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SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS): A REVIEW

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ABSTRACT:
Oral route is the most convenient route of drug administration, being non invasive, cost effective, thereby leading worldwide drug delivery market. But major problem encountered in oral formulations, is low bioavailability, giving rise to further problems like, high inter and intra subject variability, lack of dose uniformity and finally leading to therapeutic failure. For the therapeutic delivery of lipophillic drugs (BCS class II drugs), lipid based formulations are inviting increasing attention Number of technological strategies are investigated for improving bioavailability like solid dispersions, cyclodextrins, micronization etc. But Self-microemulsifying Drug Delivery System (SMEDDS) have gained exposure for their ability to increase solubility and bioavailability of poorly aqueous soluble drugs with reduction in dose and also drugs are protected from hostile environment in gut. This review gives complete overview of SMEDDS but special attention has been paid to formulation design, evaluation and little emphasis on application of SMEDDS.

Keywords: SMEDDS, Micron emulsion, Enhancement of oral bioavailability, Oil based system, Solubility enhancement of BCS class II drugs.

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INTRODUCTION

Self microemulsifying drug delivery system(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) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. 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 50 nm also the concentration of oil in SMEDDS is less than 20% as compared to 40-80% in SEDDS. Although a number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability, SMEDDS 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[1-3].

History of Micron emulsions

The term microemulsion was first used by T. P. Hoar and J. H. Shulman, Professors of chemistry at Cambridge University, in 1943. Microemulsions are formed when (i) The interfacial tension at the oil/water interface is brought to a very low level and (ii) The interfacial layer is kept highly flexible and fluid. These two conditions are usually met by a careful and precise choice of the components and of their respective proportions, and by the use of a "co-surfactant" which brings flexibility to the oil/water interface. These conditions lead to a thermodynamically optimized structure, which is stable as opposed to conventional emulsions and does not require high input of energy (through agitation) to be

formed. Because the size of the particles is much smaller than the wavelength of visible light, microemulsions are transparent and their structure cannot be observed through an optical microscope[4,5].

LIPID FORMULATION CLASSIFICATION SYSTEM

The lipid formulation classification system was first introduced in 2000 and the extra 'type' of formulation was added in 2006[6].

Type I- These systems shows poor initial aqueous dispersion and require digestion by pancreatic lipase/co-lipase in GIT to produce more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. These are a good option for drugs having sufficient solubility in oils. Valproic acid has been formulated in soft gelatine capsules containing corn oil as lipidic component[7].

Type II- Type II lipid formulations constitute SEDDS. Self emulsification is generally obtained at surfactant content above 25% (w/w). These formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allows efficient partitioning of drug between oil droplets and the aqueous phase from where absorption occurs[6,7].

Type III- Type III lipid based formulations, commonly referred to as self micro emulsifying drug delivery systems (SMEDDS), are defined by inclusion of hydrophilic surfactant (HLB > 12) and co-solvent such as ethanol, poly ethylene glycol, propylene glycol. Type III formulation can be further segregated into type IIIA and type IIIB formulations in order to identify more hydrophilic systems (type IIIB) where the content of hydrophilic surfactant and co-surfactant increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared to type IIIA although the drug precipitation risk on dispersion of the formulation is higher given the lower lipid content[6].

Type IV- These formulations commonly offer increased drug payloads when compared to the formulations containing simple glycerides lipids and also produce very fine dispersion when introduce in aqueous An example of type IV formulation is the current capsule formulation of the HIV protease inhibitor Amprenavir (Agenerase) which contains TGPS as a surfactant and PEG 400 and PG as cosolvent[6].

Advantages of SMEDDS

- Improvement in oral bioavailability by increasing solubility and efficient drug transport[3].
- Ease of manufacture and scale-up as compare to other lipid dosage forms[1].
- Reduction in inter-subject and intra-subject variability and food effects[1,3].
- Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT[3].
- No influence of lipid digestion process unlike the other lipid-based drug delivery systems[8,9].
- When polymer is incorporated in composition of SMEDDS it gives prolonged release of medicament[3].

Disadvantages of SMEDDS[1,3]

- Lack of good predicative *in vitro* models for assessment of the formulations.
- 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 needs to be developed and tested *in vivo* in a suitable animal model.
- Another is chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.

MECHANISM OF SELFMICROEMULSIFYING DRUG DELIVERY SYSTEM

The emulsion is stabilized by the surfactant molecules that form a film around the internal phase droplet. In case of SMEDDS, the free energy of formation is very low and positive or even negative which results in thermodynamic spontaneous emulsification. It has been suggested that self emulsification occurs due to penetration of water into the Liquid Crystalline (LC) phase that is formed at the oil/surfactant-water interface into which water can penetrate assisted by gentle agitation during self-emulsification. After water penetrates to a certain extent, there is disruption of the interface and a droplet formation. This LC phase is considered to be responsible for the high stability of the resulting nanoemulsion against coalescence[4].

