Self-Micro-Emulsifying Drug Delivery System (SMEDDS) - A Novel Approach.

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ABSTRACT

Self-micro-emulsifying drug delivery systems (SMEDDS) are one of the proven methods to increase solubility and bioavailability of poorly soluble drugs. SMEDDS are isotropic mixtures, consisting of oils, surfactants, and sometimes co-solvents. Designed formulations are used to improve the oral absorption of highly lipophilic compounds. Multiple lipid-based drug delivery systems are widely reported in the literature and they include simple oil solutions, coarse, multiple and dry emulsions, and more complex self-emulsifying, micro-emulsifying or nano-emulsifying drug delivery systems. The process of self-emulsification is dependent on diverse factors such as the nature of oil, surfactant, cosurfactant, oil/surfactant ratio, and the polarity of the emulsion. Considering the ease of large-scale production and the robustness of SMEDDS, several formulations are commercially available which utilize this technology. This article attempts to present an overview of SMEDDS along with their applications, compiled literature data, commercially available products, and their descriptions.

Keywords: Poorly soluble drugs, Surfactant, Cosurfactant

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INTRODUCTION

In modern drug discovery techniques, there has been a consistent increase in the number of poorly water-soluble Drug candidate compounds, and currently more than 50% of new pharmacologically active chemical entities are lipophilic and exhibit poor water solubility. Self-micro emulsifying drug delivery (SMEDDS) is one of the methods for the improvement of oral bioavailability. SMEDDS are the isotropic mixtures of oils, surfactants, solvents, and co-solvents. This review article tries to describe the formulation of SMEDDS and also talks about the construction of the phase diagram for SMEDDS. It describes the mechanism involved in self emulsification and the biopharmaceutical aspects involved. The advantages of SMEDDS over conventional emulsions are listed. Some of the marketed preparations of SMEDDS are listed in detail. A few drug delivery systems which show the scope for the usage of the SMEDDS are also described.

Self-Micro-Emulsifying Drug Delivery System (SMEDDS):

Self-micro-emulsifying drug delivery system (SMEDDS) is defined as an isotropic mixture of natural or synthetic oils, solid or liquid surfactants and hydrophilic cosolvents/co-surfactants that have a unique ability to form fine oil-in-water (o/w) microemulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. It is used for the delivery of hydrophobic drugs having low water solubility and poor bioavailability. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs. The basic difference between SEDDS and self-micro-emulsifying drug delivery system (SMEDDS) is SEDDS typically produce opaque emulsions with a droplet size between 100-300 nm while SMEDDS form transparent micro-emulsions with a droplet size of between 50-100 nm. Droplet size less than 50nm called as self-Nano-emulsifying drug delivery system (SNEDDS). Solid SMEDDS are solid dosage forms with a unique property that, they can self-emulsify rapidly into fine gentle agitation provided by the GI tract. This fine o/w emulsion results in small droplets of oil dispersed in the GI fluids that provide a large interfacial area enhancing the activity and minimizing the irritation due to contact of the drug in the gut wall. Micro-emulsions have got advantages like excellent thermodynamic stability, high drug solubilization capacity, improvement in oral bioavailability and protection against enzymatic hydrolysis. [1, 2]

Purpose
Oral delivery of poorly aqueous soluble drugs is frequently associated with low bioavailability, high inter- and intra subject variability and lack of dose proportionality. Self micro-emulsifying drug delivery system that has shown great pledge for enhancing the bioavailability of the poorly water-soluble compound.\cite{3}

**Mechanism of self-emulsification**

Different approaches have been reported in the literature. No single theory explains all aspects of microemulsion formation. The formation of emulsion droplets was due to the formation of a complex film at the oil-water interface by surfactant and co-surfactant. According to the theory of thermodynamic, emulsification takes place due to the entropy change that favors dispersion is greater than free energy required to increase the surface area between oil and aqueous phases of dispersion. Process of emulsification involves a change in free energy ($\Delta G$) can be expressed by

$$\Delta G = \Sigma N_r^2$$

$\Delta G$ - Free energy associated with the process (ignoring the free energy of the mixing),

$N$ - Number of droplets

$r$ - Radius of droplet

$\gamma$ - Interfacial energy with time.

