A Review on Self Emulsifying Drug Delivery System

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ABSTRACT
Various technological strategies are reported in the literature including solid dispersions,cyclodextrines complex formation, 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. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or micro-emulsions upon mild agitation following dilution by an aqueous phase. For lipophilic drugs, which have dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption. This review article explains how self-emulsifying drug delivery systems can increase the solubility and bioavailability of poorly soluble drug.

KEYWORDS: Self emulsifying drug delivery system (SEDDS), oil, co-surfactant, surfactant.

INTRODUCTION[1]

Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are isotropic mixtures of oils and surfactants, sometimes containing cosolvents, and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds.

SEDDSs 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 SEDDSs and their applications. 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

Why SEDDS are Needed[2,3]

SEDDS are promising approach for oral delivery of poorly water-soluble compounds. It can be achieved by pre-dissolving the compound in a suitable solvent and fill the formulation into capsules. The oral drug delivery of hydrophobic drugs can be made possible by SEDDS. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favour the drug remaining in the lipid droplets.

Potential Advantages of these Systems Include [2,3]

1. Protection of sensitive drug substances
2. More consistent drug absorption,
3. Selective targeting of drug(s) toward specific absorption window in GIT,

4. Protection of drug(s) from the gut environment.
5. Control of delivery profiles
6. Reduced variability including food effects
7. Enhanced oral bioavailability enabling reduction in
8. High drug loading efficiency
9. For both liquid and solid dosage forms

Drawback of SEDDS[2,3]

The main drawback for the development of self emulsifying drug delivery systems (SEDDS) and other lipid-based formulations is the lack of good *in vitro* models for assessment of the formulations for SEDDS .The traditional dissolution methods does not work, because these formulations potentially are dependent on digestion prior to release of the drug. To mimic this, an *in vitro* model simulating the digestive processes of the duodenum has been developed. This
in vitro model needs further development and validation is carried out before its strength can be
evaluated. Further development will be carried out on the basis of *in vitro - in vivo* correlations and therefore different prototype lipid based formulations needs to be developed and tested *in vivo* in a suitable animal model. Future studies will address the development of the *in vitro* model.

Composition of SEDDSs[4-8]

The self-emulsifying process is depends on:

- The nature of the oil–surfactant pair
- The surfactant concentration
- 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 . 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. Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride .

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.

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.

Mechanism of self-emulsification[4-8]

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

EVALUATION[9,10,11]
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.

1. 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.

2. **Centrifugation:** Passed formulations are centrifuged thaw cycles between 21 0C and +25 0C 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.

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 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.

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 is w/o type of the system.

Droplet Size Analysis Particle Size Measurements

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 percent, then formulation have transparent nature.

Techniques for Solid Formulations[12-23]

Techniques are chosen on the basis of properties of lipid excipient. The techniques reviewed hereunder facilitate the transformationof liquid or semi-solid formulations into solid particles (powders, granules or pellets) which could subsequently be filled into capsules, sachets or compressed into tablets.

1. Spray Cooling

The molten droplets are sprayed into cooling chamber, which will congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms tablets or direct filling into hard shell capsules. Many types of equipment are available to atomize the liquid mixture and to generate droplets: rotary, pressure, two-fluid or ultrasonic atomizers.

2. Spray Drying

Spray drying is defined as a process by which a liquid solution is sprayed into a hot air chamber to evaporate the volatile fraction. Polyoxylglycerides (lauroyl or stearoyl) have been used alone or in combination with a solid carrier (silicon dioxide) to form microparticles of etoricoxib and glibenclamide.Dry emulsion technology solves the stability problems associated with classic emulsions (phase separation, contamination by microorganism, etc.) during storage and helps also avoid using harmful or toxic organic solvents. Dry emulsions may be redispersed into water before use. Medium chain triglycerides are commonly used as oil phase for these emulsions.

