Recent advances in self emulsifying drug delivery system - A review

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ABSTRACT

Self-emulsifying drug delivery systems (SEDDS) are usually used to improve the bioavailability of hydrophobic drugs. Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. From time to time many workers have claimed various rational applications of Self-emulsifying formulation for enhancing bioavailability and site-specific targeting of highly lipophilic drugs. SEDDS is ideally an isotropic mixture of oils and surfactants and sometimes co solvents. The multi-component delivery systems have optimized by evaluating their ability to self-emulsify when introduced to an aqueous medium under gentle agitation, and by determination of particle size of the resulting emulsion. Upon per oral administration, these systems form fine (micro) emulsions in the gastrointestinal tract (GIT) with mild agitation provided by gastric mobility. These articles give an overview of the recent advances in the development of SEDDS and the dosage forms along with the associated problems and the possible future research directions in this field.

Keywords: Self-emulsifying drug delivery systems (SEDDS), Surfactants, Self-emulsification, GIT.

INTRODUCTION

In recent years much attention has been focused on lipid micro emulsion formulations with particular emphasis on self emulsifying or self-micro emulsifying drug delivery systems (SEDDS and SMEDDS) to improve oral bioavailability of lipophilic drugs [1]. The clinical usefulness of the SEDDS is evident from the commercially available formulations containing cyclosporin A, ritonavir and squinavir. SEDDS are comprised of mixture of drug, oil, surfactants and/or co solvents which form fine oil in water and/or water in oil emulsions upon dilution with aqueous medium or in vivo administration. In SEDDS, the primary means of self-emulsification assessment is visual evaluation [2]. The efficiency of self-emulsification could be estimated by determining the rate of emulsification and droplet size distribution. The droplet size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption [3]. A widely utilized approach for overcoming poor fasted state bioavailability of lipophilic drugs is to utilize solutions in lipid vehicles containing surfactants that constitute a self-emulsifying drug delivery system (SEDDS), to effect spontaneous emulsification upon contact of the oil with fluids in the G.I. tract [2, 10-12]. If micro emulsions are formed, these are often referred to as self-micro emulsifying drug vehicles.

The percentage release of biphenyl dimethyl dicarboxylate from SMEDDS was >12-fold higher than that from the tablet containing the drug [7]. Ginkgo biloba extracts (GBE) have become a widely used herbal remedy for increasing cognitive function in the elderly in the USA, Europe, Japan, China and many other countries. The primary active components of GBE include 5% -7% terpene lactones (ginkgolides and bilobalide) and 22%-27 % ginkgo flavonol glycosides (e.g. the flavones quercetin, kaempferol, andisorhamnetin) [8].

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delivery systems (SMEDDS). An optimal surfactant Hydrophilic Lipophilic Balance (HLB) for emulsification was found to be around 10 which can be most readily achieved using a combination of polar and non-polar surfactants [2,13].

**SELF EMULSIFYING DRUG DELIVERY SYSTEMS**

**Approaches of Delivery Systems**

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, sometimes including co-solvents, which emulsify under conditions of gentle agitation, similar to those which would be encountered in the gastro-intestinal tract. Hydrophobic drugs can often be dissolved in SEDDS allowing them to be encapsulated as unit dosage forms for per oral administration [10]. Generally, self-emulsifying formulations form a fine emulsion when exposed to aqueous media under conditions of gentle agitation. The resulting oil-in-water emulsions are thermodynamically stable due to the relatively small volume of the dispersed oil phase, the narrow range of droplet size distribution and the polarity of the oil droplets [14].

Oral administration of SEDDS, which can be conveniently encapsulated in soft gelatin capsules, the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification [14,15]. Improvement in the extent and rate of absorption of lipophilic compounds from self-emulsifying formulations is more compared to traditional oral formulations [2,13,16,17]. The potential of lipoids self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drug delivery systems (SMEDDS) for improving the extent and reproducibility of the oral absorption of Halofantrine was investigated as such and formulations have been reported to improve the rate and extent of absorption of lipophilic drugs [13,3,18,2,19].

In recent study, the self-emulsifying properties of Glyceryl Monoolate (GMO) formed a hydrophobic core, presumably micellar, to enhance the solubility of Paclitaxel (PTX) and provide a foundation for chitosan aggregation. The near 100% loading and entrapment efficiencies of PTX in this formulation are attributed to the self-emulsifying properties of GMO-mono glycerides (like GMO), a polar lipids with poor water solubility that exhibit properties resembling non-ionic surfactants have been comprehensively described [20].

**DOSE FORM DEVELOPMENT OF SEDDS**

**Self Emulsification Nature**

The self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self-emulsification occurs. The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet. A few parameters have been proposed to characterize the self-emulsifying performance including the rate of emulsification, the emulsion size distribution and the charge of resulting droplets. Among them, emulsion droplet size is considered to be a decisive factor in self emulsification/dispersion performance, since it determines the rate and extent of drug release and absorption [22]. In addition, positively charged emulsion droplets could be obtained by incorporation of a small amount of cationic lipid (oleylamine) into such system [21,22]. The oral bioavailability of progesterone was significantly enhanced in rats by forming positively charged emulsion in comparison to the corresponding negatively charged formulation [22].

