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SELF EMULSIFYING DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The oral route is the easiest and most popular route of drug administration, being noninvasive and cost-effective. But the major problem in oral drug formulations is low dissolution and low bioavailability, which mainly results from poor water solubility. The improvement of drug solubility and bioavailability are the greatest challenges in formulations. The self-emulsifying drug delivery system (SEDDS) is a new approach for enhancing the solubility of formulations. SEDDS are an isotropic mixture of oil, surfactant, and co-surfactant with a unique ability to form fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation in the gastrointestinal tract which present the drug in a solubilized form, and the small size of formed droplet provides a large interfacial surface area for drug absorption. This review gives a complete overview of SEDDS but special attention has been paid to formulation design and evaluation of SEDDS.

KEYWORDS: Self Emulsifying Drug Delivery System, Oral bioavailability, Oils, Surfactants, Co-surfactants.

INTRODUCTION

Self-emulsifying drug delivery systems (SEDDS) are a potential tool in improving the bioavailability of low solubility drugs. SEDDS formulations are isotropic pre-mixtures composed of natural or synthetic oils with lipophilic or hydrophilic surfactants and cosolvents which emulsify spontaneously when exposed to fluids of the gastrointestinal tract to form an oil in water emulsions or microemulsions. These systems bypass the first pass hepatic metabolism as *in situ* solubilized drug can be directly absorbed through the lymphatic pathway. Besides all these increased drug loading capacity has been observed in SEDDS formulations as the solubility of poorly water-soluble drugs with intermediate partition

coefficients (2<log P<4) are typically low in natural lipids as compared to high solubility in amphiphilic surfactants, co-surfactants, and co-solvents.

Self-emulsifying drug delivery systems are isotropic pre-mixtures of oil, surfactant, co-surfactant and solubilized drug substance which are physically stable. These formulations are suitable for oral delivery in soft and hard gelatin (or hard hydroxypropyl-methylcellulose) capsules. Depending on the excipient selection and relative composition of the formulation, aqueous dilution will result in the spontaneous formation of lipid droplets ranging in size from approximately 100 nm (SEDDS) to less than 50 nm (SMEDDS). Construction of a pseudo-ternary phase diagram helps to determine the optimum concentrations or concentration ranges of oil, surfactant, and co-surfactant necessary to promote self-emulsification and to assess the effect of drug loading capacity on the efficiency of self-emulsification. Generally, well-formulated SEDDS or SMEDDS are dispersed within seconds under conditions of gentle stirring in an aqueous medium.

Properties of Sedds

- They are able to self-emulsify rapidly in GI fluid and under the influence of gentle agitation provided by peristaltic and another movement.
- They form o/w emulsion
- They can effectively incorporate drug (hydrophilic or hydrophobic) with the oil-surfactant mixture.
- Use for liquid as well as a solid dosage form.
- Required lower dose of drug (dose of drug can be reduced by this novel technique)

Advantages of Sedds

- Reduce hepatic first-pass metabolism.
- Protection of drug from GI environment.
- Selective targeting of drug towards specific absorption window in GIT.
- Improve oral bioavailability.
- Consistent drug absorption profile.
- Versatility (having a wide variety of skills)
- Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT
- No influence of lipid digestion process

Components of Sedds

Oils: Oil is the most important excipient in the formulation of SEDDS as it solubilizes the lipophilic drug or facilitates self-emulsification and also enhances the absorption through the GIT by increasing fraction of lipophilic drug transported through it. Long chain triglycerides (LCTs) and medium chain triglycerides (MCTs) oils with different degree of saturation have been used as oil phase in the formulation of SMEDDS. Unmodified edible oils are the most biocompatible lipid vehicles but they are enabled to dissolve large dose of the lipophilic drug and less efficient self-emulsification limits their use in the formulation of SEDDS. Examples; Natural oils, hydrogenated soyabean oil, oleic acid, corn oil, polyoxy castor oil, polyethylene glycol ester(Labrafac cc), semi-synthetic and synthetic oil.

Surfactants

Surfactant reduces the interfacial tension between two immiscible liquids and makes them miscible. When surfactants are incorporated in oil and water mixture then their polar heads are self-associated towards water phase and non-polar tails towards oil phase or they can locate at the interface, which is thermodynamically very favourable. Among all types of surfactants, only a few surfactants are orally acceptable. The most widely preferred surfactants for the design of SEDDS are non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) value. High HLB value and subsequent hydrophilicity of surfactant are necessary for a good self-micro emulsifying performance. The concentration range for preparation of stable SMEDDS lies b/w 30 to 60%. Example; Tween 80 (hydrophilic), Labrafac CM10, Labrasol (PEG ester), Gelucire (PEG+ Glycerol+ long chain fatty acid), Cremophor (PEG+ hydrogenated castor oil), Span20, Span80, Span85, Capryol 90, emulsifier from a natural source (safer than other).

Co-surfactants/ Co-solvents

They are used to increase the solubility of the drug in oil. Example; PEG, Propylene glycol, Butanol, Ethanol, Glycerol, Transcutol and other medium chain alcohol.

