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A Review: Self Emulsifying Drug Delivery System (SEDDS)

[1]P.A.Panmand, S.S. Kad[2] ,V. D.Janjire [3] ,S. B. Barmukh

[1]DesignAssistant Professor, [2] Students, Student, Student

[1] Department of Pharmaceutics,

[1]Krishnarao Bhegade Institute of Pharmaceutical Education and Research, Talegaon Dabhade, India

Abstract: Solubility of orally administered drug is major challenge of pharmaceutical industry as nearly 35-40% of newly launched drugs posses low aqueous solubility which leads to their poor dissolution and low bioavailability, resulting in high intra & inter subject variability & lack of dose proportionality. This can be increased by different methods like salt formation, solid dispersion and complex formation. Self-Emulsifying Drug Delivery System (SEDDS) is gaining popularity for improving the solubility of lipophilic drugs. SEDDS are defined as isotropic mixtures of 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.Present review provides an updated account of advancements and disadvantages in SEDDS with regard to its composition, evaluation, different dosage forms method of preparation and various applications.

Index Terms - Solubility, Bioavailability, Self emulsified drug delivery system

I. INTRODUCTION

The drugs are most often administered by oral route, but approximately 40% of new drug candidates have poor-water solubility and the oral delivery of such drugs is difficult because of their low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality. To overcome these problems, various strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles and solid dispersions SEDDS or self emulsifying oil formulations (SEOF) 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[1]

Self-emulsifying formulations are isotropic mixtures of drug, lipids (natural or synthetic oils), and emulsifiers (solid or liquid), usually with one or more hydrophilic co-solvents/co-emulsifiers. SEDDS is a broad term encompassing emulsions with a droplet size ranging from a few nano meters to several microns. Depending upon the size of globules, these emulsions are characterized as concentrated microemulsions, nanoemulsions, or pre-concentrates. Self-micro emulsified drug delivery systems (SMEDDS) are formulations forming transparent microemulsions with an oil droplet size ranging between 100 and 250 nm. Self-nano emulsified drug delivery system (SNEDDS) is relatively a recent term indicating formulations with a globule size less than 100 nm. Although several reviews have been written previously on the subject, the diversity of SEDDS and the number of drugs encapsulated in these carriers have since been augmented significantly, and this calls for an updated review [2]

Determining suitable drug compound for SEDDS

The main challenge in any oral formulation design program is to maintain the drug solubility within the gastrointestinal tract and specially maximizing drug solubility within the primary absorptive site of the gut. SEDDS can improve the rate and extent of absorption of lipophilic drug compounds that exhibit dissolution-rate limited absorption and it also results in reproducible blood time profiles. The SEDDS can be used for all four categories of biopharmaceutical classification system (BCS) class drugs but the BCS II and IV categories of drugs are more needful as well suitable for the SEDDS formulations [3]

Table No. 1: Application to SEDDS in relation to bcs classification

BCS Class	Aqueous solubility	Membrane Permeability	Hurdles overcome by SEDDS
I	High	High	Enzymatic degradation ,Gut wall efflux
II	Low	High	Solubilisation, Bioavailability
III	High	Low	Enzymatic degradation ,Gut wall efflux, Bioavailability
IV	Low	Low	Solubilisation, Enzymatic degradation ,Gut wall efflux, Bioavailability

Advantages of SEEDS:

- **Improvement in oral bioavailability:** the ability of lipid basedformulations to present the drug to GIT in solubilised and micro emulsified form (globule size between 1-100 nm) and subsequent increase in specific surface area ,enables more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane ,leading to improved bioavailability (BA). Their contribution in improvement of the oral bioavailability of several poorly water soluble drugs.
- **Ease of manufactured and scale-up** : Ease of manufacture and scale-up is one of the most important advantages that makes lipid based formulation unique when compared to other bioavailability enhancement techniques like solid dispersions ,require very simple and economical manufacturing facilities for large-scale manufacturing .
- **Reduction in inter-subject and intra-subject variability and food effects**: There are severaldrugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug in the body.
- **Prevention of enzymatic hydrolysis in GIT**: One unique property that makes lipid based formulation 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.
- **Increased drug loading capacity:**lipid based formulations especially SMEDDS also provide the advantages 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 lipid and much greater in amphiphilic surfactant, co-surfactants and co-solvents.[4]

Disadvantages of SEDDS

- 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 need 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. [5]

Composition of SEDDSs

The self-emulsifying process depends on:

• The nature of the oil–surfactant pair

• The surfactant concentration

• The temperature at which self-emulsification occurs.