The self-emulsifying technique is depends on [9] nature of the oil–surfactant pair, surfactant concentration and the temperature at which self-emulsification occurs.

**Composition of SEDDS**

**Oils**

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. [23]. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDS. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride [23].

**Surfactant**

Nonionic surfactants with high Hydrophilic Lipophilic Balance (HLB) values are used in formulation of SEDDS (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 [24].

**Cosolvents**

Cosolvents like diehydylene 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 co surfactant in the micro emulsion systems [23].

**Excipient selection in SEDDS**

Emphasis is placed on the new excipients. Polyglycolized glycerides (PGG) with varying fatty acid and polyethylene glycol
components under mild agitation and they are thermodynamically stable.

Drawbacks of SEDDS

The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered. Moreover, volatile cosolvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs. There is a long list of water soluble, insoluble and surfactants, which can be used as solubilizing excipients. Grinding is regularly used in the pharmaceutical industry to reduce particle size but it generates heat, sound and vibration energy. It must be performed at a temperature below the melting temperature. Cryogenic grinding is chosen because it is a process carried out at low temperature with frozen samples, used for different biological materials (plants, animal tissues) and unstable compounds (vitamins, volatile substances, etc.). However, grinding induces mechanical activation and generation of energy can lead to physical and chemical changes in crystalline solid which can affect its efficacy.

RECENT ADVANCEMENTS IN SEDDS

Self-emulsifying sustained/controlled-release tablets

Combinations of lipids and surfactants have presented great potential of preparing self-emulsifying tablets that have been widely researched. After evaluation the effect of some processing parameters (colloidal silicates X1, magnesium stearate mixing time X2, and compression force X3) on hardness and coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X1 = 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face-centered cubic design. In order to reduce significantly the amount of solidifying excipients required for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release.

Self-emulsifying capsules

After administration of capsules containing conventional liquid SE formulations, micro emulsion droplets form and subsequently disperse in the GI tract to reach sites of absorption. However, if irreversible phase separation of the micro emulsion occurs, an improvement of drug absorption cannot be expected. For handling this problem, sodium dodecyl sulfate was added into the SE formulation. With the similar purpose, the super saturatable SEDDS was designed, using a small quantity of hydroxyl propyl methyl cellulose (or other polymers) in the formulation to prevent precipitation of the drug by generating and maintaining a supersaturated state in vivo. This system contains a reduced amount of a surfactant, thereby minimizing GI side effects. The SEDDS formulations, empty soft gelatin capsules were filled with the formulation using a syringe and sealed with hot gelatin. The optimized self-emulsifying formulation...
The limited drug loading capacity and incomplete emulsification characteristics of the EG formulation were improved by developing a surfactant enhanced system (SEEG). Although the drug loading capacity of these systems is still relatively low, potent, lipophilic compounds, solid SEEG formulations may provide advantages in administration and chemical stability over traditional formulation alternatives such as emulsions and liquid fill soft gels.

Self-emulsifying suppositories

Some investigators proved that Solid-SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption. Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester.

Microemulsion Drug Delivery

Dioctyl sodium sulfosuccinate (aerosol OT) has proved to increase the intestinal absorption of many drugs. While the number of publications on the possible application of aerosol OT micro emulsions for topical drug delivery is already extensive, aerosol OT applicability for oral micro emulsion drug delivery still needs to be studied. Recently, a patent cooperation treaty (PCT) provided a stable, self-emulsifying water/oil micro emulsion in which the surfactant with high Hydrophilic Lipophilic Balance (HLB) comprises a medium-chain alkyl/dialkyl sulfate, sulfonate, or sulfosuccinate salt dissolved in a polyhydric alcohol to improve the delivery characteristics of a therapeutic peptide drug.

Self-emulsifying nanoparticles

Nanoparticle techniques have been useful in the production of SE nanoparticles. Solvent injection is one of these techniques. In this method, the lipid, surfactant, and drugs were melted together, and injected drop wise into a stirred non-solvent. The resulting SE nanoparticles were thereafter filtered out and dried. This approach yielded nanoparticles (about 100 nm) with a high drug loading efficiency of 74%. More recently, a novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX) has been developed. The SE property of GMO enhanced the solubility of PTX and provided a foundation for chitosan aggregation, meanwhile causing near 100% loading and entrapment efficiencies of PTX. These advantages allow the use of lower doses of PTX to achieve an efficacious therapeutic window, thus minimizing the adverse side effects associated with chemotherapeutics like PTX.

