Self-Emulsifying Drug Delivery System (SEDDS) are lipid-based formulations which are used to improve the solubility of BCS class II drugs. Poorly water-soluble drugs are more ubiquitous i.e. approximately 60–70% of the drug molecules are challenging the researcher in terms of solubility and permeability through the gastrointestinal tract (GIT), dissolution is the rate limiting step in the absorption and oral bioavailability of such candidates. Therefore, to improve the solubility various formulation strategies have been introduced, among numerous approaches self-emulsifying drug delivery system showed markable enhancement in oral bio-availability, rate of dissolution, reduction in dose, consistent drug profiles, selective targeting of drugs, and protection of drugs from the GI environments. This review article focuses mainly on formulation of SEDDS, evaluation and their characterization. It also offers information regarding the various dosage form improvement from SEDDS.
INTRODUCTION:
In pharmaceutical drug discovery, solubility is considered as one of the prerequisite for intestinal absorption; therefore, drugs with low water solubility are susceptible to low and variable oral bioavailability. Thus, an increasingly more vital area of pharmaceutical research is finding safe and effective techniques of improving the solubility of poorly water-soluble drugs.
Self-Emulsifying Drug Delivery System (SEEDS) are a promising approach to improve the solubility of BCS class II drugs. SEDDS are defined as isotropic combinations of natural or synthetic oils, solid or liquid surfactants or as a substitute, one or more hydrophilic solvents & co-solvents/co-surfactants.[1-5]
These systems form fine emulsions (or microemulsions) in the GI tract with mild agitation provided by gastric motility. SEDDS formulations are characterized by in-vitro lipid droplet size (200 nm–5 mm) and appearance. [6,7,8]

Advantages:[6]
- Protection of drug from GIT environment.
- Selective targeting of drug toward specific absorption window in GIT.
- Enhanced oral bioavailability.
- Consistent drug absorption profile.
- Better control of drug delivery profiles.
- Versatility of dosage form.
- Predictable therapy due to reduced variability including food effects.
- Drug release is high.

Disadvantages:[6]
- Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- Further development will be based on in-vitro – in-vivo correlations.
- Chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%).

Mechanism of self-emulsification: Self-emulsification takes place at the same time as the entropy change that favors dispersion, is greater than the energy required to increase the surface area of dispersion.
Self-emulsifying process are associated with free energy, \( \Delta G \) given with the aid of:
\[
\Delta G = \sum N \pi r^2 \sigma
\]
Where,
- \( N \) = Number of droplets with radius \( r \)
- \( \sigma \) = Interfacial Energy

The two phases of the emulsion get separated, to reduce the interfacial area. The emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents that form a monolayer around the emulsion droplets, and as a result decrease the interfacial energy and act as a barrier to coalescence. [9,10]

Formulation aspects of self-emulsifying drug delivery system:
Oily phase: Oils are the most essential excipient in SEDDS formulation, because they solubilize the lipophilic drug in desired formulation, facilitate self-emulsification, and also increase the transport of lipophilic drug through the intestinal lymphatic system, thereby increasing absorption from the GI tract. [11-13,19]. Generally, oils with long and medium chain triglycerides with various degrees of saturation are used for formulation of SEDDS. The commonly used include olive oil, palm oil, corn oil, oleic acid, sesame oil, soya bean oil. Edible oils with “natural base” are not frequently preferred due to their poor ability to dissolve large amounts of drugs. Modified or hydrolyzed vegetable oils have been widely used for emulsification since they exhibit better drug solubilizing properties for oral absorption. Novel semisynthetic medium chain derivatives (amphiphilic compounds), can effectively replace the regular medium chain triglycerides in the self-emulsifying drug delivery systems. [11]

Surfactants: The self-emulsifying properties require the incorporation of large quantities of surfactant in the formulation when compared to oils. The surfactants improve the affinity between lipids and intestinal membrane i.e., improve the permeability of the intestinal membrane, by partitioning into the cell membrane and disrupting the structural organization.
of the lipid bilayer.\cite{11,15} Surfactants also exert absorption enhancing effects by increasing the dissolution rate of the drug. Non-ionic surfactants with a relatively high HLB values are preferred, considering safety as primary aspect, emulsifiers obtained from herbal sources are predicted to be more secure than synthetic surfactants.\cite{11,14,19} As compared to cationic or anionic surfactants, nonionic surfactants are recognized to be much less toxic. The percentage of surfactants in self-emulsifying formulations varies from 30-60% w/w of the total formulation, higher concentration of surfactant might cause gastric irritation as well as moderate reversible modifications in intestinal wall affecting its permeability.\cite{11,16,19} The surfactants being amphiphilic in nature can solubilize better portions of hydrophobic drugs, can prevent precipitation of the drug within the GI lumen and prolong residence time of drug molecules.