Oils: Oils can solubilize the lipophilic drug in a specific amount.It is the most important excipient because 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. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. [6]

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 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 cosurfactant/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 concentrationcould 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 surfactantmolecules 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 epithelialpermeability, increased tight junction permeability and decreased/inhibited pglycoprotein 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 eachcase.Surfactant molecules may be classified based on the nature of the hydrophilic group within themolecule.

The four main groups of surfactants are defined as follows,

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

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.

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

Ampholytic surfactants: (also called zwitter ionic surfactants) contain both a negative and a positive charge. Example: sulfobetaines.

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 (Spans), polysorbates(Tweens).[7]

Co-solvents:

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. These solvents sometimes play the role of the co-surfactant in the micro emulsion systems.

Indeed, such systems may exhibit some advantages over the previous formulationswhenincorporated in capsule dosage forms, since alcohol and other volatile cosolvents comprisedin the conventional self-emulsifying formulationsare known to migrate into the shells of soft gelatin, or hard, sealedgelatin capsules, resulting in the precipitation of the lipophilic drug. On theother hand, the lipophilic drug dissolution ability of the alcohol free formulationmay is limited. Drug release from the formulation increases with increasing amount of cosurfactant. [8]

Formulation of SEDDS

Formulation of SEDDS includes 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 [9]

Type I: These formulations are the simplest lipid products in which the drug is dissolved in digestible oil, usually a vegetable oil or medium chain triglyceride. These are generally regarded as safe (GRAS) by regulatory agencies as these are safe food substances and do not present atoxicological risk to formulators. The low solvent capacity of triglycerides often prevents formulation in oil, but oil solutions may be a realistic option for potent drugs or compounds with log P (octanol /water partition coefficient) >4. Solvent capacity for less hydrophobic drugs can be enhanced by blending triglycerides with other oily excipients such as mixed mono and di-glycerides (Myers and Stella, 1992). When an appropriate dose of the drug can be dissolved, Type I formulation may well be the system of choice, in view of its simplicity and biocompatibility. Generally, these systems exhibit poor initial aqueous dispersion and Figure 1: Potential mechanism for absorption enhancement M. Nirosha, Int. J. Rev. Life. Sci., 1(4), 2011, 206-214 208 ©JK Welfare &Pharmascope Foundation | International Journal of Review in Life Sciences thus require digestion by pancreatic lipase/co-lipase in the GIT to generate more amphiphilic lipid digestion products and to promote drug transfer into the colloidal aqueous phase. However, for readily digestible formulations this process is efficient and facilitates formulation dispersion and drug solubilization may be catalyzed by lipid digestion. [10]

Type II: These type of formulations (typically referred to as selfemulsifying drug delivery systems, SEDDS) are isotropic mixtures of lipids and lipophilic surfactants (HLB50–60% w/w depending on the materials) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface (Pouton, 1985).PWSD can be dissolved in SEDDS and can be encapsulated in hard or soft gelatin capsules to produce convenient single unit dosage forms. Type II formulations has the advantage of overcoming the slow dissolution step typically observed with solid dosage forms. SEDDS generate large interfacial areas which allow efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs (Constantinides, 1995; Gershanik and Benita, 2000). Rapid release of the drug and increased drug solubilization in the gastrointestinal lumen were responsible for the improved drug bioavailability.[11]

Type III : These type of formulations are commonly referred to as self-microemulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>12) and cosolvents such as ethanol, propylene glycol and polyethylene glycol. These formulations can be further segregated into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content decreases. Type IIIB formulations typically achieve greater dispersion rates when compared with Type IIIA although the risk of drug precipitation on dispersion of the formulation is higher. Thus SEDDS formulation typically provide opaque dispersions with particle sizes >200 nm whereas SMEDDS formulations disperse to give smaller droplets with particle sizes <200 nm to provide optically clear or slightly opalescent dispersions. SEDDS and SMEDD formulations have contributed to the improvement of the oral bioavailability of several PWSD. Some of these examples of a successfully marketed SMEDDS formulation are the Neoral® cyclosporine formulation. In contrast to the earlier Sandimmun® cyclosporin.[12]