Two phases of emulsion tend to be separate, to reduce interfacial area and subsequently, the free energy of the system. Therefore, the emulsion is stabilized by emulsifying agents and forms a monolayer of emulsion droplets and ultimately reduces interfacial energy which acts as a barrier around oil droplets to prevent coalescence.\cite{4,5}

**Advantages of SMEDDS over Conventional Emulsion**

**Ease of Formulation Technique:**

SMEDDS includes mixing of oil, surfactant, and co-surfactant, if necessary cosolvent, to dissolve the drug in oil which is a simple process as compared to conventional emulsion where high shear needed for dispersion.

**Stability of Emulsions:**

Theoretically, all emulsions including micro-emulsions are unstable (actually they are stable only kinetically but not thermodynamically) due to instability and shows characteristics like flocculation, creaming, coalescence, and breaking. In the case of SMEDDS, as emulsification is spontaneous, emulsions are stable at least for the period for which they have to remain in the body. SMEDDS themselves are as said earlier, clear, isotropic solutions posing no problem of stability.

**Storage Conditions:**
All emulsions need to be stored at specific temperature conditions as emulsion configuration may change at phase-inversion temperature (PIT). SMEDDS are sensitive to moisture and must be protected. However, they can be packed and sealed in smaller soft orchard gelatin capsules as compared to larger containers require for conventional emulsions.

**Dose Uniformity:**
Uniformity in dose with emulsions is a factor of discussion as no one can give guarantee about drug contents of droplets and dispersion media. Since SMEDDS are presented as soft/hard gelatin capsules or tablets as a unit dosage form, a high level of drugs can be targeted to lymphatic patches in the intestine and to the reticuloendothelial system of the liver due to lipid core of SMEDDS. After absorption into the enterocyte, the vast majority of orally administered drugs rapidly diffuse across the cell are absorbed into capillaries of the portal vein and thereby processed via the liver to the systemic circulation. Highly lipophilic drug molecules, however, may associate with lymph lipoproteins in enterocyte and gain access to the systemic circulation via thoracic lymph duct.

**Protection of Acid Labile Drugs in Stomach:**
Some drugs particularly newly developed drugs are very sensitive to the acidity of the stomach, get degraded to a large amount of acid pH. If droplets of emulsion formed are in a small range (SMEDDS), they can protect such drugs due to their oil core, surfactant film and they’re escaping from stomach to intestine without having the effect of food or gastric emptying time on them.

**Protection of Drugs from Recrystallization and Precipitation in GI Fluid:**
As the drug is protected in SMEDDS in its oil core, it is prevented from precipitation and recrystallization in acidic pH, which is essential in the case of acidic drugs. [6, 7]

**Disadvantages of SMEDDS**
1. Lack of good predictive *in-vitro* models for assessment of formulations.
2. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion before the release of the drug. To mimic this, an *in-vitro* model simulating the digestive processes of the duodenum has been developed. This *investor* model needs further development and validation before its strength can be evaluated.
3. Different prototype lipid-based formulations need to be developed and tested *in vivo*.
4. Chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) may irritate GIT.
5. Volatile co-solvents may migrate into shells of soft or hard gelatin capsules, resulting in precipitation of lipophilic drugs.
6. The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.

7. Formulations containing several components become more challenging for validation. [8, 9]

**BIOPHARMACEUTICAL ASPECTS OF SMEDDS:**

Biopharmaceutical aspects of SMEDDS although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via several potential mechanisms including:

- **Alterations (reduction) in gastric transit:** - thereby slowing delivery to the absorption site and increasing the time available for dissolution.

- **Increase in effective luminal drug solubility:** - The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous billiard lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these Structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity.

- **Stimulation of intestinal lymphatic transport:** - For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in the first-pass metabolism.

- **Changes in the biochemical barrier function of the GI tract:** - It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump and may also reduce the extent of enterocyte based metabolism.

