Self Emulsifying Drug Delivery System: A novel approach
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ABSTRACT

Oral route is most common route of drug administration and it is the first way investigated in the development of new dosage forms. In oral drug formulations major problem arises is the low bioavailability due to poor aqueous solubility. Mostly new drug candidates have poor water solubility resulting into low bioavailability, high intra and inter-subject variability and lack of dose proportionality and therapeutic failure. It has been observed that 40% of active substances are poorly water soluble. Various techniques have been developed to enhance the solubility of such type of drugs includes micronization, solid dispersions or cyclodextrine complex formation. Self Emulsifying Drug Delivery System is a unique approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs. Self Emulsifying Drug Delivery System includes the mixtures of oils and surfactants, which are ideally isotropic and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsion when introduced into aqueous phase under conditions of gentle agitation. The digestive motility of the stomach and intestine is sufficient to provide the agitation necessary for self-emulsification in vivo.

Key words: Self-Emulsifying Drug delivery system, Bioavailability, Lipophilic drugs, surfactant, oil, co-surfactant, pseudoternary phase diagram.

INTRODUCTION:
The oral route is the most popular route among all the route of administration. Approximately 40% of new drug candidates have poorwater solubility and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality.1

In oral drug formulations major problem arises is the low bioavailability due to poor aqueous solubility. Mostly new drug candidates have poor water solubility resulting into low bioavailability, high intra and inter-subject variability, and lack of dose proportionality and therapeutic failure. ‘Low solubility/high permeability’ (BCS class II drugs), dissolution in the environmental lumen is the rate controlling step in the absorption process.2 Efforts are on going to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. Various approaches are being used for incorporation of the active lipophilic component into drug in oils3, solid dispersions4, emulsions5, liposomes6, use of cyclodextrins,7 coprecipitates,8 micronization,9,10 nanoparticles,11 SEDDS belong to lipid-based formulations. Lipid formulations can be oils, surfactant dispersions, emulsions, SEDDS, solid lipid nanoparticles and liposomes. SEDDS are isotropic mixtures of drug, oil/lipid, surfactant, and/or cosurfactant, which form fine emulsion/lipid droplets, ranging in size from approximately 100 nm (SEDDS) to less than 50 nm for self-microemulsifying drug delivery systems (SEDDS), on dilution with physiological fluid. The drug, therefore, remains in solution in the gut, avoiding the dissolution step that frequently limits the absorption rate of hydrophobic drugs from the crystalline state.12

In various approaches SEDDS have been formulated using medium chain triglyceride oils and nonionic surfactants, the latter being less toxic. Upon administration, of this systems formulation of fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility take place.13,14 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.15,16 Advantage of SEDDS over simple oily solutions is larger interfacial area for partitioning of the drug between oil and water. Thus, for lipophilic drugs with dissolution-limited oral absorption, these systems offer an improved rate and extent of absorption and more reproducible plasma concentration profiles.17

Need of SEDDS
Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. 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 favor the drug remaining in the lipid droplets.2

In various strategies for poorly soluble drugs one is to formulate in a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, solid dispersion technique involving polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG 6000) for preparing solid solutions with poorly soluble drugs. Major problem with this type of formulation is that the drug may favor a more thermodynamically stable state, which result in the crystallization of compound in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using differential scanning calorimetry (DSC) or X-ray crystallography techniques. For this type of case SEDD system becomes a good option.

Potential advantages of these systems include;
1. Reduction in dose due to enhanced oral bioavailability,
3. Selective targeting of drug(s) toward specific absorption window in GIT.
4. Protection of drug(s) from the hostile environment in gut.
5. Control of delivery profiles.
6. Reduced variability including food effects.
7. Protective of sensitive drug substances.
8. Increased drug loading capacity.
9. Liquid or solid dosage forms.

