SELF- MICRO EMULSIFYING DRUG DELIVERY SYSTEM- A REVIEW

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ABSTRACT

Ease of administration and painless approach made oral route the most preferred. Poor oral bioavailability is pronounced with the majority of recent active ingredients because of dissolution rate limited absorption. Failure to attain intended therapeutic effect of the poor water soluble drugs by this route led to development of novel drug delivery systems which will fulfill therapeutic needs with minimum dose. Although many formulation approaches like solid dispersions, complexation, pH modifications and lipid based delivery systems finding increased appliance with the apparent increase in absorption of drug. Among lipid based formulations, self-microemulsifying formulations (droplet size < 100 nm) are evident to improve the oral bioavailability of hydrophobic drugs primarily due to their efficiency in facilitating solubilization and in presenting the hydrophobic drug in solubilized form whereby dissolution process can be circumvented. Various components that are used to formulate these dosage forms like surfactants and lipids contribute to the overall improvement in oral bioavailability via promoting the lymphatic transport; thereby hepatic first pass metabolism can be surmounted. The present article gives exhaustive information on the formulation design and characterization of SMEDDS by which the bioavailability can be improved.

KEYWORDS: SMEDDS, Lipids, Hydrophobic drugs, Lymphatic pathway, Dissolution.
INTRODUCTION

It is esteemed that about 40% of active substances identified through combinatorial screening programs are difficult to formulate as a result of their lack of significant solubility in water. One of the traditional approaches used to improve solubility of a poorly water soluble molecule without losing its biological activity is by producing various salt forms. Prodrug approach has also resulted in improved solubility. But in most of the cases, such approaches are not successful and molecules need to be abandoned during its development stage. Sometimes, product may be launched with suboptimal properties such as poor bioavailability, lack of optimal dosing etc. In order to overcome these suboptimal properties, various approaches like use of surfactants, permeation enhancers, micronization, nanoparticles, solid dispersions etc. have been used. Self-emulsifying drug delivery system is one of the popular and commercially feasible formulation approach for solving these problems.

Self – emulsifying drug delivery system (SEDDs) are isotropic mixtures of drug, lipids, surfactants, usually with one or more hydrophilic co-solvents. They form fine oil-in-water emulsions immediately upon mild agitation, followed by dilution with aqueous solution (e.g. gastrointestinal fluid). SEDDs are called as Self microemulsifying drug delivery systems (SMEDDs) when the formulation forms transparent microemulsions with oil droplets ranging between 100 to 250 nm. SMEDDs are actually useful for oral delivery of lipophilic and poorly water soluble drugs. This is due to their ability to spontaneously emulsify at a given temperature, ability to be sterilized by filtration, their solubilizing property and high physical stability.

Advantages of SMEDDs

Irritation caused by prolonged contact between the drug and the wall of the GIT can be surmounted by the formulation of SMEDDs as the microscopic droplets formed help in the wide distribution of the drug along the GIT and these are transported quickly from the stomach.

Upon dispersion in water, these formulations produce fine droplets with enormous interfacial area due to which the easy partition of the drug from the oil phase into the aqueous phase is possible which cannot be expected in case of oily solutions of lipophilic drugs.

SMEDDs are advantageous over emulsions in terms of the stability because of the low energy consumption and he manufacturing process does not include critical steps. Simple mixing
equipment is enough to formulate SMEDDs and time required for preparation is also less compared to emulsion. Poor water soluble drugs which have dissolution rate limited absorption can be absorbed efficiently by the formulation of SMEDDs with consequent stable plasma-time profile. Constant plasma levels of drug might be due to presentation of the poorly water soluble drug in dissolved form that bypasses the critical step in drug absorption, that is, dissolution. Along with the lipids, surfactants that are commonly used in the formulation of SMEDDs like Tween 80, Spans, Cremophors (EL and RH40), and Pluronics are reported to have inhibitory action on efflux transporters which help in improving bioavailability of the drugs which are substrates to the efflux pumps. Drugs which have propensity to be degraded by the chemical and enzymatic means in GIT can be protected by the formulation of SMEDDs as the drug will be presented to the body in oil droplets.