Formulation Design of Sedds

The oil in which drug has the highest solubility shall be selected. The surfactant and co-surfactant should be selected based on emulsification studies on the basis of ease of emulsification, miscibility, and percentage transparency in selected oil.[9]

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 50oC 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 50oC 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 mixtures under stirring on a magnetic stirrer. After each addition, the mixtures were observed for their appearance (turbid or clear).The turbidity of the samples would indicate the 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.[9,15]

Flow chart for preparation of SEDDS

Drug + Oil

↓

Oily solution + (Surfactant + Co-surfactant=Smix)

↓

Self-emulsifying drug delivery system (SEDDS)

↓

Dilution with water

↓

Self/Micro/Nano-emulsion

Evaluation of Sedds

Thermodynamic stability studies of formulation

The following cycles are carried out for these studies.

i. Heating cooling cycle

Six to eight cycles of cooling and heating between refrigerator temperature (4°C) and elevated temperature (40-45°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.[15,16]

ii. 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.[15,16]

iii. Freeze-thaw stress cycle: Three freeze-thaw cycles b/w -21° C & 25° C with storage at each temperature for not less than 48 hours (check for 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.[15,16]

Dispersibility Test

The dispersibility test of SEDDS is used to assess its capability to disperse into the 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 a different type depending upon which the *in vitro* performance of formulation can be assessed using the following grading system.[15,17]

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, grayish white emulsion having a 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.

Emulsification efficiency

The self-emulsification time is determined by using USP dissolution apparatus 2 at 50 rpm, where 1 ml of SEDDS formulations are introduced into 250 ml of 0.1N HCL or 0.5% SLS

(Sodium Lauryl Sulphate) solution or water or GI fluid. The time for emulsification at room temperature is indicated as a self-emulsification time for the formulation.[18] (Limitless than 1 min.).

Rheological properties (viscosity, flow, thixotropy, static yield, creep value) determination

The SEDDS system can also be administered in soft gelatin capsules and oral liquid, where, it should have appreciable flow properties for processing. Rheological properties of the formulation (diluted to 5 % v/v water) are determined by Brookfield viscometer. The viscosity of the formulation is inversely proportional to dilution.[15,19]

Robustness to Dilution

Emulsions upon dilution with various dissolution media (water, GI fluid, 0.5% SLS) should not show any phase separations or precipitation of drug even after 12 hrs of storage, such formulation is considered as robust to dilution.[20]

Turbid Metric Evaluation

Turbidity is a parameter for determination of droplet size and self-emulsification time. A fixed quantity of SEDDS is added to a fixed quantity of suitable medium (0.1 N HCL or Phosphate Buffer or water) under continuous stirring at 50 rpm on a magnetic stirrer at optimum temperature and the turbidity is measured using a nephelo turbidimeter.[13,21]

Droplet size analysis

Photon correlation spectroscopy (PCS) or dynamic light scattering (DLS) or Laser Diffraction Techniques are used to determine droplet size of the emulsion. Zetasizer (also measure the charge on droplet) is also used which are able to measure sizes between 10 -5000 nm.[15,18]

Refractive index (R.I.) & Percent Transmittance

Refractive Index & percent transmittance are determined to check the transparency of formulation. Refractive Index of the formulation is measured by refractometer by placing a drop of solution on slide & then comparing with water (R.I = 1.333). The percent transmittance of the formulation is measured at a particular wavelength using UV spectrophotometer by using distilled water as a blank.[13,14]

Optical Clarity

The test is performed on the diluted formulation. Absorbance is determined which should less than 1%(transmittance 99%), mean formulation is clear.

Drug Content

Drug from pre-weighed SEDDS is extracted by dissolving in a suitable solvent. The drug content in the solvent extract is analyzed by the suitable analytical method.

Liquefaction Time

This test is done to determine the time required by solid SEDDS formulation to melt *in vivo* in the absence of agitation in simulated gastric fluid Water. The formulation is packed in a transparent polyethylene film and tied to the bulb of the thermometer. The thermometer is then placed in round bottom flask in which simulated gastric fluid without pepsin is filled. The temperature is maintained at 37±0.5ºC by using heating mantle.[1]

***In vitro* Dissolution Test**

In vitro dissolution studies are carried out to assess drug release from oil phase into the aqueous phase by USP type 2 dissolution apparatus using 500 ml of simulated gastric fluid or water containing 0.5% w/v of SLS at 50 rpm and maintaining the temperature at 37±0.5ºC. Samples taken are then analyzed by using UV spectrophotometer,[13-15]

***In vitro* Diffusion study**

This study is done to determine release behavior of formulation using dialysis technique. One end of the dialysis membrane/ tubing (intestine of animal or cellulose acetate phthalate membrane) is tied with a thread and 1 ml of the SEDDS formulation and 0.5 ml of dialyzing medium (phosphate buffer pH 6.8) are filled in the membrane. The other end of the membrane is also tied with thread and then allowed to rotate in the 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. The volume of samples withdrawn is replaced with the fresh dialyzing medium. Samples taken are then analyzed by using UV spectrophotometer.[11-13]

Permeation studies

In this studies, isolated and perfuse organ system is used. Three techniques are available as follows.

i. *In-situ* single pass perfusion technique

SEDDS is placed in the jejunum (not isolated from the body) and determines the amount of drug not absorbed from jejunum (part of the intestine). The sample is taken by using the tube (from the intestine) and also directly from blood.

ii. Everted sec technique

A small part of the intestine (2-4 cm) is tied at one end and everted using glass rod. Kinetic parameters are determined by this method.

iii. Diffusion cell technique

A small part of the intestine is used in the diffusion cell. Amount of drug is determined which cross the membrane at specific pH and temperature.

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