- **Changes in the physical barrier function of the GI tract:** - Various combinations of lipids, lipid digestion products, and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs. [10, 11]

**Drug Properties Suitable for SMEDDS**

1. The dose should not be so high.

2. The drug should be oil soluble.

3. A high melting point drug is poorly suited to SMEDDS.

4. The log P value should be high. [12]

**EXCIPIENTS USED IN SMEDDS:**

The Self-Emulsifying Process Depends on: -

1. The nature of the oil-surfactant pair
2. The surfactant concentration
3. The temperature at which self-emulsification occurs.

1. Oils: -

The majorities of hydrophobic drugs are lipophilic and have greater solubility in triglycerides than in surfactants. It can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract which avoids the first-pass metabolism of drugs, which increases overall GI bioavailability of poorly water-soluble drugs. Triglycerides such as medium-chain and long-chain with different degrees of saturation have been used for the solvation of hydrophobic therapeutic agent in the design of SMEDDS. For the formulation of a self-emulsifying system both long-chain triglycerides (LCT) eg. Soya bean, Sesame, Olive, Peanut, corn and rapeseed oils and medium-chain triglycerides (MCT) eg. Fractionated Coconut oil and palm seed oil, triglycerides of caprylic/capricacid eg. Miglyol 812, Captex 355 are utilized, but as compared to LCT. The MCT has more capacity to solubilize lipophilic drugs, provides higher fluidity and good emulsification. In recent years much attention has been focused on MCT (C12- C18) for the formulation of SEDDS. These MCT is nothing but a fractionated coconut oil. MCT is easy for digestion as compared to LCT, which converts to diglycerides, monoglycerides, and free fatty acids. This conversion is facilitated by several gastric and intestinal enzymes like lipase, pancreatic lipase, etc.

2. Surfactant: -

The surfactant molecule consists of polar or charged hydrophilic moieties as well as nonpolar hydrophobic (lipophilic) moieties i.e. a surfactant compound must be amphiphilic. Combinations of surfactants are used in the formulation of SMEDDS one of which is hydrophilic while the remaining surfactant or surfactants being hydrophilic or hydrophobic. Surfactants used in SMEDDS are mainly (i) non-ionic, (ii) anionic, (iii) cationic or zwitterionic Surfactants. Surfactants with lower lipophilic values are more hydrophobic and greater solubility in oils, whereas surfactants with higher HLB values are more hydrophilic and have greater solubility in aqueous mediums. The non-ionic surfactants are generally considered to be those compounds having an HLB value greater than about 10 are providing fine, uniform emulsion. These non-ionic surfactants are less toxic than that of cationic and anionic surfactants. During the formulation design of any dosage form, it is to be considered that excipients utilized in the formulation should not cause any toxicity to the patient. While in the case of self-emulsifying system usual concentration of surfactant to form and maintain the emulsion state in GIT, ranged from 30-60% w/w of the formulation, which is very high. Emulsifier of natural origin such as polyoxyl 35 castor
oil (Cremophor EL), polyoxyl 40 castor oil (CremophorRH40), polysorbate 80(Tween 80), etc, are safer than that of synthetic surfactants. Surfactants are amphiphilic and they can dissolve or solubilize a relatively high amount of hydrophobic drug compounds. A surfactant having a high HLB (8-18) is preferred for the formation of o/w microemulsion whereas, surfactants having a low HLB (3-6) are preferred for the formation of w/o microemulsion. Anionic, cationic or zwitter ionic compound for which the HLB scale is not generally applicable. In most of the literature it is revealed that, as the concentration of surfactant in self-emulsifying system increases, there is a marked decrease in droplet size. Surfactants increase the permeability by interfering with the lipid bilayer of a single layer of the epithelial cell membrane, which with an unstirred aqueous layer, forms a rate-limiting barrier to drug absorption/diffusion. Therefore, most drugs are absorbed via the passive transcellular route. Surfactants partition into the cell membrane and disrupt the structural organization of lipid bilayer leading to permeation enhancement. They also exert their absorption enhancing effects by increasing the dissolution rate of the drug.

