ISSN: 2582-8118 ***Volume 2, Issue 1; Jan 2022***

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYSIS IN SCIENCE AND ENGINEERING

Web: https://www.iarj.in/index.php/ijrase/index

5. Compressive Review on Self Emulsifying Drug Delivery System for Diabetes Mellitus

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ABSTRACT

Poorly water-soluble drug candidates are becoming more prevalent. It has been estimated that approximately 60–70% of the drug molecules are insufficiently soluble in aqueous media and/or have very low permeability to allow for their adequate and reproducible absorption from the gastrointestinal tract (GIT) following oral administration. Formulation scientists have to adopt various strategies to enhance their absorption. Lipidic formulations are found to be a promising approach to combat the challenges. In this review article, potential advantages and drawbacks of various conventional techniques and the newer approaches specifically the self-emulsifying systems are discussed. Various components of the self-emulsifying systems and their selection criteria are critically reviewed. The attempts of various scientists to transform the liquid self-emulsifying drug delivery systems (SEDDS) to solid-SEDDS by adsorption, spray drying, lyophilization, melt granulation, extrusion, and so forth to formulate various dosage forms like self emulsifying capsules, tablets, controlled release pellets, beads, microspheres, nanoparticles, suppositories, implants, and so forth have also been included. Formulation of SEDDS is a potential strategy to deliver new drug molecules with enhanced bioavailability mostly exhibiting poor aqueous solubility. The self-emulsifying system offers various advantages over other drug delivery systems having potential to solve various problems associated with drugs of all the classes of biopharmaceutical classification system (BCS).

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 modification, and cocrystals exist, 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 paper gives exhaustive information on the formulation design and characterization of SMEDDS along with the probable mechanisms by which the bioavailability can be improved with SMEDDS.

KEYWORDS

Self-Emulsifying, Drug Delivery System, Diabetes Mellitus, SEDDS.

Introduction:

SEDDS are used to solve low bioavailability issues of poorly soluble & highly permeable compounds. Hydrophobic drugs can be dissolved in these systems, enabling them to be administered as a unit dosage form for per-oral administration. [1-4]. Oral delivery of solid dosage form of lipophilic drug compounds is obstructed due to their hydrophobicity [5-7] Therefore, generating proper formulations for such drugs is extremely important, that improves dissolution/solubility[8,9]. promise to enhance the dissolution of drug, because more surface area is provided on dispersion. SEDDS is isotropic combination of drug, lipid/oil, cosolvents and surfactants [10].

When SEDDS formulation is released in the lumen of the gastrointestinal tract, they come in contact with GI fluid and form a fine emulsion (micro/ nano) So called as *in situ* emulsification or self-emulsification which further leads to solubilization of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect [11]. To achieve self-emulsification there is need of ultra-low oil-water interfacial tension. The mechanism of self-emulsification is specific to a particular oil and surfactant.

Additionally, it also depends upon the amount of surfactant and oil and the temperature at which self emulsification take place [12-15]. SEDDS are generally formulated by triglyceride oils and ethoxylated nonionic surfactants. In general, the concentration of surfactant is greater than 25% in the formulation. The size of droplets ranges approximately less than 100 nm. [16-20]. SEDDS are prepared in two forms liquid and solid SEDDS (S-SEDDS). S-SEDDS are prepared by solidification of liquid self-emulsifying components into powder. This powder is then used to produce various solid dosage forms, for example self-emulsifying pellets, self-emulsifying tablets etc [21-24]. Certain lipid excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism[25-29].

Advantages of self-emulsifying drug delivery system over conventional drug delivery systems

1. They are able to self-emulsify rapidly in gastro-intestinal fluids & under the influence of gentle agitation provided by peristaltic and other movements of gastro intestinal tract, they form a fine o/w emulsion.
2. They can effectively incorporate drug (hydrophobic or hydrophilic) within the oil surfactant mixture.

They can be used for liquid as well as solid dosage forms.

3. They require lower dose of drug with respect to conventional dosage forms.
4. Fine oil droplets of SMEDDS would pass rapidly facilitating wide distribution of the drug throughout the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.

Emulsions are sensitive and metastable dispersed forms while SMEDDS are physically stable formulations.

5. As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.
6. Potential advantages of these systems include enhanced oral bioavailability, more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut. 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.
7. Ease of manufacture and scale- up is one of the most important advantages that make SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposome, nanoparticles, etc., as they require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing [30].

Disadvantages of Self-Emulsifying Drug Delivery Systems:

1. One of the obstacles for the development of SMEDDS and other lipid-based formulations is the lack of good predicative *in vitro* models for assessment of the formulations.
2. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
3. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.
4. Volatile co-solvents in the conventional SMEDDS formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
5. Formulations containing several components become more challenging to validate.
6. High production costs.
7. Low drug incompatibility.
8. Drug leakage. So it may allow less drug loading [31-33].

Method of preparation of self emulsifying drug delivery system:

Solidification Techniques for Transforming Liquid SEDDS to Solid-SEDDS (S-SEDDS). Solid SEDDSs are being developed from liquid/semisolid SEDDS mainly by adsorption on solid carriers spray drying, lyophilization, melt extrusion and nanoparticle technology. Such powders/nanoparticles, which are referred to as SE nanoparticles/dry emulsions/solid

dispersions, are usually further processed into other solid SE dosage forms or, alternatively, filled into capsules (i.e., SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDSs are directly filled without any solidifying excipient. Other solid SE dosage forms that have emerged in recent years include SE pellets/tablets, SE microspheres/nanoparticles, and SE suppositories/implants [34, 35].

Spray Drying. In this technique, the liquid SEDDS is added to a solution of suitable solid carrier with stirring to obtain the o/w emulsion. This is then atomized into a spray of droplets in a drying chamber, where the volatile phase (e.g., the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules.

