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Basics of Self Micro Emulsifying Drug Delivery System

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Abstract

About 70-75% of drugs is taken orally and is found not to be as useful as desired. A self-micro emulsifying drug delivery system (SMEDDS) is a drug delivery system that uses a micro-emulsion achieved by chemical rather than mechanical means. Micro-emulsions have significant potential for use in drug delivery, and SMEDDS are the best of these systems. SMEDDS are of particular value in increasing the absorption of lipophilic drugs taken orally. SMEDDS are 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. SMEDDS can be encapsulated in hard or soft gelatin capsules or can be converted to solid state (Solid SEDDS/SMEDDS). This review article provides an overview of SMEDDS and its advantages over conventional dosage forms.

Keywords: SMEDDS, Micro-emulsions, Co-solvents

1. Introduction

In recent years, much attention has been focused on oral dosage forms using a self-micro emulsifying drug delivery system (SMEDDS) for the purpose of improving the solubility and absorption of poorly water-soluble drugs. SMEDDS consists of a mixture of drugs, oils, surfactants and/or other additives. Gentle mixing of these ingredients in aqueous media generates micro-emulsions with a droplet size in a range of 10-100 nm. SMEDDS has been shown to improve absorption of drugs by rapid self-micro emulsification in the stomach, with the micro-emulsion droplets subsequently dispersing in the gastrointestinal tract to reach sites of absorption [4]. The resultant small droplet size from SMEDDS provides a large interfacial surface area for drug release and absorption, and the specific components of SMEDDS promote the intestinal lymphatic transport of drugs [5]. Oral absorption of several drugs has been enhanced by SMEDDS [5-8].

2. Formulation of SMEDDSS

SMEDDS are composed of oil, hydrophilic surfactant, and a co-solvent. The process of self-emulsification is only specific to certain combinations of pharmaceutical excipients. It depends on the type of oil and surfactant pair, their ratios, the surfactant concentration and the temperature at which self-emulsification occurs. The primary step during formulation of a S(M)EDDS is the identification of these specific combinations of excipients and construct a phase diagram which shows various concentrations of excipients that possess self-emulsification. Mutual miscibility of these excipients is also important for producing a stable liquid formulation. Long chain triglycerides (LCT) are usually immiscible with hydrophilic surfactants and co-solvents. Polar oils such as mixed glycerides show an affinity towards hydrophilic surfactants and thus are miscible with the surfactant and also aids in self-dispersion of the formulation. The

diversity of chemical nature of lipids used may lead to immiscibility on long-term storage, so it is essential to perform physical stability tests on the formulation. If waxy excipients are used, they should be melted before weighing and then mixed with other liquid excipients [9]. With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water soluble co-solvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions. The following should be considered in the formulation of a SMEDDS:

1. The solubility of the drug in different oil, surfactants and co-solvents.

2. The selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram[10]

3. The preparation of SMEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co-solvent.

The addition of a drug to a SMEDDS is critical because the drug interferes with the self emulsification process to a certain extent, which leads to a change in the optimal oil–surfactant ratio. So, the design of an optimal SMEDDS requires preformulation-solubility and phase-diagram studies. In the case of prolonged SMEDDS, formulation is made by adding the polymer or gelling agent [11].

3. Excipients used in SMEDDS

3.1 Tween 80

Tween 80 is the partial fatty acid ester of sorbitol and it forms anhydrides as a result of copolymerization of approximately 20 moles of ethylene oxide for each mole of sorbitol. They are hydrophilic nonionic surfactants (HLB-15) and are used as emulsifiers in the preparation of oil-in-water emulsions, oral and injectable suspensions and solutions and as solubilizing agents for oil soluble vitamins [12, 13].

Tween 80 has been reported to protect proteins from surface induced denaturation during freeze drying [14]. It is one of the most widely used surfactant in the preparation of self dispersing type of formulations [15]. It is approved by the FDA for oral use. Peroxide impurities present in Tween 80 causes protein denaturation when such products are stored for extended periods of time.

3.2 Cremophor RH 40

It is a polyoxyethylene of derivative castor oil containing 70% of components which are hydrophobic in nature with an HLB of 14-16. Cremophor RH 40 contains fatty acid esters of glycerol polyethylene glycol and fatty acid esters of polyethylene glycol. It aids in improving aqueous solubility of propellant in water based aerosol vehicles [13].