The purpose of the present study was to formulate a self-nanoemulsifying system (SNES) containing model lipophilic drug, felodipine (FLD), to improve its solubility. The SNES was formulated using varying amounts of Miglyol 840 (as an oil), Cremophor EL (as a surfactant), and Capmul MCM (as a co-surfactant). The SNES were characterized for turbidity, droplet size and in vitro FLD release. The SNES containing oil, surfactant, and co-surfactant in the weight ratio of 3.5:1.0:1.0, respectively, showed good emulsification, median droplet size (of 421 nm), and rapid FLD release (more than 90% release in 15 min).

Self-emulsifying sustainedcontrolled-release pellets

To formulate and prepare SEDDS, there were some basic guidelines needed to conform: safety, compatibility, drug solubility, efficient self-emulsification efficiency and droplet size, etc. Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reduction of intrasubject and intersubject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it seems very appealing to combine the advantages of pellets with those of SEDDS by SE pellets. Spherical pellets with low friability and self-emulsifying properties can be produced by the standard extrusion/spheronization technique. The pellets are capable of transferring lipophilic compounds into the aqueous phase and have a high potential to increase the bioavailability of lipophilic drugs.

Formulation of SE controlled-release pellets by incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release are also very useful. Pellets were prepared by extrusion/spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained mono-diglycerides and Polysorbate 80. The combinations of coating and SES could control in vitro drug release by providing a range of release rates and the presence of the SEDDS did not influence the ability of the polymer film to control drug dissolution.

Table: 1 A List of formulations in the form of SEDDS and SMEDDS

(Poorly soluble drug converted into enhanced bioavailability form)

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>REFERENCE</th>
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<tbody>
<tr>
<td>Win 54954</td>
<td>[13]</td>
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<tr>
<td>Cyclosporin</td>
<td>[67]</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>[18]</td>
</tr>
<tr>
<td>Ontazolast</td>
<td>[68]</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>[69]</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>[28]</td>
</tr>
<tr>
<td>Ro-15-0778</td>
<td>[2]</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>[30]</td>
</tr>
<tr>
<td>Biphenyl Dimethyl Dicarboxylate</td>
<td>[29]</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>[54]</td>
</tr>
<tr>
<td>Progesterone</td>
<td>[71]</td>
</tr>
<tr>
<td>Tocotrienols</td>
<td>[72]</td>
</tr>
<tr>
<td>Danazol</td>
<td>[37]</td>
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<tr>
<td>Carvediol</td>
<td>[73]</td>
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<tr>
<td>Silymarin</td>
<td>[74]</td>
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<tr>
<td>Atorvastatin</td>
<td>[75]</td>
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<tr>
<td>Itraconazole</td>
<td>[32]</td>
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<tr>
<td>Atovaquone</td>
<td>[76]</td>
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<tr>
<td>Seocalcitol</td>
<td>[77]</td>
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<tr>
<td>PNU-91325</td>
<td>[78]</td>
</tr>
<tr>
<td>Model Compounds including</td>
<td>[79]</td>
</tr>
<tr>
<td>disopyramide, ibuprofen,</td>
<td></td>
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<tr>
<td>Ketoprofen, and Tolbutamide</td>
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</tr>
</tbody>
</table>
OTHER NEW TECHNOLOGIES

Solidification techniques for transforming liquid/semisolid SEDDS to S-SEDDS

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process starting from heating of the semisolid excipient to at least 20°C above its melting point, incorporation of the active substances (with stirring), capsule filling with the molten mixture and cooling at room temperature. For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by microspray sealing.[80]. In parallel with the advances in capsule technology proceeding, liquid-oros technology (Alza Corporation) has been designed for controlled delivery of insoluble drug substances or peptides. This system is based on osmotic principles and is a liquid SE formulation system. It consists of an osmotic layer, which expands after coming into contact with water and pumps the drug formulation through an orifice in the hard or soft capsule. [81, 82]

Formulation of Emulsifying and Self-Assembling Systems

The feasibility of obtaining micro emulsions with the liquid copolymers as lipophilic phase was evaluated by the ternary phase diagrams. The surfactant used was Poloxamer 105. This surfactant was selected because of the presence of a PEG chain, its liquid phase at room temperature and 37°C and its cloud point superior to 37°C. Briefly, 9 binary systems containing various ratios of polymer and surfactant ranging from 10/90 to 90/10 w/w were prepared and equilibrated at 37°C. Ultra pure water at 37°C was then added to the mixture aliquot by aliquot. The self-assembling properties of the liquid copolymers were assessed by adding water gradually under gentle stirring at 37°C. The formation of a clear fluid was evaluated visually [34].

CONCLUSION

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds or newly existing moieties with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDS, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDS will continue to enable novel applications in drug delivery and solve deficiency associated with the delivery of poorly soluble drugs. Thus this field required further exploration and research so as to bring out commercially available self-emulsifying formulation.

REFERENCES


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