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Self micro emulsifying drug delivery system (SMEDDS): An approach to enhance an oral bioavailability

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Abstract:

Approximately 40%of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system because of their low bioavailability. The oral bioavailability of poorly water soluble drugs may be enhanced when co administered with meal rich in fat has led to increasing recent interest in the formulation of poorly water soluble drugs in lipids. One of the most new way for such a mentioned problem is the Self microemulsifying drug delivery system (SMEDDS). Self micro emulsifying drug delivery systems are isotropic mixtures of oil, surfactant, co-surfactant and drug with a unique ability to form fine oil in water microemulsion upon mild agitation following dilution with aqueous phase. The hypothesis behind dissolution rate enhancement with SMEDDS is the spontaneous formation of the emulsion in the gastrointestinal tract which presents the drug in solubilized form and the small size of the formed droplet provides a large interfacial surface area for drug absorption. This article gives a complete overview of SMEDDS as a promising approach to effectively tackle the problem of poorly soluble molecules.

Introduction:

The oral route is one of the preferred routes for chronic drug therapy. Approximately 35-40% of new drug candidates have poor water solubility. The oral delivery of such drugs is frequently associated with low bioavailability, high inter and intra subject variability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. To overcome these problems new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrins, solid dispersation (suspension), co-precipitation, micronisation, salt formation, emulsion, use of micelles and cogrindin [1,2]. Self micro emulsifying drug delivery system (SMEDDS) are defined as isotropic 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 [3,4]. The basic difference between self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation (SEOF) and SMEDDS is SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 50 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS. When compared with emulsions, which are sensitive and metastable dispersed Forms SMEDDS are physically stable formulations that are easy to manufacture. 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. SMEDDS formulation is in theory comparatively simple. The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gelatin capsules. A typical SMEDDS formulation contains oils surfactants and if required an antioxidants. Often co-surfactants and co-solvents are added to improve the formulation characteristics [5,6].

History of Micron Emulsions:

The term microemulsion was first used by T. P. Hoar and J. H. Shulman professors of chemistry at Cambridge University in 1943. Alternative names for these systems are often used such as transparent emulsion, swollen micelle, micellar solution and solubilized oil. Microemulsions are formed when (i) The interfacial tension at the oil/water interface is brought to a very low level. (ii) The interfacial layer is kept highly flexible and fluid. These two conditions are usually met by a careful and precise choice of the components and of their respective proportions and by the use of a “co-surfactant” which brings flexibility to the oil/water interface. These conditions lead to a thermodynamically optimised structure which is stable as opposed to conventional emulsions and does not require high input of energy (i.e. through agitation) to be formed. Because the size of the particles is much smaller than the wavelength of visible light, microemulsions are transparent and their structure cannot be observed through an optical microscope [7,8].

Advantages of SMEDDS:

Improvement in oral bioavailability

Dissolution rate dependant 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 solubilised and micro emulsified form 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. E.g. In case of halofantrine approximately 6-8 fold increase in bioavailability of drug was reported in comparison to tablet formulation.

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, nanoparticles, 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.

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 boon 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.

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

One unique 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 prodrug by cholinesterase can be protected if Polysorbate 20 is emulsifier in micro emulsion formulation. 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

Unlike the other lipid-based drug delivery systems the performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SMEDDS are not necessarily digested before the drug is absorbed as they present the drug in micro-emulsified form which can easily penetrate the mucin and water unstirred layer.

Increased drug loading capacity

SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient ($2<\log P>4$) are typically low in natural lipids and much greater in ampiphilic surfactants, co surfactants and co-solvents [9,10].

Advantages of SMEDDs Over Emulsion:

- 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.
- 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.
- 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 [11,12].

Biopharmaceutical Aspects:

The ability of lipids or food to enhance the bioavailability of poorly water-soluble drugs is well known. Although incompletely understood the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms including [13,14].