It is used as a solubilizing agent for various hydrophobic Active Pharmaceutical Ingredients (API), fat soluble vitamins, and essential oils; and as an emulsifier in the preparation of pharmaceutical emulsions and SEDDS. It aids in solubilization of Lopinavir and Ritonavir in Kaletra® oral solution and Cyclosporine in Neoral® oral microemulsions(16)

3.3 Labrafac Lipophile WL 1349

Labrafac Lipophile WL 1349 is a medium chain triglyceride of fractionated vegetable C8 and C10 fatty acids (mainly fractionated coconut oil or palm kernel oil) with an HLB of 1. It is a non rancidable fluid used as a vehicle in oral and topical preparations, emulsions, self-emulsifying drug delivery systems, suspensions, ointments, suppositories, and creams. It can be used as filler in capsules and as an anti adherent in tablets. In combination with long chain triglycerides, it serves as a total parenteral nutrition (TPN) component. They possess excellent spreadability, skin penetration, and solvent properties when compared to long-chain triglycerides [17].

3.4 Polyethylene Glycol 400

Polyethylene glycols (PEG) have a wide range of applications including topical, oral, parenteral, ophthalmic and rectal delivery. Liquid grade PEG‟s are used as a water miscible co-solvents which possess

good solvent properties for poorly water soluble drugs. Due to this property, they are widely used in lipid based drug delivery systems such as solid dispersions and self-emulsifying mixtures. When used in soft gelatin capsules, they are known to cause hardening of capsule shells by absorption of moisture from gelatin in the shell [18].

3.5 Capyrol 90

Soluble in ethanol, chloroform, methylene chloride, and vegetable oils, insoluble in water Capryol 90 contains more than 90% monoester of C8 fatty acid (caprylic acid). It is used as an emulsifier in oil-in-water emulsions and self emulsifying drug delivery systems. It is reported to possess bioavailability enhancing properties due to its inhibitory action on CYP3A4 enzyme [19].

3.6 Transcutol P

Transcutol P has good solvent properties for poorly water soluble drugs. It enhances drug penetration, permeation, and produces a drug depot effect. It is used as a co-solvent in the formulation of SMEDDS [20].

3.7 Neusilin US2

Neusilin US2 is a very fine powder of amorphous magnesium aluminosilicate. It possesses very large surface area enabling it to adsorb oils up to three times of its weight. It has good flowability and compressibility and can be directly compressed into tablets. It has been used as an adsorbent for oil-emulsifier mixtures [21] in SEDDS and for melt granulation in solid dispersion technology [22]. Upon co-grinding with a crystalline drug, it converts the drug into an amorphous form [23].

4. Tests for Self Emulsification

The SMEDDS are either visually clear Nano-emulsions, or a slightly turbid emulsions, or milky emulsions that have immediate phase separation. The formulations that are emulsified into a clear, transparent nano-emulsion and showed no signs of instability for 24 hours are described in ternary phase diagrams using Sigmaplot® software. The spontaneity of emulsification, clarity of dispersion and apparent stability are usually performed to evaluate SMEDDS [23].

4.1 Drug Solubility

For Drug solubility in SMEDDS, Excess amount of drug is added to few ml of each excipients placed in microtubes and the mixture is vortexed, heated to 40 ℃ in a water bath to facilitate drug solubilization. The mixture is finally kept at ambient room temperature (25 ℃) under continuous shaking for 2 days to attain equilibrium. The mixtures are then centrifuged at 2500-3000 rpm for 15-20 min. Aliquots of supernatant are then diluted with alcohol, and the drug content is quantified using a UV spectroscopic method. The solubility of drug is determined from a calibration curve of respective active drug in alcohol [24].

4.2 Droplet size and Zeta potential of nano-emulsion

Liquid SMEDDS and Solid SMEDDS are dispersed in 400-500 ml of water to obtain a nano-emulsion. The droplet size and zeta potential of the resultant nano-emulsion is measured using Dynamic Light Scattering. The nano-emulsion samples are taken in disposable glass culture tubes and volume weighted diameter is determined by placing the sample in the path of a Helium Neon laser of suitable wavelength at a scattering angle of 90 ℃ and a temperature of 25 ℃ [25].

4.3 Morphological Analysis of Solid SMEDDS

The surface morphology of Solid SMEDDS is analyzed in an Electron Microscope. The samples are fixed on an aluminum stump using a double sided carbon adhesive tape and are made electrically conductive by coating with palladium under vacuum. An accelerating voltage of 5 kV is used to visualize the samples.

