SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM- A RECENT APPROACH IN DRUG DELIVERY SYSTEM

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Abstract

Self micro emulsifying drug delivery systems (SMEDDSs) have gained much attention for their capability to increase solubility and bioavailability of poorly soluble drugs. SMEDDS are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, and they can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. SMEDDS can be administered by oral route in soft or hard gelatin capsules and form fine relatively stable oil-in-water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids. So, only selected pharmaceutical excipient combinations will lead to efficient self-microemulsifying systems. Much improvement in the oral bioavailability of these drug compounds has been demonstrated for each case.

Keywords: Self-microemulsifying drug delivery systems (SMEDDSs), Lipophillic compound, Oral Bioavailability.

Introduction

Self-microemulsifying drug delivery system formulations are isotropic mixtures of an oil, a surfactant, a co-surfactant (or solubilizer) and a drug. The basic principle of this system is its ability to form fine oil in water (o/w) microemulsions under gentle agitation following dilution by aqueous phases that is, the digestive motility of the stomach and intestine provide the agitation required for self-emulsification *in vivo* in the lumen of the gut.[1] This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug

absorption.[2,3] Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption.

Properties of SEDDS

- SEDDS can incorporate hydrophobic or hydrophilic drug within the oil surfactant mixture.
- Used for solid as well as liquid dosage form.
- It require low dose of drug as compare to conventional dosage form.

Advantages of SEEDS: [4, 5]

- Quick Onset of Action
- Reduction in the Drug Dose
- Ease of Manufacture
- Scale-up Improvement in oral bioavailability
- 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 of SEDDS: [5]

- Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- 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.

- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

BCS class II and Class III are suitable candidates for SEDDS [6]

Methods of preparation

Spray drying:

A process in which a liquid solution is sprayed into a hot air chamber to evaporate the volatile fraction, i.e. the organic solvent or the water contained in an emulsion is known as spray drying. This process produces solid particles. Before spray drying, the formulation is prepared by forming a mixture of excipients with drug, followed by solubilization of the mixture in an organic solvent. The solubilized formulation then spray dried to remove the solvent. Dry emulsion also prepared by this method. Instead of dissolving the excipients in an organic solvent, an oil-in-water emulsion can be formulated and spray dried in same equipment to remove the aqueous phase [7].

Spray congealing:

Spray congealing also referred as spray cooling, where the molten formulation is sprayed into a cooling chamber. When the molten mixture comes in contact with cooling air, the molten droplets congeal and recrystallize into spherical solid particles which collect at the bottom of the chamber as fine powder. The fine powder then used for the development of solid dosage forms like, tablets and capsules. For spray cooling the main parameter is the melting point of the excipients that should be in the range of 50-800C. This technique can be used for enhancement of bioavailability and for sustained release formulation depending on the drug behavior and lipid matrix [8].

Melt extrusion

It is also known as extrusion spheronization. It is a solvent free process. Extrusion is a process of converting a raw material into a product of uniform shape and density by forcing it through a die under controlled temperature, product flow and pressure conditions. This approach has been successfully tied on 17β- estradiol and methyl and propyl paraben by using surfactant such as sucrosemonopalmitate, lauroylpolyoxyglycerides and polysorbate 80 [9].

Melt granulation

Melt granulation also known as thermoplastic pelletization. It is the one step process in which the transformation of a powder mixture into granules or spheronized pellets. This technique requires high shear mixing in presence of a meltable binder which may be sprayed in the molten state onto the powder mixture likewise wet granulation process. This referred to as pump on technique. Otherwise the binder may be blended with the powder mixture in its solid or semi-solid state and allowed to melt by the heat generated from the friction of particles during high shear mixing. This is referred as melt-in process. The melted binder forms liquid bridges with the particles and shape into small granules which is transformed to spheronized pellets by further mixing under controlled conditions [8].

Supercritical fluid technology

The lipids may be used in supercritical fluid technology for preparing solid dispersions or for coating of drug particles. The coating process involves dispersion of the drug particles in a supercritical fluid containing one or more coating materials in it. The solubility of coating material is sustained by elevated temperature & pressure and then coating is

facilitated by a gradual decrease in pressure & temperature which decreases the solubility of the coating material in the supercritical fluid leading to its gradual deposition onto drug particles. Lipid based excipients used for preparation of controlled release formulation are glyceryltrimyristate (dynasan 114) and stearoyl poly oxyl glycerides (gelucire 50/02) [10,11]

The following factors considered during this formulation technique.