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

b) Increases 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 biliary 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 BS structures either directly (if sufficiently polar) or secondary to digestion leads to swelling of the micellar structures and a further increase in solubilization capacity.

c) 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 first-pass metabolism. A hydrophilic drug is less likely to be absorbed through the lymphatic (chylomicron) and instead may diffuse directly in to the portal supply. Hence in this case increased dissolution from the large surface area afforded by emulsion may be a contributing factor to enhanced absorption of drugs.

d) 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 thus reduce the extent of enterocyte based metabolism.

e) 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.
[15,16].

Biopharmaceutical drug classification system
Biopharmaceutical drug classification is a fundamental guideline classifying drugs based on the solubility and permeability as shown in Table 1.

Table 1: Biopharmaceutical drug classification

CLASS	SOLUBILITY	PERMEABILITY
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Mechanism of Self- Micro Emulsification
According to Reiss the energy required to increase the surface area of the dispersion for self-emulsification process bear less importance when compared to the entropy change that favours dispersion. Self- micron emulsifying process is related to the free energy. That is free energy of the conventional emulsion is a direct function of the energy essential to create a new surface between the oil and water phases and can be described by the equation:
DG= S N p r 2 s
Where, DG is the free energy related to the process, N is the number of droplets of radius r and s represents the interfacial energy. The emulsion is stabilized by emulsifying agents only after the two phases of emulsion is separated with respect to time to reduce the interfacial area. The emulsifying agent forms a monolayer of emulsion droplets and hence reduces the interfacial energy and providing a barrier to avoid coalescence. In the case of self-micron emulsifying systems the free energy required to form the emulsion is either very low or positive or negative. Emulsification requires very little input energy involves destabilization through contraction of local interfacial regions [17].

Excipients Selection
The oily/lipid component is generally a fatty acid ester or a medium/long chain saturated partially unsaturated or unsaturated hydrocarbon in liquid, semisolid or solid form at room temperature. Examples include mineral oil, vegetable oil, silicon oil, lanolin, refined animal oil, fatty acids, fatty alcohols, and mono-/di-/tri-glycerides. The most widely recommended surfactants are non-ionic surfactants with a relatively high hydrophilic–lipophilic balance (HLB) value. The surfactant concentration ranges between 30% and 60% (w/w) in order to form stable SMEDDS.

Excipients Used In SMEDDS
Pharmaceutical acceptability of excipients and the toxicity issues of the components used makes the selection of excipients really critical. There is a great restriction as which excipients to be used. Early studies revealed that the self-micro emulsification process is specific to the nature of the oil/surfactant pair the surfactant concentration and oil/surfactant ratio the concentration and nature of cosurfactant and surfactant/co-surfactant ratio and the temperature at which self-micro emulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient self- micro emulsifying systems [18,19].

OILS

The oil represents one of the most important excipients in the SMEDDS 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. 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. Furthermore edible oils which could represent the logical and preferred lipid excipient choice for the development of SMEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semisynthetic medium chain derivatives which can be defined as amphiphilic compounds with surfactant properties are progressively and effectively replacing the regular medium chain triglyceride oils in the SMEDDS. This is in accordance with findings of Deckelbaum showing that MCT is more soluble and have a higher mobility in the lipid/water interfaces than LCT associated with a more rapid hydrolysis of MCT. In general when using LCT a higher concentration of cremophor RH40 was required to form microemulsions compared with MCT [20].

Surfactants:

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). The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate. Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants. However these surfactants have a limited self-emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS. There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases increasing the surfactant concentration could lead to droplets with smaller mean droplet size this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface. On the other hand in some cases the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase. The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability increased tight junction permeability and decreased/ inhibited p-glycoprotein drug efflux. However the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. Formulation effect and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case. Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows

1. Anionic surfactants
2. Cationic surfactants
3. Ampholytic surfactants
4. Nonionic surfactants

1. 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.
2. Cationic surfactants: where the hydrophilic group carries a positive charge. Example: quaternary ammonium halide.
3. Ampholytic surfactants (also called zwitterionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.
4. Nonionic surfactants where the hydrophilic group carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (OCH2CH2O). Examples: Sorbitan esters (Span), polysorbates (Tween) [21,22].