**DISADVANTAGES OF SEDDS**

1. Lack of good predictive in vitro models for assessment of the formulations.
2. Traditional dissolution methods do not work, because formulations dependent on digestion prior to release of the drug.
3. In vitro model needs further development and validation.
4. Different prototype lipid based formulations needs to be developed and tested in vivo.
5. Chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) may irritate GIT.
6. Volatile co-solvents may migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

**Excipients used**

Pharmaceutical acceptability of excipients and the toxicity issues of the components is critical for the selection of excipients. Self-emulsification process is depends on the nature of the oil/surfactant pair; the surfactant concentration and oil/surfactant ratio; the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-microemulsification occurs.\(^{16,19}\) In self-emulsified drug delivery system the specific combinations of pharmaceutical excipients play a major role. The formulated Self-Micro Emulsifying Drug Delivery Systems is specific to that particular drug only.

**oil**

The oil is one of the most important excipients because it can solubilize the required dose of the lipophilic drug or facilitate self-emulsification as well as increases the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride.\(^{20}\) Unmodified edible oils are not preferred over Modified or hydrolyzed vegetable oils because of their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-microemulsification. Modified or hydrolyzed vegetable oils are widely used to formulate SEDDS owing to their biocompatibility.\(^{21}\) Long and medium chain triglycerides are commonly used for the design of self-emulsifying formulations due to different degrees of saturation since these excipients form good emulsification systems with a large number of surfactants to exhibit better drug solubility properties.\(^{22}\) Recently novel semi synthetic medium chain triglycerides containing compound such as GELUCIRE has replaced the medium chain triglycerides. Because of higher fluidity these excipients, better solubilising potential and self-microemulsification ability form a good emulsification systems. Other suitable oil phases are digestible or non-digestible oils and fats such as olive oil, corn oil, soya bean oil, palm oil and animal fats.\(^{23}\) It has reported that more lipophilic surfactant may play the role of the hydrophilic oil in the formulation.\(^{24,25}\) Solvent capacity for less hydrophobic drugs can be improved by blending triglycerides with mono- and di-glycerides.\(^{26}\)

**Surfactants**

Several surfactants are employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The non-ionic surfactants due to relatively high hydrophilic-lipophilic balance (HLB) is the first choice in the formulation. The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants.\(^{27}\) Ethoxylated polyglycolyzed glycerides, Tween 80, and other long chain alkyl sulphonate sulfatesurfactants (sodium dodecyl benzene sulphonate, sodium lauryl sulfate, dialkyl sulfo succinate) and quaternary ammonium salts, fatty alcohols (lauryl, cetyl and stearyl, glycercly esters, fatty acid esters and polyoxyethylene) derivatives are also employed. However, these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen.\(^{28}\) The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SEDDS.\(^{29}\) 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. The concentration of the surfactant may affect the droplet size. In some cases it is observed that increasing the surfactant concentration may lead to droplets with smaller mean droplet size, this can be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface.\(^{30}\) While on the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations.\(^{31}\) This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase. The usual surfactant concentration in SEDDS required forming and maintaining an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation.\(^{32}\) It is essential to investigate the effect of formulation and surfactant concentration on gastrointestinal mucosa.

**Cosolvents**

For effective self-emulsifying system a relatively high surfactant concentrations (usually more than 30% w/w) of cosolvents are needed. Organic solvents such as ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc. are used to dissolve larger amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents play major role of the co-surfactant in the self emulsification systems. Organic solvents are suitable for oral administration are ethanol, propylene glycol, and polyethylene glycol, which may help to dissolve large amounts of hydrophilic surfactant or drug in liquid base.\(^{33}\) Addition of an aqueous solvent such as Triacetin, (an acetylated derivative of glycerol) for example glyceryl triacetate or other suitable solvents act as co-solvents. Triacetin is suitable since it is miscible in the oil liquid phases and it can be used to solubilize a hydrophobic drug.\(^{34}\)

**Mechanism of self emulsification**

Different approaches have been reported in the literature. No single theory explains all aspects of microemulsion formation. Schulman et al.\(^{35}\) Formation of emulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant. According to theory of thermodynamic, emulsification takes place due to the entropy change that favours dispersion is greater than the free energy required to increase the surface area between the oil and aqueous phases of the dispersion. Process of emulsification involves the change in free energy (δG) can be expressed by\(^{36}\)

\[
\delta G = \Sigma N \pi r^2 s
\]

where, \(N\) is the number of droplets of radius \(r\) whereas \(s\) is the interfacial energy.