4.4 Differential Scanning Calorimetry of Solid SMEDDS

The physical state of SMEDDS is characterized by differential scanning calorimetry equipped with an Intercooler 1P. Samples of SMEDDS are run on DSC. The samples (about 3-6 mg) are placed in standard

aluminum pans using nitrogen as effluent gas. Samples are scanned at a temperature speed of 10 ℃/min from 0 to 140 ℃. The acquired data is analyzed using Pyris Manager Software.

4.5 Powder X-ray Diffraction of Solid SMEDDS

The physical state of active drug in Solid SMEDDS is characterized by X-ray powder scattering measurements using X ray diffractometer. The measurements are performed at room temperature using monochromatic radiation with a continuous scanning speed of 4 °/min. The analyzed samples are compactly packed in the cavity of an aluminum sample holder using a glass slide.

5. Mechanism of Self-Emulsification

Conventional emulsions are formed by mixing two immiscible liquids namely water and oil stabilized by an emulsifying agent. When an emulsion is formed surface area expansion is created between the two phases. The emulsion is stabilized by the surfactant molecules that form a film around the internal phase droplet. In conventional emulsion formation, the excess surface free energy is dependent on the droplet size and the interfacial tension. If the emulsion is not stabilized using surfactants, the two phases will separate reducing the interfacial tension and the free energy [25]. In case of S(M)EDDS, 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 [26, 27].

6. Advantages of SMEDDS

6.1 Improvement in oral bioavailability

Dissolution rate dependent absorption is a major factor that limits the bioavailability of numerous poorly water soluble drugs. The ability of SMEDDS to present the drug to GIT in solubilized and micro emulsified form (globule size between 1-100 nm) and subsequent increase in specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability [28].

6.2 Ease of manufacture and scale-up

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, liposomes, nano particles, etc., dealing with improvement of bio-availability. SMEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of industry in the SMEDDS.

6.3 Reduction in inter-subject and intra-subject variability and food effects

There are several drugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a benefit for such drugs. Several research papers specifying that, the performance of SMEDDS is independent of food and, SMEDDS offer reproducibility of plasma profile are available [29].

6.4 Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT

One distinctive property that makes SMEDDS superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis. The intestinal hydrolysis of pro drug by cholinesterase can be protected if Polysorbate 20 is emulsifier in micro emulsion formulation [4]. These systems are formed spontaneously without aid of energy or heating thus suitable for thermo labile drugs

such as peptides. No influence of lipid digestion process and increased drug loading capacity are the two other advantages of SMEDDS [30].

7. Advantages of SMEDDS over emulsion

1. SMEDDS not only offer the same advantages of emulsions of facilitating the solubility of hydrophobic drugs, but also overcomes the drawback of the layering of emulsions after sitting for a long time. SMEDDS can be easily stored since it belongs to a thermodynamics stable system.

2. Microemulsions formed by the SMEDDS exhibit good thermodynamics stability and optical transparency. The major difference between the above microemulsions and common emulsions lies in the particle size of droplets. The size of the droplets of common emulsion ranges between 0.2 and 10 μm, and that of the droplets of microemulsion formed by the SMEDDS generally ranges between 2 and 100 nm (such droplets are called droplets of nano particles).Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of solid dosage form and it can easily penetrate the gastrointestinal tract and be absorbed. The bioavailability of the drug is therefore improved.

3. SMEDDS offer numerous delivery options like filled hard gelatin capsules or soft gelatin capsules or can be formulated in to tablets whereas emulsions can only be given as an oral solutions.

8. Disadvantages of SMEDDS

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. This in vitro model needs further development and validation before its strength can be evaluated.

4. 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.

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

6. Moreover, volatile co solvents in the conventional self-micro emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

7. The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.

8. Formulations containing several components become more challenging to validate.

5. Conclusion

In this article some basics of SMEDDS are discussed. Excipients discussed for SMEDDS are Tween 80 and Cremophor RH 40 as surfactants, Transcutol P, Capyrol 90 and PEG 400 as cosurfactants and Labrafac Lipophile (a medium chain triglyceride) as oil. SMEDDS is known to improve dissolution characteristics of a poorly water soluble drug since they maintain the drug in a solubilized state in the GI tract. As a conclusive note we can say that SMEDDS can be potentially used for delivering a poorly water soluble drug.

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