Co-Solvents:

The production of an optimum SMEDDS 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. At this value the interface would expand to form fine dispersed droplets and subsequently adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. This process known as spontaneous emulsification forms the microemulsion. 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 SMEDDS but also to solubilization of the drug in the SMEDDS. Organic solvents suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG) etc) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self-emulsifying drug delivery systems although alcohol- free self-emulsifying micro emulsions have also been described in the literature. Indeed such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug. On the other hand the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Hence proper choice has to be made during selection of component [23, 24].

Formulation of SMEDDS

With a large variety of liquid or waxy excipients available ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants to water-soluble co-surfactant/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 emulsion

The following should be considered in the formulation of a SMEDDS

1. The solubility of the drug in different oil, surfactants and co surfactant/ 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.
3. The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and co-surfactant/co-solvents. 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.

Methods:

a. Dilution method

Ternary mixtures with varying compositions of surfactant, co-surfactant and oil were prepared. The percentage of surfactant, co-surfactant and oil decided on the basis of the requirements. Compositions are evaluated for micro emulsion formation by diluting appropriate amount of mixtures with appropriate double distilled water. Globule size of the resulting dispersions was determined by using spectroscopy. The area of micro emulsion formation in Ternary phase diagram was identified for the respective system in which micro emulsion with desire globule size were obtain.

b. Water Titration Method

The pseudo-ternary phase diagrams were also constructed by titration of homogenous liquid mixtures of oil, surfactant and co-surfactant with water at room temperature. Oil phase, Surfactant and the co-surfactant (surfactant: co-surfactant ratio) were prepared varied from 1:1 to 1:9 and weighed in the same screw-cap glass tubes and were vortexed. Each mixture was then slowly titrated with aliquots of distilled water and stirred at room temperature to attain equilibrium. The mixture was visually examined for transparency. After equilibrium was reached the mixtures were further titrated with aliquots of distilled water until they showed the turbidity. Clear and isotropic samples were deemed to be within the micro emulsion region. No attempts were made to completely identify the other regions of the phase diagrams. Based on the results, appropriate percentage of oil, surfactant and co-surfactant was selected correlated in the phase diagram and were used for preparation of SMEDDS[25].

Phase Diagrams:

The micro emulsion region is usually characterized by constructing ternary-phase diagrams. Three components are the basic requirement to form a micro emulsion: an oil phase, an aqueous phase and a surfactant. If a cosurfactant is used it may sometimes be represented at a fixed ratio to surfactant as a single component and treated as a single "pseudo-component". The relative amounts of these three components can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system. The three components composing the system are each found at an apex of the triangle where their corresponding volume fraction is 100 %. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally according to the Gibbs' phase rule) of one, two or three phases. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant temperature and pressure. The Gibbs phase diagram however is an empirical visual observation of the state of the system and may or may not express the true number of phases within a given composition. Apparently clear single phase formulations can still consist of multiple iso-tropic phases (e.g. the apparently clear heptane/AOT/water micro emulsions consists of multiple phases). Since these systems can be in equilibrium with other phases many systems, especially those with high volume fractions of both the two immiscible phases can be easily destabilised by anything that changes this equilibrium e.g. high or low temperature or addition of surface tension modifying agents. However examples of relatively stable micro emulsions can be found. It is believed that the mechanism for removing acid build up in car engine oils involves low water phase volume, water-in-oil (w/o) micro emulsions. Theoretically transport of the aqueous acid droplets through the engine oil to micro dispersed calcium carbonate particles in the oil should be most efficient when the droplets are small enough to transport a single hydrogen ion (the smaller the droplets the greater the number of droplets the faster the neutralisation). Such micro emulsions are probably very stable across a reasonably wide range of elevated temperatures [26-27].