The two phases of emulsion tend to be separate with respect of time in order to reduce the interfacial area, and due to this the emulsion is stabilized by emulsifying agents and form a monolayer of emulsion droplets and ultimately reduces the interfacial energy which act as a barrier around the oil droplets to prevent coalescence.\(^{37}\)
BIOPHARMACEUTICAL ASPECTS

It is well known that bioavailability of poorly water-soluble drugs can be enhanced by using lipids or food. A number of potential mechanisms are available by which lipids may enhance bioavailability are:

a) Slower delivery to the absorption site and increasing the time available for dissolution by reducing gastric transit.  
b) By increasing effective luminal drug solubility. Lipids in the GI tract stimulates the secretion of bile salts and endogenous biliary lipids including phospholipids and cholesterol causing increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these bile salts structures either directly (if sufficiently polar), or secondarily to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity.  
c) Stimulation of intestinal lymphatic transport. The lymphatic transport and increase bioavailability of highly lipophilic drugs may be enhanced by the lipids, which may be directly or indirectly via a reduction in first-pass metabolism. Whereas, a hydrophilic drug absorbs less through the lymphatic (chylo)micon and instead may diffuse directly into the portal supply. Hence in this case, emulsions provide increased dissolution from the large surface area which may be important contributing factor in enhancing absorption of drugs.  
d) Changes in the biochemical barrier function of the GI tract. Some lipids and surfactants may affect the activity of intestinal efflux transporters, as indicated by the glycoprotein efflux pump, and thus reduce the extent of enterocyte-based metabolism.

Formulation

The formulation of a self-emulsifying drug delivery system with a view for increasing the bioavailability of a drug and/or pharmaceutical ingredient by emulsifying the drug with the self-emulsifying excipient includes various steps as described below:

1. Preparation of phase diagram  
2. Poorly water-soluble drug and/or pharmaceutical ingredient is solubilised in a mixture of surfactant, co-surfactant and solvent. The oil phase prepared is mixed with the solubilized drug formulation and if necessary, by heating or other preparatory means.  
3. The emulsion thus obtained can then be added to a suitable dosage form such as soft or hard-filled gelatin capsules and allowed to cool.

Capsule Filling with liquid and semisolid self-emulsifying Formulations

Capsule filling is the most common and simplest technology used for encapsulating liquid or semisolid self-emulsifying formulations for the oral route. Semisolid self-emulsifying formulations encapsulation includes four steps:

(i) heating of the semisolid excipient to at least 208°C above its melting point;  
(ii) with continuous stirring active substance is incorporated into melt.  
(iii) molten mixture is then filled into capsules.  
(iv) Lastly, cooling to room temperature.  
Whereas for liquid formulations, it involves a two-step process:

1. filling of the formulation into the capsules, and  
2. sealing of the body and cap of the capsule, either by banding or by microspray sealing.

In addition an advanced technology called liquid-Oros technology (Alza Corporation) has been designed. It is based on the principle of osmosis and therefore is a liquid self-emulsifying formulation system. In this system osmotic layer expands after coming into contact with water and drug is pumped through an orifice in the hard or soft capsule.

Spray drying

In this technique, formulation is prepared by mixing lipids, drug, surfactants, solid carriers, and solubilization of the mixture before spray drying. The liquid formulation is then atomized into a spray of droplets. These droplets are introduced into a drying chamber, the volatile phase (e.g. the water contained in an emulsion) evaporates, resulting in the formation of dry particles under controlled temperature and airflow conditions. The particles thus obtained can be prepared into tablets or capsules. The selection of atomizer, temperature, airflow and drying chamber design is based on the characterization of the product and powder specification.

