SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM OF CARDIOVASCULAR DRUGS FOR ENHANCED BIOAVAILABILITY

**Introduction:**

Use of high throughput screening in drug discovery has led to large proportions of new drug candidates having poor water solubility and hence poor and highly variable oral bioavailability. To overcome this problem many formulation strategies, such as micronization, complexation with cyclodextrin, solid dispersions and nanosuspensions were developed. In recent years, self-emulsifying and self-microemulsifying drug delivery systems (SEDDS and SMEDDS) have shown a reasonable success in improving oral bioavailability of poorly water soluble and lipophilic drugs. [Yi T., et.al. 2008]

SMEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) microemulsion upon mild agitation followed by dilution in aqueous media, such as GI fluids. The basic difference between self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation (SEOF) and SMEDDS is SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 100 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS. [Tang J. L., et.al, 2007]

Fine O/W emulsions produce small droplets of oil dispersed in the gastro-intestinal fluids that provide a large interfacial area increasing the activity of pancreatic lipase to hydrolyze triglycerides and, thereby, promote a faster release of the drug and/or formation of mixed micelles of the bile salts containing the drug. Furthermore, in most cases the surfactant used for such formulations increases the bioavailability of the drug by activation of different mechanisms, maintaining the drug in solution and, thus, avoiding the dissolution step from the crystalline state and enhancing intestinal epithelial permeability at the same time. [Katteboina S., 2009]

The free energy of microemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil–water interface and the change in entropy of the system such that,

\[ \Delta G_f = \gamma \Delta A - T \Delta S \]

Where \( \Delta G_f \) is the free energy of formation, \( \gamma \) is the surface tension of the oil-water interface, \( \Delta A \) is the change in interfacial area on microemulsification, \( \Delta S \) is the change in
entropy of the system which is effectively the dispersion entropy, and T is the temperature. It should be noted that when a microemulsion is formed the change in $\Delta A$ is very large due to the large number of very small droplets formed. Originally workers proposed that in order for a microemulsion to be formed a (transient) negative value of $g$ was required, it is now recognized that while value of $g$ is positive at all times, it is very small (of the order of fractions of $mN/m$), and is offset by the entropic component. [Lawrence M. J., et.al., 2000]

SMEDDS are among the methods used to improve the oral bioavailability of poorly soluble drugs by presenting the drug in solubilised and micro emulsified form. SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient ($2<\log P>4$) are typically low in natural lipids and much greater in amphiphilic surfactants, co surfactants and co-solvents [Porter C. J. H., et.al., 2008]. SMEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing.

Major components of SMEDDS are Oils, Surfactants and Co-surfactant. Long chain triglyceride and medium chain triglyceride oils with different degree of saturation have been used in the design of SMEDDS. The choice of surfactants is limited as very few surfactants are orally acceptable. Non-ionic surfactants with high HLB value are used in formulation of SMEDDS. Co-surfactant of HLB value 10-14 is generally used for SMEDDS. Hydrophilic co-surfactants are preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion. [Gupta R. N., et. al., 2009]

SMEDDS can exist in either liquid or solid states. However, SMEDDS are usually limited to liquid dosage forms because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years as they are frequently more effective alternatives to conventional liquid SEDDS. There are different techniques for transferring liquid SMEDDS into Solid SMEDDS such as spray-cooling, spray drying, adsorption onto solid carriers, melt granulation, melt extrusion, super-critical fluid based methods and high pressure homogenization (to produce solid lipid nanoparticles (SLN) or nanostructured lipid carriers (NLC)). [Katteboina S., et.al., 2009]

Advantages and Disadvantages of SMEDDS [Shukla J. B., et.al., 2010]

Advantages:
- Improvement in oral bioavailability
- Ease of manufacture and scale-up
- Reduction in inter-subject and intra-subject variability and food effects
• Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT
• No influence of lipid digestion process
• Increased drug loading capacity

Disadvantages:
• The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent
• Formulations containing several components become more challenging to validate
• 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 (but this drawback can be overcome by solid SMEDDS)

SMEDDS are promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SMEDDS. Hence present work aimed towards formulation of Self microemulsifying drug delivery system of cardiovascular drug for enhanced bioavailability.