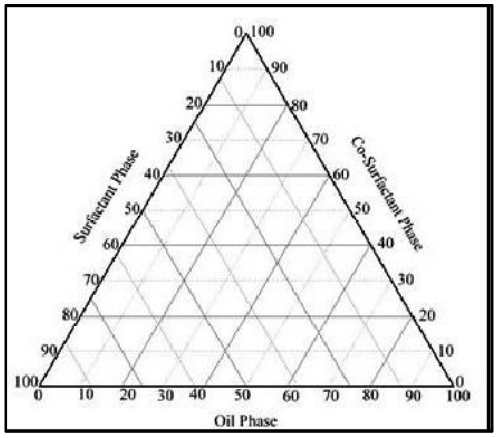

Fig 1.. ternary-phase diagrams

Characterization of SMEDDS

Fourier transform-infrared spectroscopy

Fourier transform-infrared for SMEDDS can be determined using FT-IR. Liquid/solid sample should be placed in the liquid sample holder and result can be recorded. Any type of chemical interaction should be determined using FT-IR.

Macroscopic evaluation

Macroscopic analysis is carried out in order to observe the homogeneity of micro emulsion formulations. Any change in color and transparency or phase separation occurred during normal storage condition (37±2 ºC) was observed in optimized micro emulsion formulation.

Determination of self-emulsification time

The emulsification time of SMEDDS is determined according to USP XXII dissolution apparatus. Each formulation is added drop wise to purified water at 37 ºC. Gentle agitation can be provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time is assessed visually.

Transmittance test

Stability of optimized micro emulsion formulation with respect to dilution is checked by measuring Transmittance through U.V. Spectrophotometer. Transmittances of samples are measured at 650 nm and for each sample three replicate assays are performed.

Droplet size determination

It is a precise method for evaluation of stability. Size of droplet is measured by Dalsa nano sizer. All measurements are carried out at scattering angle of 90 °C and 25 °C temperatures. Prior to measurement, micro emulsion is diluted in two steps with pure water then it is filtered through a 0.22 μm filter just before it is added to cuvette. In first step it is diluted with equal amount of water. In second step the mixture is further diluted to appropriate concentration for the measurement. That depends on droplet size (Usually diluted 100-200 times.) [28].

Zeta potential measurement

Zeta potential for micro emulsion is determined using Zetasizer. Samples are placed in clear disposable zeta cells and results are recorded. Before putting the fresh sample, cuvettes are washed with the methanol and rinsed using the sample to be measured before each experiment.

Stability:

a. Temperature

Shelf life as a function of time and storage temperature is evaluated by visual inspection of the SMEDDS system at different time period. SMEDDS are diluted with purified distilled water and to check the temperature stability of samples they are kept at three different temperature range 2-8 °C (refrigerator) room temperature and observed for any evidences of phase separation, flocculation or precipitation.

b. Centrifugation

In order to estimate metastable systems, the optimized SMEDDS formulations are diluted with purified distilled water. Then micro emulsion is centrifuged at 1000 rpm for 15 minute at 25 °C and is observed for any change in homogeneity of micro emulsions [29].

Cloud point measurement

Dilute the formulation with 50 ml of water in beaker and placed on a water bath with gradually increasing the temperature until the diluted formulation turned to cloudy. It gives the information about the stability of the micro emulsion at body temperature.

Refractive index

The refractive index of drug loaded SMEDDS and oil was determined by using Abbes refractometer.

Viscosity determination

The rheological properties of the micro emulsion are evaluated by Brookfield viscometer.

***In vitro* release**

The quantitative *in vitro* release test is performed with suitable dissolution medium, which is based on USP 24 method. SMEDDS are placed in gelatin capsule during the release period to compare the release profile with conventional dosage form. Sample solutions are withdrawn at predetermined time intervals, dilute suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium is replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals is calculated using the Beer Lambert's equation [30].

Conclusion:

Self-Micro Emulsifying Drug Delivery Systems appear to be unique and industrially feasible approach to over come the problem of low oral bioavailability associated with the lipophillic drugs. As there is increase in oral dru g absorption of BCS II class drugs, so we can say it is one of the method for enhancing oral bioavailability of drug

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