3. Adsorption on Solid Carriers

Solid carriers are used for the adsorption of liquid formulation to get final solid product and it will be free flowing so that it can becompressed or directly filled in hard gelatincapsules. A significant benefit of the adsorption technique is good content uniformity as well as the possibility for high lipid exposure.The adsorption technique has been successfully applied to gentamicin and erythropoietin with caprylocaproylpolyoxylglycerides (Labrasol) formulations that maintained their bioavailability enhancing effect after adsorption on carriers .

4. Melt Granulation

Melt granulation or pelletization is a one stepprocess allowing the transformation of a powder mix containing the drug into

granules or spheronized pellets .The melted binder formsliquid bridges with the powder particles thatshape into small agglomerates (granules) whichcan, by further mixing under controlledconditions transform to spheronized pellets. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder during melt granulation. Nucleation (onset of granule formation) is largely affected by binder viscosity at high impeller speed and binder particle size at low speed.Depending on the combination of process parameters, two distinct mechanisms namely "distribution" and "immersion" may be at play in the development of granules. Fine or atomized excipients with low viscosity at high impeller speed favour a homogenous "distribution" of the binder onto the surface of the powder. Immersion of the powder on the other hand is the preferred mechanism which is assisted by combination of large binder particles possessing high viscosity and mixing under low impeller speed. The granule size distribution is controlled by the combined effect of the impeller and chopper speeds. Generally, lipids with low HLB and high melting point are suitable for sustained release applications. Semi-solid excipients with high HLB on the other hand may serve in immediate release and bioavailability enhancement. The progressive melting of the binder allows the control of the process and the selection of the granule's size. Also, the melt granulation process may be used for adsorbing semi-solid selfemulsifying systems on solid neutral carriers (mainly silica and magnesium aluminometa silicate). Gupta M.K., Bogner RH, Tseng YC, Goldman D. Hydrogen bonding with adsorbent during storage governs drug dissolution from solid dispersion granules, Pharmaceutical Research 19: 1663-72 (2002). The main advantages of melt granulation/pelletization with lipids are process simplicity (one-step), absence of solvents, and more importantly the potential for the highest drug loading capacity −85% theoretically, and up to 66% actually reported in the literature.

5. Melt Extrusion/ Spheronisaton

Extrusion is a process of converting a raw material with plastic properties into a product of uniform shape and density by forcing it through a die under controlled temperature, product flow
and pressure conditions.This approach has been successfully tried for 17β-estradiol and two model drugs with surfactants such as sucrose monopalmitate, lauroylpolyoxylglycerides and polysorbate80 (Tween® 80) .Gelucire 44/14 to be used directly in the core of the formulation matrix. An innovative "system-incylinder" molding technique was recently employed to develop a dual purpose (enhanced bioavailability and controlled release) formulation with propranolol hydrochloride.Melt extrusion is a solvent free process that allows high drug loading as well as content uniformity for low dose high potency actives.

6. Supercritical Fluid Based Method

Lipids may be used in supercritical fluid based methods either for coating of drug particles, or for producing solid dispersions. For environmental reasons, the preferred supercritical fluid of choice is supercritical carbon dioxide. Examples include controlledreleaseapplications using glyceryltrimyristate (Dynasan™ 114) and stearoylpolyoxylglycerides (Gelucire® 50/02).

7. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

SLN and NLC are two types of submicron size particles (50– 1000 nm) composed of physiologically tolerated lipid components. SLN are produced by high-pressure homogenization of the solid matrix and drug with an aqueous solution of the glyceryldibehenate as solid lipid matrix and poloxamers 188 or polysorbates 80 as surfactants. They typically contain a liquid lipid excipient such as medium chain triglycerides in addition to classic components of SLN. Theyhave been mainly used for controlled-release applications in oral86, intravenous87 or topical route.

CONCLUSION
Substantially improved solubility/

dissolution, absorption and bioavailability of poorly water-soluble compounds. Most importantly, Solid- SEDDS are very flexible to develop various solid dosage forms for oral and parenteral administration and GI irritation is avoidable and controlled and sustained release of drug of drug release is achievable.

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