SMEDDs are advantageous over SEDDs as the former are less dependent on bile salts for the formation of droplets by which better absorption of the drug is expected compared to SEDDs.

**Disadvantages of SMEDDs**[^8]

One of the obstacles for the development of SMEDDs and other lipid-based formulations is the lack of good predictive in vitro models for assessment of the formulations. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug. This in vitro model needs further development and validation before its strength can be evaluated. Further development will be based on in vitro-in vivo correlations and therefore different prototype lipid-based formulations need to be developed and tested in vivo in a suitable animal model. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT. Moreover, volatile co-solvents in the conventional self-microemulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs. The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvents. Formulations containing several components become more challenging to validate.

**Mechanism of self microemulsification**[^8,^9]

Self microemulsification takes place when entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion. In a conventional emulsion, the energy required to create a new surface between the oil and water phases is related to the
free energy of the formulation. As time progresses, the two phases separate trying to reduce the interfacial area and free energy of the system.

But in case of SMEDDs, the free energy required to form the emulsion is either low or positive or negative. Therefore, emulsification occurs spontaneously. It is essential for the interfacial structure to show no resistance against surface shearing such that emulsification takes place. Ease of emulsification may be due to the ease of water penetration into various liquid crystalline or gel phases on the droplet surface.

**Formulation of SMEDDs**

Upon dilution, the SMEDDs formulation immediately forms a clear dispersion and remains stable. The hydrophobic drug dispersed in the SMEDDs formulation remains solubilized it is absorbed. Efficient release of the drug from the formulation mainly depends on two factors, globule size and polarity of the droplets. In case of oil-in-water microemulsions, the polarity of oil droplets are not considerable, since the drug incorporated in the oil globules reach the capillaries.\[1,6\]

The following parameters must be considered during the formulation of SMEDDs:

(i) Solubility of the drug in different oil, surfactants and cosolvents.

(ii) Selection of oil, surfactant and cosolvent based on the solubility of the drug, and preparation of the phase diagram.

**Composition of SMEDDs**

SMEDDs formulation mainly comprises of the following substances.

**Lipids (Oils)**

Lipids are the important component of SMEDDs, as solubilization and access of the drug to the lymphatic circulation of poor water soluble drugs depend on the type and concentration of oil used in the formulation. Digestive lipids such as triglycerides, diglycerides, fatty acids, phospholipids, cholesterol and other lipids based on synthetic origin offer improvement in bioavailability of the drug in contrast to the nondigestible lipids with which reduced bioavailability may occur due to impairment in absorption caused by retention of the fraction of administered drug in the formulation itself. Lipids are generally insoluble in water and are often identified by their fatty acid composition, melting point, Hydrophilic-Lipophilic Balance (HLB), and solubility in non-polar organic solvents.\[2,3\] Lipids with low HLB and
high melting point are suitable for sustained release. Semi-solid excipients and those with high HLB serve as immediate release and bioavailability enhancement excipients. Lipid based excipients include dietary oils composed of medium (palm seed oil or coconut oil) or long chain triglycerides (corn, olive, peanut, sesame oil).

**Surfactants**
Selection of a surfactant is mainly governed by the following two factors: HLB and safety. In order to achieve high emulsifying property, the emulsifier used in SMEDDs formulation should have high HLB and high hydrophilicity. This ensures immediate formation of oil-in-water droplets and rapid dispersion of formulation in aqueous media (e.g. gastrointestinal fluid). The drug dispersed in the SMEDDs formulation would remain solubilized for a prolonged period of time at site of absorption for efficient absorption, thus preventing precipitation of drug compound within GI lumen.\(^4\) Non-ionic surfactants are most widely recommended as they possess relatively high HLB value. Concentration of surfactant ranging in between 30% and 60% w/w form stable SMEDDs. Pharmaceutically acceptable surfactants include Cremophor® EL, Cremophor® RH40, Cremophor® RH60, polysorbate 80, various grades of gelucires, etc.