Type IV: These types of formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug payloads (due to higher drug solubility in the surfactants and co-solvents) when compared to formulations containing simple glyceride lipids. It can also produce very fine dispersions when introduced in to an aqueous media which in turn leads to rapid drug release and increased drug absorption. An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase) which contains tocopherol polyethylene glycosuccinate (TPGS) as surfactant and polyethylene glycol (PEG) 400 and propylene glycol as co-solvents.[13]

Types of SEDDS in drug delivery system [14, 15, 16]

1. Oral delivery

A.self emulsifying controlled/sustained release pallets

The most widely used techniques for pellet production in the pharmaceutical industry are extrusion/spheronization (ES), solution/suspension layering, and powder layering.

Flexibility in designing and developing the dosage form, and improving the safety and efficacy of bioactive agents are among these advantages. Due to the factthat pellets disperse freely in the gastro-intestinal tract,drug absorption is maximized with a subsequent reductionin peak plasma fluctuations and hence minimizing potentialside effects without lowering drug bioavailability. Pelletsalso reduce variations in gastric emptying rates and overalltransit time and therefore a reduction of intra- and intersubjectvariability of plasma profilesis achieved.

B. Solid self-emulsifying drug delivery systems

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties. S-SMEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/ nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticles technology, and so on). Such powders/nanoparticles, which refer to SE nanoparticles/dry emulsions/solid dispersions are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipient. To some extent, S-SMEDDS are combinations of SMEDDS and solid dosage forms, so many properties of S-SMEDDS (e.g. excipients selection, specificity, and characterization) are the sum of the corresponding properties of both SMEDDS and solid dosage forms. For instance, the characterizations of SE pellets contain not only the assessment of self-emulsification, but also friability, surface roughness, and so on. In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres/nanoparticles and SE suppositories/implants.

C. Self emulsifying capsule

After administration of capsules containing conventionalliquids SEformulations,microemulsion droplets form anddisperse in the GIT to reach site of absorption.Ifirreversible phase separation of microemulsion occur anImprovement of drug absorption cant be expected. Thisproblem can beovercome by sodium dodecyl sulfate maybe added into the SE formulation. The super saturatableSEDDS canbe designed using small quantity of HPMC toprevent precipitation of drug by generating andmaintaining asupersaturatable state *in vivo*. Liquid SEingredients can be filled into capsules in solid or semi solidstateobtains by adding solid carriers (absorbentspolymers). As an example, a solid PEG matrix can bechosen.

D.**Solid carriers** These solid carriers have property to absorbliquid/ semisolid formulation as self emulsifying system (SES).It is a simple procedure, where SES is incorporated into a free flowing powder material which has adsorption quality. The mixture is uniformly adsorbed by mixing in a blender. Thissolid mixture is filled into capsule or added to more excipient before compression into tablets. The above mixture wassolidified to powderforms using three kinds of adsorbents: microporous calcium silicate, magnesium aluminium silicate and silicon dioxide.

E. Self-Emulsifying Beads.

Self-emulsifying system can be formulated as a solid dosage form by using minimum amounts of solidifying excipients. Patil and Paradkar Investigated loading SES into the micro channels of porous polystyrene beads (PPB)using the solvent evaporation method. PPB has complex internal void structures typically produced by copolymerizing styrene and di vinyl benzene. It is inert and stable over a wide range of pH, temperature and humidity. PPB was found to be potential carriers for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form.Bead size and pore architecture of PPB werefoundtoaffecttheloadingefficiencyandinvitrodrug releasefromSES-loadedPPB .Inanotherstudy,floating alginate beads containing SEDDS of tetrahydrocurcumin were developed to increase drug solubility and prolong gastricresidencetime.Useofdifferentproportionsofsodium alginate, calciumchloride, andwater solublepore former (polyvinyl alcoholpolyethyleneglycol copolymer) inbead formulationswas found to have different effects on the floatingabilitiesandinvitrodrugreleaserate.

2. Topical Delivery: Topical administration of drugs can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first pass metabolism of the drugs and related toxicity effects.