3. Co-solvents and Co-Surfactant: -

Co-solvents are used to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the co-surfactant in the micro emulsion systems. Commonly used cosolvents include polyethylene glycol 400, propylene glycol, ethanol, and glycerol diethylene glycol monomethyl ether (transcutol), polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glyco-ether(glycofurol), etc. The physical state of these excipients at ambient room temperature is determined by their molecular weight. PEG ranging from 200 to 600 in molecular weight is liquid at ambient room temperature where those possessing a molecular weight of 1000or greater exit as thermo softening semi-solid. Polymeric liquid and semi-solid excipients, most of which are glycolic in nature and relatively non-toxic, are used as solvents for formulating poorly water-soluble drugs. Generally co-surfactant of HLB value 10-14 is used with surfactant together to decrease the interfacial tension to a very small even transient negative value. At this value, the interface would expand to form finely dispersed droplets and subsequently adsorb more surfactant until their bulk condition is depleted enough to make interfacial tension positive again. This process is known as spontaneous emulsification. However, for many non-ionic surfactants, it is not compulsory/mandatory to use co-surfactant in micro-emulsion. The selection of co-surfactant and surfactant is crucial not only to form the formation of micro-emulsion but also to solubilization in micro-emulsions. Such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in conventional self-emulsifying formulations
are known to migrate into shells of soft gelatin or hard sealed gelatin capsules resulting in precipitation of lipophilic drug. But drugs in alcohol-free formulations may exhibit limited solubility. Hence, the proper choice has to be made during the selection of components. [13, 14, 15]

**FORMULATION METHODOLOGY:**

The method of making self-microemulsion drug delivery system includes various steps as described below: [16]

**Solubility determination of drug in various components**

The saturation solubility of the drug was determined in various oils, surfactants, and cosurfactants. [17, 18]

**Preparation of phase diagram (pseudo ternary phase diagram)**

The pseudo ternary phase diagram is used to study the phase behavior of a simple microemulsion system. These diagrams are helpful to identify the self-micro emulsifying regions and to optimize the emulsifier to co-emulsifier ratio and the concentration of the oil. Pseudo ternary phase diagram can be represented in a triangular format in which each corner of the diagram represents 100% of that particular component., pseudo-ternary phase diagrams are used where a corner will typically represent a binary mixture of two components such as surfactant / Co-surfactant, water /drug or oil /drug. The number of different phase’s present for a particular mixture can be visually assessed. The procedure most often employed is to prepare a series of (pseudo) binary compositions and titrate with the third component evaluating the mixture after each addition. The mixtures were usually examined for transparency. The mixtures were further titrated with distilled water until it shows turbidity to transparency. Clear and isotropic mixtures were deemed to be within the microemulsion region. Within the phase diagram, existence fields are shown where conventional micelles, reverse micelles or water-in-oil (w/o) micro emulsion and oil-in-water micro-emulsion are formed along with the continuous microemulsion. At very high surfactant concentrations two-phase systems are observed. [19, 20]

**Techniques of solidification**

1 Adsorption to Solid Carriers

Solid carriers are used to adsorb liquid self-micro emulsifying formulations to get free-flowing powders. In this process, the liquid formulation is added to the carrier in a blender and mixed. The powder obtained may then be filled directly into capsules or, alternatively, maybe mixed with suitable excipients to form tablets by compression. The most important tablet’s significance in this method is that it gives good content uniformity. SMEDDS can be bead orbed at high levels (up to 70% w/w onto suitable carriers. Solid carriers can bew/w)microporous inorganic substances, cross-
linked polymers, high surfaced surface-area colloidal inorganic adsorbent substances or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, crospovidone, cross-linked sodium carboxymethylcellulose, cross-linked magnesium hydroxide, talcum and crosslinked polymethyl methacrylate. Cross-linked polymers are used to create a favorable environment to sustain drug dissolution. Porous environment silicon dioxide (Sylysia 550), carbon nanotubes, carbon nanohorns, fullerene, charcoal and bamboo charcoal are the adsorbents in involved in nanoparticles.

2 Freeze Drying

Lyophilization (freeze-drying) is the removal of water from frozen material. It is an excellent method for preserving microbes and heat-sensitive materials such as proteins, heat-sensitive plasma, etc. In freeze-drying water is removed from frozen samples mainly by sublimations where water is converted from the frozen state into vapor, thus passing the liquid phase. The rate of sublimation depends on vapor pressure, which is affected by the system vacuum and sample temperature. The frozen sample absorbs heat, causing water in the sample to enter the vapor phase and migrate into the instrument atmosphere where it is removed by refreezing on the condenser. Drying first occurs at the surface of the sample. As drying proceeds, water is removed from deeper layers of the sample. There are three steps in freeze-drying.