**Co-surfactants**
Pharmaceutically acceptable co-surfactants include polyethylene glycol 400, ethanol, propylene glycol. Lipid soluble solvents are used in the formulation of SMEDDs as they enable dissolution of large quantities of hydrophilic surfactants. The lipid mixture with higher surfactant and co-surfactant: oil ratios lead to the formation of stable SMEDDs.\(^4\)

**Characterization of SMEDDs**\(^7\)
The primary means of assessment of SMEDDs is visual observation. 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.\(^9\)

**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. Photon correlation spectroscopy, microscopic techniques or a coulter nanosizer are mainly used for the determination of the emulsion droplet size. This reduction of droplet size values below 50 μm lead to the formation of SMEDDs which are stable, isotropic and clear o/w dispersion.

**Zeta potential measurement:** this is used to identify the charge of the droplets. In conventional SEDDs, the charge on an oil droplet is negative due to presence of free fatty acids.

**Determination of emulsification**

To promote emulsification in a crude nephelometer, the efficiency of emulsification of various compositions of the Tween 85 and medium-chain triglyceride systems using a rotating paddle has been quantified. This enabled an estimation of the time taken for emulsification was complete, samples were taken for particle sizing by photon correlation spectroscopy, and self-emulsified systems were compared with homogenized systems. The process of self-emulsification was observed using light microscopy.\(^5\) It was concluded that the emulsification process involved erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size.

**Small-angle neutron scattering**

Small-angle neutron scattering can be used to obtain information on the size and shape of the droplets. Small-angle neutron scattering experiments use the interference effect of wavelets scattered from different materials in a sample.\(^5\)

**Construction of Pseudo ternary phase diagram**

The number and types of phases, the % weight of each phase and the composition of the system can be determined by ternary phase diagram. Usually these diagrams are three dimensional but it can be illustrated in two dimensions for ease of drawing and interpretation. On further incorporation of water, these occurs a correlation between emulsification efficiency and region of enhanced water solubilization and phase inversion region, formation of lamellar liquid crystalline dispersion phase.\(^12\) With the help of equilibrium phase diagram, the comparison of different surfactant and their synergy with co-surfactant can be determined. For three component system, phase behavior can be represented by a ternary phase diagram.
Supersaturable SMEDDS (S-SMEDDs)

To overcome the toxic effects of surfactants a new class of supersaturable formulations, called as supersaturable SMEDDs (S-SMEDDs) formulations have been designed and developed. The S-SMEDDs 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. Super-saturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and hence, to result in an increased driving force for transit into and across the biological barrier. The S-SMEDDs formulations contain a reduced level of surfactant and a polymeric precipitation inhibitor to yield and stabilize a drug in a temporarily supersaturated state. Hydroxypropyl methylcellulose (HPMC) related cellulose polymers are well recognized for their propensity to inhibit crystallization and thereby, generate and maintain the supersaturated state for prolonged time periods. It is worth emphasizing that the significantly reduced amount of surfactant used in S-SMEDDs formulation approach provides a better Toxicity and safety profile than the conventional SMEDDs formulations.\textsuperscript{14} However, the underlying mechanism of inhibited crystal growth and stabilized supersaturation by means of these polymers is poorly understood even although several studies have been carried out to investigate this.

CONCLUSION

SMEDDDS are a promising approach for the formulation of drug candidate having poor aqueous solubility. The oral delivery of hydrophilic/lipophilic drugs is now possible by SMEDDDS and further can be extended with great ease if certain factors can be solved out. However the efficiency of the SMEDDDS formulation is case specific in most cases, so the composition of SMEDDDS formulation should be determined very carefully. Since a relatively high concentration of surfactants is generally employed in the SMEDDDS formulation, toxicity of surfactant that is being used should be done between the toxicity and self-emulsification ability of the surfactant that is considered for use. Despite the proven ability of these systems, relatively few lipid based product have been commercialized. The reason underlying the lack of application of these technologies is not clear, but the fact that relatively few \textit{in vivo} studies in human have been reported in literature when compared with conventional dosage forms have been reflected. Perhaps more importantly the lack of effective \textit{in vitro} tests that are predictive of \textit{in vivo} performance has significantly hindered successful development of these self-microemulsifying drug delivery systems.
REFERENCES