3. Oculars and Pulmonary delivery: For the treatment of eye disease, drugs are essentially delivered topically o/w microemulsion have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

4. Parenteral delivery: Parenteral administration of drugs with limited solubility is a major problem in industrybecause of the extremely low amount of drug actually delivered as target site.

Method of preparation of SEDDS [17, 18]

1. High pressure homogenizer

Nano-formulation is prepared under high pressure. The formation of fine emulsiondepends upon the high shear stress applied. The droplet size can be explained bytwo theories i.e., cavitation and turbulence. This method can produce nanoemulsionof droplet size smaller than 100 nm. The droplet size of nanoemulsions produced byhigh pressure homogenizers depend on sample composition, homogenizer type, andhomogenizer operating conditions such as energy intensity, time, and temperature.High-pressure homogenization is widely used to form food, pharmaceutical andbiotechnological ingredient nanoemulsions

2. Sonication method

The sonication method is the very useful method for the preparation of the SNEDDS.Ultrasonication is better than other high energy methods in terms of operation andcleaning. In ultrasonic emulsifications, ultrasonic waves provide cavitation forces thatbreak the macroemulsion to nanoemulsion

3. High energy approach

The high energy approach requires high mechanical energy by which mixture of components like oil, surfactants and co- solvent are mixed to form nanoemulsion. High energy methods are extensively used to formulate nanoemulsion. High mechanical energy is used that provide strong disruptive forces, which break up large droplets to nano-sized droplets and produce nanoemulsions with high kinetic energy However, SNEDDS are based on the self-emulsification phenomenon and require low energy

4**. Micro-fluidization**

The micro-fluidization method requires a device called Micro-Fluidizer. The positive displacement pump pushes the product to the interaction chamber. This system contains a small droplet channel known as micro channel. The obtained product was sent through the micro channels to the impingements area, which produces very fine droplets of nanoemulsion. The mixture of oil phase and aqueous phase gets into the homogenizer, which yield course emulsion. It is further processed and forms homogeneous, stable, transparent nanoemulsion[

Consequently, drugs loaded into SEDDS preconcentrates avoid the dissolution step that frequently limits their absorption. However, the widespread application of liquid SEDDS is challenged by low stability during handling or storage and irreversible drug and/or excipient precipitation . Thus, the majority of marketed liquid SEDDS are filled into soft gelatin (e.g., SandimunneNeoral®, Norvir®, Fortovase®, and Convulex®) or hard gelatin capsules (e.g., Gengraf® and Lipirex®) to be administered as a unitdosage form Thus, to address these limitations solid self-emulsifying drug delivery systems (s-SEDDS) were developed by converting the conventional liquid SEDDS into powders which are subsequently filled into capsules or formulated as solid dosage forms such as self-emulsifying tablets, granules, pellets, beads, microspheres, nanoparticles, suppositories and implants . Various solidification techniques for converting liquid SEDDS into s-SEDDS are discussed below.[16]

Spray drying

In this technique, formulation is prepard by mixing lipids, drug, surfactants, solid carriers, and solubilization of the mixture before spray drying. The liquid formulation is then atomized into a spray of droplets. These droplets are introduced into a drying chamber, the volatile phase (e.g. the water contained in an emulsion) evaporates, resulting in the formation of dry particles under controlled temperature and airflow conditions. The particles thus obtained can be prepared into tablets or capsules. The selection of atomizer, temperature, airflow and drying chamber design is based on the characterization of the product and powder specification

Evaluation / charactrization of SEDDS: **[19, 20, 21]**

A number of tests are carried out for characterization and evaluation of SEDDS.

1. Drug Content: Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is analyzed by suitable analytical method

2. Dispersibility Test: The dispersibility test of SEDDS is carried out to assess its capability to disperse into emulsion and categorize the size of resulting globules. It is carried by using a standard USP dissolution apparatus 2 (Paddle Type). One ml of each formulation is added to 500 ml of water at 37 + 0.5ºC and the paddle is rotated at 50 rpm. On titration with water the SEDDS formulation forms a mixture or gel which is of different type depending upon which the in vitro performance of formulation can be assessed using the following grading system15

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. The stability of the formulation decreases from micro emulsion to emulgel given in table

Table No.2: Types of formulation depending on visual observation

Types of formulation	Mixture /gel
Micro emulsion	Transperant mixture
Micro emulsion gel	Transparent gel
Emulsion	Milky or cloudy mixture
emulgel	Milky gel

3. Thermodynamic stability studies: The physical stability of a lipid –basedformulation 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.