1. Manifold drying is the most commonly used method. Drying flasks or ampoules are attached to individual ports on a central manifold. The samples are usually frozen by shell method, and are quickly attached to the manifold and placed under vacuum to prevent melting. Room temperature provides heat for these ampoules. This method is useful for relatively small volumes.

2. The batch method is used when large numbers of similar-sized containers are simultaneously freeze-dried, eg. Serum vials. A tray system is used instead of a manifold. Heating elements in trays supply heat. Most batch systems have a mechanism to seal vials before they are exposed to air.

3. The bulk method is used for large volumes of a single sample. The sample is poured into special trays, frozen, and then dried in a lyophilizer. Bulk dried samples cannot be sealed while in the instrument. Exposure to air before packaging may affect the shelf life.

3 Spray Drying

There are many applications of SMEDDS that require the conversion of the liquid formulation into a dry product. SMEDDS granulates or powders could be put into capsules, pressed into tablets or incorporated into a pellet. For prolonged long-term stability especially for i.e. administered systems can be achieved when stored as a dry product. This may be of interest to SMEDDS
containing drugs that are susceptible to hydrolysis or on exposure to elevated temperatures or light in aqueous dispersion. The less cost-intensive spray-drying technique was investigated for solid SMEDDS as an alternative method to liquid SMEDDS. Spray-drying is widely used in the chemical, the food, and the pharmaceutical industries. It is commonly used to process milk, eggs, ceramics, and fertilizers. It converts a liquid into a dry system in a one-step process and can produce fine, dust-free powders, as well as agglomerate, is done, to precise specifications.

4 Melt Granulation
Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a ‘one-step’ operation, melt granulation having several advantages as compared to conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. The granulation process can be controlled by several parameters such as 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. Gelucire1 derived from the mixtures of mono-/di-/tri-glycerides and polyethylene glycols (PEG) esters of fatty acids, is having the ability to further increase the dissolution rate as compared to PEG usually used. Other lipid-based excipients evaluated for melt granulation to create solid SMEDDS include lecithin, partial glycerides, or polysorbates. Melt granulation process was usually used for adsorbing SES (lipids, surfactants, and drugs) onto solid neutral carriers.

5 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 uniformly sized spheroids (pellets). The extrusion–spheronization process requires the following steps: dry mixing of the active ingredients and excipients to achieve a homogeneous powder; wet massing with a binder; extrusion into a spaghetti-like extrudate; spheronization from the extrudate to spheroids of uniform size; drying; sifting to achieve the desired size distribution and coating. In the wet masses comprising SES (polysorbate 80 and mono-/di-glycerides), lactose, water and MCC, relative quantities of SES and water had a significant effect on the extrusion force, size spread, disintegration time, and surface roughness of pellets. Studies suggested that the maximum quantity of this SES that can be solidified by extrusion spheronization occupies 42% of the dry pellet weight. Generally, the higher
the water level, the longer the disintegration time. The rheological properties of wet masses may be measured by an extrusion capillary. It has been shown that SES containing wet mass with a wide range of rheological characteristics can be processed, but a single rheological parameter cannot be used to provide a complete characterization of how well it can be processed by extrusion spheronization. [21, 22, 23]

**EVALUATION OF SMEDDS:**

The primary means of self micro emulsification assessment is visual evaluation. The efficiency of self micro emulsification could be estimated by determining the rate of micro emulsification, droplet size distribution and turbidity measurement.

**Droplet size and particle size measurement:** The particle size of the micro emulsion is determined by photon correlation spectroscopy or SEM (Scanning Electron Microscopy) which can measure sizes between 10 and 5000 nm. The nanometric size range of the particle is retained even after 100 or 1000 times diluted with distilled water, which proves the system's compatible with excess water. [24, 25]

**Refractive index and percent transmission:** Refractive index and percent transmittance proves the clearness of formulation. The refractive index of the SMEDDS is measured by a refractometer and compared with that of water. The percent transmittance of the system is measured at a particular wavelength using a UV-Vis spectrophotometer keeping distilled water as blank. If the refractive index of the system should be similar to that of water. Formulation showing transmittance >99 percent is transparent.