**Cosurfactant:** The function of the co-surfactant in SEDDS is to facilitate the dispersion process and dispersion rates. The presence of the cosurfactants decreases the pressure of interface and provides the interfacial film enough flexibility to form nano emulsions over a wide variety of composition.\cite{11,17,19} Addition of co-surfactants to the excessive surfactant concentrations (30% W/W) in the SEDDS formulation facilitate self-emulsification. Organic solvents inclusive of spans, ethanol, propylene glycol, glycerol, PEG, capryol-90, transcutol, glycofurol, aids in dissolving huge amount of both hydrophilic surfactants and drug in lipid base. It has been found that the drug release from the formulations improves with increasing quantity of cosurfactant. Alcohol and different cosolvents in conventional self-emulsifying formulations may also migrate into the shells of capsule resulting the precipitation of lipophilic drug. Thus, alcohol free formulations have been designed.\cite{11,14,19}

**Evaluation:**

**Thermodynamic stability studies:**\cite{19,20} involves three stages of estimation,

**Heating cooling cycle:** Six cycles at refrigerator temperature (4°C) and 45°C, storage at each temperature for not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

**Centrifugation:** Formulations are centrifuged between 21°C and 25°C with storage at each temperature for not less than 48 h, at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

**Freeze thaw cycle:** After three freeze-thaw cycles for the formulations. The formulations that passed this test showed good stability with no phase separation, creaming, or cracking.

**Dispersibility test:**\cite{19,20}
The efficiency of self-emulsification was assessed using a standard USP XXII dissolution apparatus. Five hundred milli litres of water at 37 ± 0.5 °C was used as dissolution medium. A standard stainless-steel dissolution paddle rotating at 50 rpm provides gentle agitation. The *in-vitro* performance of the formulations is visually assessed.

**Turbidimetric Evaluation:**\cite{19,21,22}
Fixed quantity of Self-emulsifying system is added to fixed quantity of suitable medium 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, rate of emulsification cannot be monitored accurately.

**Viscosity Determination:**\cite{19,21,22}
The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination confirms 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:**\cite{19,21,22}
The droplet size of the emulsions is determined by photon correlation spectroscopy using a Zeta-sizer. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads.
Refraction Index and Percent Transmittance:
[19,21,22]

Refraction index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide, water (1.333) is used as a standard for comparison. The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99%, then formulation is said to have transparent nature.

Electro conductivity Study:
[19,21,22]

The SEDD system contains ionic or non-ionic surfactant, oil, and water. This test is used to measure the electroconductive nature of system. The electro conductivity of resultant system is measured by electro-conductometer.

Drug content:
[19,21,22]

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analysed by suitable analytical method against the standard solvent solution of drug.

Physicochemical Characterization Parameters for Self-Emulsifying Formulations

Percentage Transmittance: The percentage transparency of the self-emulsifying formulations can be measured using UV-visible spectrophotometer. [11,23]

Globule Size: The globule size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as absorption. [24-26] The globule size of the reconstituted formulations was measured using Malvern Zeta Sizer based on the principle of dynamic light scattering (DLS). [11]

Robustness to Dilution: Robustness to dilution is important for SEDDS/SNEDDS to ensure that the emulsion/nano-emulsion formed have similar properties at different dilutions to achieve uniform drug release profile and to ensure that the drug will not get precipitated at higher dilutions in-vivo which may significantly retard the absorption of the drug from the formulation. [11,27]

Zeta Potential: This is used to identify the charge of the oil droplets of SEDDS. Generally, the increase in electrostatic repulsive forces between the nano-emulsion droplets prevents the coalescence of nano-emulsion droplets. On the contrary, a decrease of electrostatic repulsive forces causes phase separation. The zeta potential of the reconstituted SEDDS is measured using Malvern Zeta Sizer based on the electrophoresis and electrical conductivity of the formed nano-emulsion. [11]

Effect of pH: The pH of the aqueous phase has significant influence on the phase behaviour of the self-emulsifying systems, the pH of the formulation was measured using pH-meter. [28]

Effect of Temperature: Self-emulsification has been shown to be specific to the temperature at which self-emulsification occurs. [18]

Centrifugation Test: This test is performed to determine the stability of the SEDDS after emulsion formation, the samples diluted with distilled water and centrifuged at specified rpm for specified time and then studied for phase separation. [11,29]

Dye Solubilization Test: This test is used to identify the nature of the formed nano-emulsion and its continuous phase. For this, the water-soluble dye is sprinkled onto the surface of the prepared nano-emulsion. By spotting the dispersion of dye or the clump formation, the nature of the internal, external phase of the emulsion can be determined. [11]

Transmission Electron Microscopy: The morphology of the nano-emulsion obtained from SEDDS can be investigated using transmission electron microscopy. [11]

Dosage form development from SEDDS:

Dry emulsions: Dry emulsions are the powders where emulsion spontaneously occurs in-vivo or when exposed into an aqueous solution. It is in particular o/w emulsion, can be made stable by using the use of numerous strategies which include spray drying or
freeze-drying approach. Dry emulsions may be dispersed in water before use. Advantages: Avoids the use of harmful or toxic organic solvents. Effectively removes the stability problems (such as Phase separation, creaming and contamination by micro-organism during storage) associated with classic emulsion.