• **Heating cooling cycle:** Six cycles between refrigerator temperature (4°C) and 45°C with storage at eachtemperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

• **Centrifugation:** Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 48 h 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.

• **Freeze thaw cycle:** Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking .[19]

4. Turbidimetric test: Turbidity is a measurable characteristic that may be used toestimate droplet size and self-emulsification time. After agiven amount of SEDDS is administered to a fixed amount ofsuitable medium under continual stirring at 50 rpm on amagnetic stirrer at optimal temperature, the turbidity ismeasured using a turbidity meter. As the time required forcomplete emulsification is too short, the rate of turbidityshift, or rate of emulsification, cannot be measured.Turbidimetric analysis is used to track the growth of dropletsfollowing emulsification.

5. Determination of self-emulsification time: Usinga primitive nephelometer and a rotating paddle toassist emulsification, we investigated the efficiency ofemulsification of several formulations of Tween 85/medium-chaintriglyceride systems. This allowed the emulsificationperiod to be measured. Samples were obtained for particlesize using photon similarity spectroscopy after emulsification and self-emulsified and homogenized systems were com-pared. The self-emulsification process was studied using lightmicroscopy. The process of emulsification was preciselydefined as the erosion of a thin cloud of microscopic par-ticles off the surface of big droplets, rather than asteadydecrease in droplet scale.

6. 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 is w/o type of the system.

7. **Electro conductivity Study**

The SEDD system contains ionoc or non-ionic surfactant, oil, and water.so, this test is used to measure the electoconductive nature of system. The electro conductivity of resultant system is measured by electoconductometer.

8. In Vitro Diffusion Study

An in vitro diffusion study is performed to study the release behavior of formulation from liquid crystalline phase around the droplet using dialysis technique.

APPLICATIONS OF SEDDS [22,23]

Improvement in solubility: If a drug is incorporated in SEDDS, it increases the solubility because it circumvents the dissolution step in case of BCS Class-2 drug. A SMEDDS formulation of candesartan cilexetil was prepared for directly filling in hard gelatin capsules for oral administration. The results of the

study show the utility of SMEDDS to enhance solubility and dissolution of sparingly soluble compounds like candesartan.

Enhanced bioavailability: Ketoprofen, a moderately hydrophobic 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. Ketoprofen is presented in SEDDS formulation. This formulation has enhanced bioavilability due to increase in the solubility of drug which minimizes the gastric irritation. 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 (41-44). In another study aceclofenac loaded SNEDDS formulation was developed by Akkuş-Arslan et al45. The anti-inflammatory effect of aceclofenac loaded SNEDDS was investigated with carrageenan induced rat paw edema. As result of the study, it was seen that the anti-inflammatory effect increased with the use of SNEDDS, when compared with the solution and suspension forms of aceclofenac.

Protection against biodegradation: The ability of SEDDS 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, because of acidic pH in stomach, enzymatic degradation or hydrolytic degradation etc. Such drugs when presented in the form of SEDDS can be well protected against these degradation processes as liquid crystalline phase in SEDDS might act as barrier between degradating environment and the drug

Table No.3: Marketed formulation of SEDDS

Active moiety	Trade name	Dosage forms
Tretinoin	Vesanoid (Roche)	Soft gelatin capsule,10mg
Isotretinoin	Accutane (Roche)	Soft gelatin capsule,10,20 and 40 mg
Cyclosporine	Panimumbioral (panacea biotec)	Capsule,50 and 100 mg
Cyclosporin A	Gengraf (Abbott)	Hard gelatin capsule, 25 and 100 mg
Cyclosporin A	Sandimmune (Novartis)	Soft gelatin capsule, 25,50 and 100 mg
Lopinavir and ritonavir	Kaletra (abbott)	Soft gelatin capsule, lopinavir 133.33 mg and ritonavir 33.3 mg
Sanquinavir	Fortovase (Roche)	Soft gelatin capsule,200 mg
Tipranavir	Aptivus (Boehringer ingelheim	Soft gelatin capsule,250 mg
Amprenavir	Agenerase (GSK)	Soft gelatin capsule

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