The atomizer, the temperature, the most suitable airflow pattern, and the drying chamber design are selected according to the drying characteristics of the product and powder specification. Solid state emulsions are reported by Myers and Shivley (1993). Shivley has used sucrose and mineral oil for preparing solid state emulsions [36].

Lyophilization Technique. Lyophilization or freezedrying involves transfer of heat and mass to and from the product under preparation. Freeze drying of an oil-in-water emulsion can be an alternative method for the production of dry emulsions. Lyophilization has been thought as a molecular mixing technique where the drug and carrier are codissolved in a common solvent, frozen, and sublimed to obtain a lyophilized molecular dispersion. The potential applications of lyophilization in manufacturing of solid dispersions have successfully been investigated. A slow cooling rate and addition of amorphous cryoprotectants has been reported to have the best stabilizing effects during lyophilization of oil-in-water emulsions [37]

Melt Granulation. Melt granulation is a technique in which powder agglomeration is obtained through the addition of a lipid as binder that melts or softens at relatively low temperatures. Melt granulation offers several advantages over the conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Furthermore, it is also a good alternative to the use of solvent.

The main parameters that control the granulation process are 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. For example, Gelucires, a family of vehicles derived from the mixtures of mono-/di-/ triglycerides and polyethylene glycols (PEG) esters of fatty acids, is able to increase the dissolution rate compared with PEG usually used before, probably owing to its SE property. Other lipid-based excipients evaluated for melt granulation to create solid SES include lecithin, partial glycerides, or polysorbates. In all cases, the lipidic excipients used must be semisolid at room temperature [38].

Melt Extrusion/Extrusion Spheronization. Melt extrusion is a solvent-free process that allows 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 spheroids. The extrusion-spheronization process is commonly used in the

pharmaceutical industry to make uniform sized spheroids (pellets). The extrusion-spheronization process requires the following steps: dry mixing of the active ingredients and excipients to achieve a homogenous powder; wet massing with binder; extrusion into rope-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating [39].

Evaluation of SEDDS:

Drug Content:

Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is analyzed by suitable analytical method [40].

Dispersibility Test:

The dispersibility test of SEDDS is carried out to assess its capability to disperse into emulsion and categorize the size of resulting globules. It is carried by using a standard USP dissolution apparatus 2 (Paddle Type). One ml of each formulation is added to 500 ml of water at 37 + 0.5ºC and the paddle is rotated at 50 rpm. On titration with water the SEDDS formulation forms a mixture or gel which is of different type depending upon which the in vitro performance of formulation can be assessed using the grading system [41].

Rheological Properties Determination:

The SEDDS system can also be administered in soft gelatin capsules, where, it should have appreciable flow properties for processing. The rheological properties (viscosity, flow, thixotropy, static yield, creep value) of formulation (diluted to 5 % v/v water) are determined by rotational viscometers, digital instruments coupled with either cup and bob or coaxial measuring device [42].

Thermodynamic Stability Studies:

The following cycles are carried out for these studies).

a. Heating cooling cycle 17: Six cycles of cooling and heating between refrigerator temperature (4°C) and elevated temperature (45°C) with exposure at each temperature for not less than 48 hours are carried. Those formulations, which are stable, are then subjected to centrifugation test.
b. Centrifugation: Formulations which pass the heating cooling cycle are centrifuged at 3500 rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze thaw stress test.
c. C. Freeze thaw stress cycle: Three freeze thaw cycles b/w -21° C & 25° C with storage at each temperature for not less than those formulations which pass this test show good stability with no phase separation, cracking or creaming. The formulations that pass this test are then further taken for dispersibility test for assessment of self-emulsification efficiency [43].

Robustness to Dilution:

Emulsions upon dilution with various dissolution media should not show any phase separations or precipitation of drug even after 12 hrs of storage, such formulation is considered as robust to dilution

Turbid Metric Evaluation: Turbidity is a parameter for determination of droplet size and self-emulsification time 19 Fixed quantity of SEDDS is added to fixed quantity of suitable medium (0.1 N HCL or Phosphate Buffer) under continuous stirring at 50 rpm on magnetic stirrer at optimum temperature and the turbidity is measured using a turbidimeter. Since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity i.e. rate of emulsification. Turbidimetric evaluation is carried out to monitor the growth of droplet after emulsification.

Droplet size analysis & Particle size measurements: Photon correlation spectroscopy (PCS) or dynamic light scattering (DLS) or Laser Diffraction Techniques are used to determine droplet size of emulsion. A number of equipments are available for measurement of particle size viz. Particle Size Analyzer, Mastersizer, Zetasizer etc. which are able to measure sizes between 10 and 5000 nm 4. 8. Self-Emulsification Time: The selfemulsification time is determined by using USP dissolution apparatus 2 at 50 rpm, where 0.5 g of SEDDS formulations is introduced into 250 ml of 0.1N HCL or 0.5% SLS (Sodium Lauryl Sulphate) solution. The time for emulsification at room temperature is indicated as selfemulsification time for the formulation.

In vitro Diffusion study: This study is done to determine release behavior of formulation using dialysis technique where phosphate buffer (pH 6.8) is generally used as dialyzing medium 20. One end of the dialysis membrane is tied with a thread and 1 ml of the SEDDS formulation along with 0.5 ml of dialyzing medium are filled in the membrane. The other end of membrane is also tied with thread and then allowed to rotate in dialyzing medium at 100 rpm using magnetic stirrer or dissolution apparatus. Samples are withdrawn at different time intervals and then after suitable dilution are analyzed. Volume of samples withdrawn is replaced with fresh dialyzing medium.

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