The thermodynamic relationship for the net free energy change is described by Equation 1.

$$\Delta G = \Sigma Ni \pi ri 2\sigma \quad (1)$$

where, ΔG is the free energy associated with the process, ri is the radius of droplets, Ni is the number of droplets, σ is the interfacial energy[10].

FORMULATION COMPONENTS OF SMEDDS

- **Active Pharmaceutical Ingredient**: Drug should be soluble in oil phase as this influence the ability of SMEDDS to maintain the API in solubilised form. Lipophilic drugs, such as cinnarizine with log P values greater than 5, are good candidate for SMEDDS[11].
- **Oil**: Oil is the most important excipient in the formulation of SMEDDS as it solubilizes the lipophilic drug in a required quantity. The main

criterion for selecting the oil is that the drug should have high solubility in it so this will minimize the volume of the formulation for the delivery of effective dose[11, 12].

- **Surfactant**:
  - Anionic Surfactants, where the hydrophilic group carries a negative charge. Examples: Potassium laurate, sodium lauryl sulphate.
  - Cationic surfactants, where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.
  - Ampholytic surfactants (also called zwitterionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.
  - Nonionic surfactants, where the hydrophilic group carries no charge but derives its water solubility from highly polar groups. Examples: Sorbitan esters (Spans), polysorbates (Tweens)[3].
- **Co-surfactant**: For the production of an optimum SMEDDS, high concentration of surfactant is required in order to reduce interfacial tension sufficiently, which can be harmful, so co-surfactants are used to reduce the concentration of surfactants. Generally co-surfactant of HLB value 10-14 is used like ethanol, propylene glycol, polyethylene glycol[11, 12].
- **Co-solvents**: Organic solvents enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in oil phase. Examples include ethanol, butanol, propylene glycol etc., esters such as ethyl propionate, tributyl citrate and amides as 2-pyrolidine, caprolactum and polyvinyl pyrollidine[11, 13].
- **Other components**: Other components include pH adjusters, flavours, and antioxidants, consistency builder, enzyme inhibiter, polymers etc[11].

FORMULATION DESIGN OF SMEDDS

- **Screening of Oil**: In order to find out appropriate oil with good solubilizing capacity of API, the saturation solubility of API was investigated in some oils by shake flask method. An excess amount of API was added to vial containing 0.5 g of each solvent. After sealing, the mixture was vortexed using a cyclomixer for 10 min in order to facilitate proper mixing of API with the vehicles. Mixtures were kept for 72 hr at ambient temperature to attain equilibrium, and afterwards, mixtures were centrifuged at suitable rpm for 15 min. Aliquots of supernatant was filtered through membrane filter (0.45 µm) and diluted with mobile phase. Drug content was quantified directly by using high performance liquid chromatography (HPLC) technique[11, 14].
- **Screening of Surfactant**: In order to find appropriate surfactant with good solubilizing capacity, after screening of oil emulsifying ability of different surfactants with the screened oil was investigated. 0.3 g of surfactant and 0.3 g of oil phase were weighed and vortexed for two minutes followed by warming at 40-45°C for 30 seconds, so we can obtain an isotropic mixture. 50 mg of isotropic mixture was taken and diluted with double distilled water previously filtered through (0.45 µm) membrane filter in a volumetric flask. Number of volumetric flask inversions was observed visually to form a clear emulsion. The resulting emulsions allowed standing for 2 hours after that transmittance were observed at 638 nm. The surfactant which forms a clear emulsion with lesser number of inversions and with more transmittance was selected[11].
- Screening of Co-Surfactant: In order to find appropriate co-surfactant with good solubilizing capacity, after screening of oil emulsifying ability of different co-surfactants with the screened oil was investigated. 0.2 g of co-surfactant and 0.3 g of oil phase were weighed and vortexed for two minutes followed by warming at 40-45°C for 30 seconds, so we can obtain an isotropic mixture. 50 mg of isotropic mixture was taken and diluted with double distilled water previously filtered through (0.45 µm) membrane filter in a volumetric flask. Number of volumetric flask inversions was observed visually to form a clear emulsion. The resulting emulsions allowed standing for 2 hours after that transmittance were observed at 638 nm. The co-surfactant which forms a clear emulsion with lesser number of inversions and with more transmittance was selected[11].
- **Construction of Phase Diagram**: Phase diagrams were constructed to obtain the proportion of components that can result in maximum microemulsion existence area. These diagrams were constructed with oil, surfactant/co-surfactant and water using water titration method at room temperature. The procedure consisted of preparing solutions of different ratio of surfactant to co-surfactant by weight such as: 1:1, 2:1, 3:1 etc, these solutions then vortexed for 5 min and placed at 50°C for 1 h so that an isotropic mixture was obtained. Each of these solutions was then used for preparing a mixture containing oil and Smix (mixture of surfactant and co-surfactant) in the

following ratios by weight: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 and after preparation vortexed for 5 min followed by placing in oven at 50°C for 1 hr. All the mixtures were then placed at room temperature for 24 h. Water from 5% to 95% of the mixture was added at 10-15 min interval to each of the mixture under stirring on magnetic stirrer. After each addition the mixtures were observed for their appearance (turbid or clear). Turbidity of the samples would indicate formation of a coarse emulsion, whereas a clear isotropic solution would indicate the formation of a microemulsion. Percentage of oil, smix and water at which clear mixture was formed were selected and the values were used to prepare ternary phase diagram[11].

