulations, have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs [32-34]. The S-SEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Supersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and, therefore, to result in an increased driving force for transit into and across the biological barrier [34] eg. A supersaturable self-emulsifying drug delivery system (S-SEDDS) of paclitaxel was developed employing HPMC as a precipitation inhibitor with a conventional SEDDS formulation. eg. A poorly soluble drug, PNU-91325, was formulated as a super saturable SEDDS.

It is worth emphasizing that the significantly reduced amount of surfactant used in the S-SEDDS formulation approach provides a better toxicity/safety profile than the conventional SEDDS formulations. [35-38]

2. Solid SEDDS

SEDDS are normally prepared as liquid dosage forms that can be administered in soft gelatine capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SEDDS has been prepared by the process of extrusion/spheronization to provide a good *in vitro* drug release (100% within 30 min, T50% at 13 min).[39]

3. SEDDS for TCM

Silybin, the principal component of a *Carduus marianus* extract, is known to be very effective in protecting liver cells from harmful effects caused by smoking, drinking, overworking, environmental contaminants, stress or liver-damaging drugs. However, the bioavailability of orally administered silybin is very low due to its low solubility in water. Woo *et al.* discloses an oral microemulsion consisting of a *Carduus marianus* extract containing a major amount of silybin, or a silybin derivative as an active ingredient. The composition of the invention consists of Miglyol 812 and ethyl linoleate as oils, HCO 50 and Tween 20 as surfactant, dimethyl isosorbide as co-surfactant and D- α -tocopherol as an anti-oxidant. The formulation provides a greatly increased level of *in vivo* bioavailability of silybin, the level being at least 4-fold higher than that achievable by conventional formulations [40]

Recent approaches in SEDDS

1. SEDDS of co-enzyme Q10 was prepared resulted in enhanced bioavailability and reduced toxicity. [41]
2. Lipophilic compound WIN 54954 was formulated as SEDDS in triglyceride oil/non-ionic surfactant mixtures and resulted in improved reproducibility of the plasma profile in terms of C_{max} and T_{max}. [42]
3. Self-microemulsifying drug delivery system (SMEDDS) of simvastatin was developed to enhance its oral bioavailability. This study illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds.[43]
4. A novel SEDDS of Paclitaxel (used for the treatment of solid tumors) was prepared and found that SEDDS was chemically stable for at least 1 year when kept as two part formulation and also the drug loading was increased by approximately 5fold compared to marketed iv formulation, the excipient presented a significantly reduced cytotoxicity and led to a stable microemulsion.[44]
5. An antimalarial drug Halofantrine was prepared as SEDDS and SMEDDS and resulted in 8 fold improvement in absolute oral bioavailability relative to previous data of the solid. [45]
6. Enhanced bioavailability upto 1.88 of silymarin by self microemulsifying drug delivery system.[46]
7. Using SEDDS self nanoemulsified drug delivery system (SNEDDS) of ubiquinone was prepared and study revealed that SNEDDS overcome the drawbacks of the traditional emulsified system such as low solubility and irreversible precipitation of the active drug in the vehicle with time. [47]
8. The two novel SMEDDS containing Labrasol with different dilutions on tight junction was studied and found that Labrasol with concentration of 0.1 and 1 % was shown to increase the permeability of mannitol by 4.6 fold and 33.8 fold respectively.[48]
9. The solid self emulsifying system was used in the delivery of diclofenac and result indicated that diclofenac could be comfortably administered in the form of self-emulsifying tablets using goat fat and Tween 65 admixtures. [49]
10. SEDDS containing Ketoprofen was formulated as sustained release dosage form and found that drug released was increased. [50]

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.

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