- Solubility of the formulation components in the supercritical fluid
- The energy or environmental conditions relating to the evaporation of solvents
- The integrity and stability of the active substance under the process conditions

Solid lipid nanoparticles and nanostructure lipid carriers

Solid lipid nanoparticles and nano structured lipid carriers have size in the range 50-1000 nm and differ in state of core as SLN have a solid core while NLC have a liquid core. In the preparation of SLN, drug is dissolved in aqueous solution of the surfactants & then high pressure homogenization of the solid matrix & drug solution is carried out. NLC are reservoir system derived from SLN to increase the drug loading capacity of system. In addition to the classic SLN components, NLC also contain liquid lipid excipients such as MCT (medium chain triglycerides). They have been mainly used for controlled release formulations via the oral or topical route [12,13]. Solid lipid nanoparticlesof clozapine have been prepared by using soya lecithin 95%, triglycerides,Poloxamers 188 and Stearylamine as a positive charge inducer by hot homogenization followed by ultrasonication [14].

Adsorption on solid carriers

Free flowing powders may be obtained from liquid lipid formulations by adsorption onto solid carriers. The adsorption process involves addition of the liquid formulation onto the

carrier of choice by mixing in a blender. Calcium silicate, magnesium alumino silicate, silicon dioxide used as carrier for these preparations. This technique has benefit like good content uniformity, require minimum investment in equipment and facilitates formulation of tablets [14].

Excipients:

Oils [15,16,17]

The oil represents one of the most important excipients in the SEDDS formulation not only because it can solubilize the required dose of the lipophilic drug or facilitate self emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride[18-20]. Both long and medium chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations.

Surfactants [21, 22]

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) [23]. Safety is a major determining factor in choosing a surfactant

The four main groups of surfactants are defined as following

a. Anionic surfactants
b. Cationic surfactant
c. Ampholytic surfactants
d. Nonionic surfactants

a. **Anionic Surfactants**: where the hydrophilic group carries a negative charge such as carboxyl (RCOO-), sulphonate (RSO3 -) or sulphate (ROSO3 -). Examples: Potassium laurate, sodium lauryl sulphate.

b. **Cationic surfactants:** where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.

c. **Ampholytic surfactants:** (also called zwitterionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

d. **Nonionic surfactants:** where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene. Examples: Sorbitan esters (Spans), poly - sorbates (Tweens)

Co-solvents [24]:

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant. Role of the co surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value [25] . .At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant and surfactant/cosurfactant until their bulk condition is depleted enough to make interfacial tension positive again. However, the use of co-surfactant in self emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SEDDS, but also to solubilization of the drug in the SEDDS.

Evaluation [26-28]

Thermodynamic stability studies

The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

a) Heating cooling cycle: Six cycles between refrigerator temperature (40ºC) and 45ºC with storage at each temperature of not less than 48 hr is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

b) Centrifugation: Passed formulations are centrifuged thaw cycles between 21 ºC and +25 ºC with storage at temperature for not less than 48 hr is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

c) Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility test:

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 mL of water at 37 ± 0.5 0 C. A standard stainless steel dissolution paddle rotating at 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, grayish 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 formulation falling in Grade C could be recommend for SEDDS formulation.

Turbidimetric Evaluation

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Selfemulsifying 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),

Viscosity Determination

The SEDDS system is generally administered in soft gelatin or hard gelatin capsules. So, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform 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 are w/o type of the system.

Droplet Size Analysis

a. Particle Size Measurements: The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm.

Applications:

Improvement in Solubility and bioavailability:

If drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in of Class-II drug (Low solubility/high permeability). Ketoprofen, a moderately hydrophobic (log P 0.979) nonsteroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations. This formulation enhanced bioavailability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of Ketoprofen. In SEDDS, the lipid matrix interacts readily with water, forming a fine particulate Oil in-water (o/w) emulsion. The emulsion droplets will deliver the drug to the gastrointestinal mucosa in the dissolved state readily accessible for absorption. Therefore, increase in AUC i.e. bioavailability and Cmax is observed with many drugs when presented in SEDDS.

Protection against Biodegradation:

The ability of self emulsifying drug delivery system to reduce degradation as well as improve absorption may be especially useful for drugs, for which both low solubility and degradation in the GI tract contribute to a low oral bioavailability. Many drugs are degraded in physiological system, may be because of acidic PH in stomach, enzymatic degradation or hydrolyte Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might be an act as ebarrier between degradating environment and the drug. Ex: - Acetylsalicylic acid (Log P = 1.2, Mw=180), a drug that degrades in the GI tract because it is readily hydrolyzed to salicylic acid in an acid environment. The oral bioavailability of undegraded acetylsalicylic acid is improved by 73% by the Galacticles Oral Lipid Matrix

Controlling the release of drug:

Different formulation approaches that have been sought to achieve sustained release, increase thebioavailability, and decrease the gastric irritation of ketoprofen include preparation of matrix pellets of nanocrystalline ketoprofen, sustained release ketoprofen microparticles and floating oral ketoprofen systems and transdermal systems of ketoprofen. Preparation and stabilization of nano-crystalline or improved solubility forms of drug may pose processing, stability, and economic problems. This problem can be successfully overcome when Ketoprofen is presented in SEDDS formulation. This formulation enhanced bioavilability due to increase the solubility of drug and minimizes the gastric irritation. Also incorporation of gelling agent in SEDDS sustained the release of Ketoprofen.

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