- **Preparation of SMEDDS**: From the ternary phase diagram ratio of surfactant to co-surfactant was optimized. Then by varying ratio of oil to Smix, different formulations were prepared with and without drug. Formulations were prepared by preparing optimized ratio of smix first, for this surfactant and co-surfactant were accurately weighed and then vortexed for 5-10 min. After that smix was placed in oven at 50°C for 1 h. Oil with different ratio was added to smix then these formulations were vortexed for 5-10 min and placed in oven at 50°C for 1 h so that an isotropic mixture was formed. Drug was loaded to these isotropic formulations at the end and vortexed by vortex shaker until clear solution was obtained[11].

EVALUATION OF SMEDDS

- **Determination of Droplet Size/Distribution and Zeta-Potential**: Method use for the determination of droplet size include photon correlation spectroscopy (which analyses fluctuations in light scattering due to Brownian moment of particles) using a zetasizer able to measure size in range 10-5000nm. This technique can only be employed at relatively low dilutions for accurate droplet size evaluation. Oil droplets possess some charge on their surface due to presence of some groups like conventional SMEDDS is negative due to presence of free fatty acids; however, incorporation of cationic lipids in concentration range 1-3% will yield cationic SMEDDS Thus, such systems have a positive n-potential value of about 35-45 mV. This positive n-potential value is preserved following the incorporation of the drug compounds[11,15].
- **Rheological Determination**: Brookfield viscometer, rotational viscometer Rheomat 108 can be use for evaluation of rheological properties of microemulsion. This study confirms whether the system is o/w or w/o. It should be performed in triplicate[11,16].
- **Polarity:** Polarity of oil droplet is governed by some parameters such as, the HLB, chain length and degree of unsaturation of the fatty acids, molecular weight of the hydrophilic portion and concentration of the emulsifier. Polarity has an impact on affinity of the drug for oil and/or water, and the type of forces formed. Highest release will be obtained with the formulation that have oil phase with highest polarity[11].
- **Dispersibility Test:** The efficiency of self-emulsification of oral nano or micro emulsion is assessed by using a standard USP XXII dissolution apparatus 2 for Dispersibility test. One millilitre of each formulation was added in 500 ml of water at 37 ± 10°C. A standard stainless steel dissolution paddle is used with rotating speed of 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, greyish 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 formulations falling in Grade C could be recommend for SEDDS formulations[11,15].
- **Turbidimetric Evaluation:** Growth of emulsion can be monitored by doing Nephaloturbidimetric evaluation. Fixed quantity of Self emulsifying 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)[11,17].
- **Refractive index and Percent Transmittance:** Transparency of the formulation is proved by the refractive index and percent transmittance. Refractive index is measured by Refractometer by

placing a drop of solution on slide and then by comparing 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[11,16,17].

- **Electro Conductivity Test:** This test is performed for measurement of the electro conductive nature of system. The electro conductivity of resultant system is measured by electroconductometer. In conventional SMEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids[11,18].
- **Drug Content:** Drug from pre-weighed SMEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug[11,18].
- ***In- vitro* Dissolution Testing:** The quantitative *in-vitro* release test is performed in US Pharmacopoeia XXIV Dissolution apparatus 2, using 900 ml of buffer with pH (given in pharmacopoeia for particular drug) as dissolution media, the paddles are set to rotate at 100 rpm and temperature is set at 37°C. The SMEDDS formulations are put in hard gelatin capsules (size 00), during the drug release studies 5 ml sample of dissolution media is to be taken out for analysing the sample using HPLC. The removed volume is to be replaced each time with 5 ml of fresh medium. Dissolution studies are also performed in other media (buffer with different pH) to study the effect of pH on drug release[11,18-22].

APPLICATIONS OF SMEDDS

- **Enhancement in Solubility and Bioavailability**: SMEDDS formulation enhances the bioavailability by increasing solubility of drug and also decreases the gastric irritation. Also incorporation of gelling agent in SMEDDS sustains the release of ketoprofen[11].
- **Supersaturable SMEDDS (S-SMEDDS)**: S-SMEDDS have been developed to overcome the toxic effect of surfactant or GI side effects produced by surfactant when used in very high concentration as typically used in SMEDDS[3,11].
- **Protection From Biodegradation**: Drugs for which both solubility and degradation is low in the GI tract contribute to a low oral bioavailability, SMEDDS is useful for such drugs due to ability to reduce degradation as well as improve absorption[11].

CONCLUSION

As per the novel drug delivery system self-microemulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs which belongs to BCS class II can be made possible by SMEDDSs, which have been shown to substantially improve oral bioavailability and thus the dose of the drug can be reduced. With future development of this technology, SMEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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