The technique of spray drying is more frequently used in preparation of dry emulsions. The O/W emulsion was formulated and then spray dried to remove the aqueous phase.

Self-emulsifying tablets: Self-nano emulsion system prepared is absorbed on granular material and then compressed to form tablets. The recent advancement is the self-emulsifying osmotic pump tablet, in which the elementary osmotic pump system was chosen as the carrier of self-emulsifying solid dispersion.

Self-emulsifying beads: Self-emulsifying system can be formulated as a solid dosage form by using minimum amounts of solidifying excipients.

Loading of Self-emulsifying system into the microchannels of porous polystyrene beads using the solvent evaporation method showed better results as, polystyrene beads have a complex internal void structure, is inert and stable over a wide range of pH, temperature and humidity. Bead size and pore architecture of polystyrene beads were found to affect the loading efficiency and in-vitro drug release. Another study suggested that, floating alginate beads containing SEDDS were developed to increase drug solubility and prolong gastric residence time.

Self-emulsifying sustained release microspheres: Solid self-emulsifying sustained-release microspheres were prepared by using the quasi-emulsion-solvent-diffusion method of the spherical crystallization technique. Studies show that the administration of sustained release microspheres showed improved bioavailability in comparison to conventional formulations.

Self-emulsifying nanoparticles: Nanoparticle techniques are useful in the production of self-emulsifying nanoparticles. Solvent injection and sonication emulsion-diffusion-evaporation methods can be used to formulate self-emulsifying nanoparticles. In solvent injection, the lipid, surfactant, and drugs are melted together and injected dropwise into a nonsolvent with constant stirring.

Self-emulsifying phospholipid suspension (SEPS): Self-emulsifying phospholipid suspension (SEPS) consisting of high amounts of phospholipids has the ability to maintain the drug in solubilized form in-vivo, for enhancement of bioavailability. Phospholipids are endogenous lipids which emulsify in-vivo, higher concentrations of these lipids might be toxic.

Self-emulsifying suppositories: Self-emulsifying suppositories were formulated to fasten the onset of action and prolong the effect of poorly absorbed drugs, as research studies revealed that, S-SEDDS could increase GI absorption along with rectal/vaginal adsorption, formulation of self-emulsifying suppositories could possibly overcome this.

Self-emulsifying capsules: It is the capsule containing conventional liquid or semisolid form of self-emulsifying system that disperse in the GI tract to reach sites of absorption. The formula consists of reduced amount of surfactant and minimize any gastrointestinal side effects. Besides liquid filling, liquid self-emulsifying components additionally may be filled into capsules in a solid or semisolid state by adding solid carriers (adsorbents, polymers, spray drying, freeze drying and so on). Oral administration of self-emulsifying capsules has been found to enhance patient compliance when compared to the previously used parenteral route.

Self-emulsifying controlled / sustained release pellets: Pellets, as a multiple unit dosage form, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, decreasing intrasubject and intersubjective variability of plasma profiles and minimizing GI irritation without decreasing drug bioavailability. Self-emulsifying controlled release pellets can be prepared by the using extrusion-spheronization. A combination of coating and self-emulsification could effectively manipulate in-vivo release of drug.

Self-emulsifying solid dispersions: Solid dispersions are extensively being used to increase the dissolution rate and bioavailability of poorly water-soluble drugs; stability is a primary concern during their production.
To overcome the drawbacks of self-emulsifying excipients like Gelucire44/14, Gelucire 50/20, Labrasol, Transcutol and TPGS (tocopheryl polyethylene glycol one thousand succinate) were broadly used. Hot melt granulation is a widely used technique for the preparation of solid dispersion. [11,30]

Applications: [6,11]
- Improvement in solubility and bioavailability
- Controlling the release of drug
- Protection against biodegradation

CONCLUSION:
Self-emulsifying drug delivery systems offer a promising delivery for BCS class II drugs which exhibit low solubility and permeability. These drug delivery systems are advantageous over other conventional formulations as they show improved solubility, drug profile, absorption and oral bioavailability. Recent developments include, manufacture of super saturable self-emulsifying drug delivery systems from SEDDS, super saturable SEDDS are favoured, due to reduction in production cost, improved stability profile.

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