Adsorption to solid carriers

Solid carriers are used to adsorb liquid self-emulsifying formulations to get free-flowing powders. In this process liquid formulation is added on the carrier in a blender and mixed. The powder obtained may then be filled directly into capsules or, alternatively, may be mixed with suitable excipients to form tablets by compression. The most important significance of this method is that it gives good content uniformity. SEDDS can be adsorbed at high levels (up to 70% (w/w)) onto suitable carriers.

Solid carriers can be microporous inorganic substances, cross-linked polymers, high surface-area colloidal inorganic absorbent substances or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, crospovidone, cross-linked sodium carboxymethyl cellulose, magnesium hydroxide, talcum and crosslinked polyethylene methacrylate. Cross-linked polymers are used to create a favorable environment to sustain drug dissolution. Porous silicon dioxide (Sylasia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal are the adsorbents involved in Nanoparticle.

Melt granulation

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a ‘one-step’ operation, melt granulation having several advantages as compared to conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Granulation process can be control by several parameters such as impeller speed, mixing time, binder particle size, and the viscosity of the binder.

A wide range of solid and semisolid lipids can be applied as meltable binders, Gelucire 1 derived from the mixtures of mono-/di-/tri-glycerides and polyethylene glycols (PEG) esters of fatty acids, is having ability to further increase the dissolution rate as compared to PEG usually used. Other lipid-based excipients evaluated for melt granulation to create solid SEDDS include lecithin, partial glyc erides, or polysorbates. The melt granulation process was usually used for adsorbing SES (lipids, surfactants, and drugs) onto solid neutral carriers (mainly silica and magnesium aluminoemeta silicate) or solid neutral carriers (mainly silica and magnesium aluminoemeta silicate).

Melt extrusion/extrusion spheronization

Melt extrusion is a solvent-free process used for high drug loading (60%) as well as content uniformity. Extrusion is a procedure 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. The size of the extruder aperture will determine the approximate size of the resulting spheroi ds. In recent most of the pharmaceutical industry involves extrusion–spheronization process to make uni-
formly sized spheroids (pellets). The extrusion–spheronization process involves various steps such as dry mixing of the active ingredients and excipients to achieve a homogenous powder, wet massing with binder; extrusion into a spaghetti-like extrudate, spheronization from the extrudate to spheroids of uniform size; drying, sifting to achieve the desired size distribution and coating. Generally, it is seen that the higher the water level, the longer the disintegration time. The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SEDDS containing wet mass with a wide range of rheological characteristics can be processed, but a single rheological parameter cannot be used to provide complete characterization of how well it can be processed by extrusion–spheronization.

EVALUATION OF SEDDS

1. Visual assessment may provide important information about the self-emulsifying property of the SEDDS as well as about the resulting dispersion. Efficiency of the self-emulsification can be estimated by evaluating the rate of emulsification and particle size distribution. Turbidity measurement is also used to identify efficient self-emulsifying can be done to establish whether the dispersion has reached equilibrium rapidly and in reproducible time.

2. Droplet polarity and droplet size are also an important emulsion characteristics. Polarity of oil droplets is governed by the HLB value of oil, chain length and degree of unsaturation of the fatty acids, the molecular weight of the hydrophilic portion and concentration of the emulsifier. Small droplets with appropriate polarity (lower partition coefficient o/w of the drug) permit acceptable rate of release of the drug. Estimation of polarity of the oil droplets is done by the oil/water partition coefficient of the lipophilic drug.

3. Size of the emulsion droplet is also a factor to characterize the self-emulsification / dispersion performance, since it determine the rate and extent of drug release and absorption. The Coulter nano-sizer can be used to provide comparative measure of mean particle size for such system. This instrument detects dynamic changes in laser light scattering intensity due to particle oscillates due to Brownian movement. This technique is used when particle size range is less than 3µm, size range for SEDDS is 10 to 200 nm.

4. For sustained release characteristic, dissolution study will be done for SEDDS. Drugs known to be insoluble at acidic pH can be made fully available when it is incorporated in SEDDS.

CONCLUSION

Self Emulsifying Drug Delivery Systems is an unique approach used to overcome the problem of the lipophilic drugs having poor oral bioavailability. SEDDS can be a mile stone in the world of pharmacy for this type of drug.

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