SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS): A REVIEW

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Abstract: 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 containing co solvents, and 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 orally administered in soft or hard gelatine capsules and form fine, relatively stable oil-in-water emulsions upon aqueous dilution. This article presents an overview of SEDDS and their applications.

Key words: solubility, isotropic mixture, co solvent, surfactant, drug delivery, SEDDS, administration.

INTRODUCTION

In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 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[1].

In the oral formulation of such compounds, a number of attempts—such as decreasing particle size, use of wetting agents, co precipitation, and preparation of solid dispersions— have been made to modify the dissolution profile and thereby improve the absorption rate. Recently, much attention has focused on lipid-based formulations to improve the bioavailability of poorly water soluble drugs. Among many such delivery options, like incorporation of drugs in oils[2], surfactant dispersion[3], emulsions[4] and liposomes[5], one of the most popular approaches are the self-emulsifying drug delivery systems (SEDDS).

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 an aqueous phase under gentle agitation. Self-emulsifying formulations spread readily in the gastrointestinal (GI) tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self emulsification. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption[6]. 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. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles[7].

COMPOSITION OF SEDDS

The self-emulsifying process is depends on[7]

- The nature of the oil–surfactant pair

- The surfactant concentration

- The temperature at which self-emulsification occurs.

Oils. Oils can solubilise the lipophilic drug in a specific amount. It is the most important excipients 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 SEDDS. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages[8]. Novel semi synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride[9].

Surfactant. Non-ionic 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 solubilise 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[10]. Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SDLF (self dispersed lipid formulation). Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents, but they may cause moderate reversible changes in intestinal wall permeability. Amemiya et al. proposed a new vehicle based on a fine emulsion using minimal surfactant content (3%) to avoid the potential toxicological problems associated with high surfactant concentration. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of self-micro emulsifying formulations (SMEDDS). Formulations consisting only of the surfactant mixture may form emulsions or micro emulsions (when surfactants exhibit different low and high HLB), micelle solution or, in some particular cases, niosomes, which are non-ionic, surfactant-based bilayer vehicles.

Cosolvents. Cosolvents like diehylene glycol monoethyle 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 SEDDS

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[10]. 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[11].

- The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and co solvent.

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.

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:

$$DG = SNpr2s$$

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.

In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions.

CHARACTERIZATION OF SEDDS

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 micro emulsifying property of the mixture and about the resulting dispersion[13, 14, 15].

Thermodynamic stability studies: 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. Heating cooling cycle: Six cycles between refrigerator temperature (40C) and 450C 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.

Centrifugation: Passed formulations are centrifuged thaw cycles between 21 ^{0}C and +25 ^{0}C with storage at each temperature for not less than 48 h 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.

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 2. One milliliter of each formulation was added to 500 mL of water at 37 ± 0.5 0C. 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.

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

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 a high viscosity then it is w/o type of the system.

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 percent.

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[10, 18]. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size[10, 16, 17]. 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[6].

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[13].

Determination of emulsification time. Self-emulsification time, dispersibility, appearance and flowability was observed and scored according to techniques described as used for the grading of formulations.

Application

SEDDS formulation is composed of lipids, surfactants, and cosolvents. The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation. SEDDSs present drugs in a small droplet size and well-proportioned distribution, and

increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism. Table I shows the SEDDSs prepared for oral delivery of lipophilic drugs in recent years.

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.

ADVANTAGES OF SEDDS

Improvement in oral bioavailability

Dissolution rate dependant absorption is a major factor that limits the Bioavailability of numerous poorly water soluble drugs. The ability of SEDDS to present the drug to GIT in solubilised and micro emulsified form (globule size between 1- 100 nm) and subsequent increase in specific surface area enable more efficient drug transport

through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability. E.g. In case of halofantrine approximately 6-8 fold increase in bioavailability of drug was reported in comparison to tablet formulation.

Dosage form development of SEDDS

Dry emulsions

Dry emulsions are powders from which emulsion spontaneously occurs in vivo or when exposed to an aqueous solution. Dry emulsions can be useful for further preparation of tablets and capsules. Dry emulsion formulations are typically prepared from oil/ water (O/W) emulsions containing a solid carrier (lactose, maltodextrin, and so on) in the aqueous phase by rotary evaporation[2], freeze-drying[3] or spray drying[4–6]. Myers and Shively obtained solid state glass emulsions in the form of dry 'foam' by rotary evaporation, with heavy mineral oil and sucrose. Such emulsifiable glasses have the advantage of not requiring surfactant[2]. In freeze-drying, a slow cooling rate and the addition of amorphous cryoprotectants have the best stabilizing effects, while heat treatment before thawing decreases the stabilizing effects [3]. The technique of spray drying is more frequently used in preparation of dry

emulsions. The O/W emulsion was formulated and then spray-dried to remove the aqueous phase. The most exciting finding in this field ought to be the newly developed enteric-coated dry emulsion formulation, which is potentially applicable for the oral delivery of peptide and protein drugs. This formulation consisted of a surfactant, a vegetable oil, and a pH-responsive polymer, with lyophilization used[7].Recently, Cui et al. prepared dry emulsions by spreading liquid O/W emulsions on a flat glass, then dried and triturated to powders

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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