**Determination of percentage drug content:** One capsule of each formulation was taken in a 100 mL volumetric flask, and added 100 mL of extracting solvent. Then the mixture was shaken for 1 h in a mechanical shaker and kept aside for 24 h. After 24 h, filtered the solution through Whatman filter paper (0.45 μm) to collect the filtrate. The filtrate was then analyzed in UV-spectrophotometer. The concentration of drug in solution was calculated from absorbance and standard graph. [26, 27]

**Phase separation study:** One-milliliter SMEDDS was added to a glass test tube containing 5 mL of 0.1 N HCl, buffer pH 6.8 and distilled water. After inverting the test tube for 3-4 times, each mixture was stored for a period of 2 h and phase separation was observed visually. [28]

**Visual assessment:**

To assess the self-emulsification properties, the formulation was introduced into 100 ml of water in a glass Er-lennmeyer flask at 25°C and the contents were gently stirred manually. The tendency to spontaneously form a transparent emulsion was judged as good and it was judged bad when there
was poorer no emulsion formation. A phase diagram was constructed identifying the good self-emulsifying region. [29]

**Transmittance Test:**

The stability of optimized micro emulsion formulation concerning dilution was checked by measuring Transmittance through U.V. Spectrophotometer (UV-1700 SHIMADZU). The transmittance of samples was measured at suitable wavelengths and for each sample, three replicate assays were performed. [30]

**Droplet size determination:** It is a precise method for evaluation of stability. The size of the droplet is measured by photon correlation spectroscopy (PSC) with Zetasizer. All measurements are carried out at a scattering angle of 90° and 25°C temperatures. Before measurement, the microemulsion is diluted in two-steps with pure water then it is filtered through a 0.22um filter just before it is added to cuvette. In the first step, it is diluted with an equal amount of water. In the second step, the mixture is further diluted to the appropriate concentration for the measurement. That depends on droplet size (usually diluted 100-200 times) [31]

**Zeta potential measurement**

Zeta potential for microemulsion was determined using Zetasizer HSA 3000 (Malvern Instrument Ltd., UK). Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment. [32]

**In vitro release**

The quantitative in vitro release test was performed in 900 ml purified distilled water, which was based on USP 24 methods. SMEDDS was placed in a dialysis bag during the release period to compare the release profile with the conventional tablet. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 μ membrane filter, dilute suitably and analyzed spectrophotometrically. An equal amount of fresh dissolution medium was replaced immediately after the withdrawal of the test sample. Percent drug dissolved at different time intervals was calculated using the Beer Lambert’s equation. [33]

**Thermodynamic Stability Studies** The physical stability of a formulation is very important for its performance as it can be adversely affected by precipitation of the drug in the excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficacy. Also, the incompatibilities between formulation & gelatin shell of the capsule (if formulation filled in capsule) may cause brittleness, softness and
delayed disintegration or incomplete release of the drug. The following cycles are carried out for these studies.

**FUTURE PERSPECTIVE:**

Concerning formulation development of poorly soluble drugs in the future, new techniques are being used to convert liquid/semi-solid SEDDS and SMEDDS formulations into powders and granules which can then be further processed into conventional 'powder-fill' Capsules or even compressed into tablets. Hot melt granulation is a technique for producing granules or pellets and by using a waxy solubilizing agent as a binding agent, up to 25% solubilizing agent can be incorporated in a formulation. There is also increasing interest in using inert adsorbents products for converting liquids into powders which can then be processed into powder fill capsules or tablets. However, to obtain solids with suitable processing properties the ratio of SMEDDS to solidifying excipients must be very high which seems to be practically non-feasible for drugs having limited solubility in the oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for the transformation of SMEDDS in solid dosage forms will be significantly reduced if SMEDDS is gelled. Colloidal silicon dioxide (Aerosol 200) is selected as a gelling agent for the oil-based systems which may serve the dual purpose of reducing the amount of solidifying excipients required and aiding in slowing drug release. [34, 35]

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