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Bioavailability Enhancement of Poorly Soluble Drugs by Self Micro Emulsifying Drug Delivery System (SMEDDS): A Review

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ABSTRACT:

Oral route has always been the favorite route of drug administration in many diseases and till today it is the first way investigated in the development of new dosage forms. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility, thereby pretense problems in their formulation. More than 40% of potential drug products suffer from poor water solubility. For the therapeutic delivery of lipophilic active moieties (BCS class II and IV drugs), lipid based formulations are inviting increasing attention. Currently a number of technologies are available to deal with the poor solubility, dissolution rate and bioavailability of insoluble drugs such as micronization, solid dispersions or cyclodextrin complex formation and different technologies of drug delivery systems. One of the promising techniques is Self-Micro Emulsifying Drug Delivery Systems (SMEDDS). Self emulsifying drug delivery system has gained more attention due to enhanced oral bioavailability, enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug toward specific absorption window in GIT, and protection of drug from the unreceptive environment in gut. This article gives a complete overview of SMEDDS as a promising approach to effectively deal with the problem of poorly soluble molecules.

KEY WORDS: SMEDDS, surfactant, oil, co-surfactant, bioavailability

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INTRODUCTION:

Oral route has been the major route of drug delivery for the chronic treatment of many diseases. However, oral delivery of 50% of the drug compounds is hampered because of the poor aqueous solubility of the drug itself. Moreover, major of new chemical entities having poor aqueous solubility and due to that the oral delivery of such drugs show low bioavailability, high intra and inter subject variability, and lack of dose proportionality. After Oral delivery of poorly soluble drug over one-half of the drug compounds are diminished in the gastrointestinal (GI) tract. BCS class-II drugs are major challenge to pharmaceutical industries and to modern drug delivery system, because of their poor water solubility and there by poor dissolution which leads to low bioavailability^{1,2}.

The oral delivery of lipophilic drugs presents a major challenge because of the low aqueous solubility. Lipid-based formulations have been shown to enhance the bioavailability of drugs administered orally^{1,2,3,4}. Wide availability of lipidic excipients with specific characteristics offers flexibility of application with respect to improving the bioavailability of poorly water-soluble drugs and manipulating their release profiles⁵. 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

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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 fluids⁶.

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^{7,8,9}. After self dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. The large surface area enhances the dissolution. The emulsion globules are further solubilized in the gastrointestinal tract by bile fluids. The presence of surfactant causes enhanced absorption due to membrane induced permeation changes. The droplets formed are either positively charged or negatively charged. As the mucosal lining is negatively charged it was observed that positively charged particles penetrated deeper into the ileum¹⁰. A cationic emulsion has greater bioavailability than an anionic emulsion^{11,12}. Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of

HLB <12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed with surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion. The emulsified form itself is readily absorbable which ensures a rapid transport of poorly soluble drugs into the blood.

NEED FOR SMEDDS

BCS class II or class IV compounds, when given orally to the gastrointestinal tract are typically dissolution rate-limited i.e. the absorption rate from the gastrointestinal (GI) lumen is controlled by dissolution.¹³

There is currently no single or simple solution to the challenge. Different formulation approaches can be used for this like,¹³

Modification of the physicochemical properties, such as

- Salt formation,
- Particle size reduction (micronization) of the compound,
- Solid dispersion,
- Complexation with cyclodextrins,

Use of Permeation enhancers.

Indeed, in some selected cases, these approaches have been successful. However, these methods have their own limitations.¹³

For instance,^{13,14}

- Salt formation of neutral compounds is not feasible and the synthesis of weak acid and weak base salts may not always be practical. Moreover, the salts that are formed may convert back to their original acid or base forms and lead to aggregation in the gastrointestinal tract.
- Particle size reduction may not be desirable in situations where handling difficulties and poor wettability are experienced for very fine powders.
- Problem with micronization is chemical / thermal stability, many drug may degrade and lose bioactivity when they are micronized by conventional method.
- Complexation with cyclodextrins techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents.

Lipid based formulations can sometimes resolve these challenges of BCS class II and IV.¹⁵

- Lipid excipients with surfactive properties can increase the solubility of the API.
- Lipid excipients that improve the transport of API across or through gastrointestinal enterocytes can enhance permeability.
- Long-chain fatty acid lipid excipients can target lymphatic transport.

ADVANTAGES OF SMEDDS

Improvement in oral bioavailability:

The ability of SMEDDS 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 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 formulation¹⁶.

Ease of manufacture and scale-up:

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 SMEDDS¹⁶.

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 available¹⁷.

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

SMEDDS are superior as compared to the other drug delivery systems due to 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 formulation¹⁸. These systems are formed spontaneously without aid of energy or heating thus suitable for thermolabile 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.

Increased drug loading capacity:

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 amphiphilic surfactants, co surfactants and co-solvents.

In SMEDDS, 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 C max is observed with many drugs when presented in SMEDDS.

Fine oil droplets empty rapidly from the stomach and promote wide distribution of drug throughout the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall¹⁸.

Selective targeting of drug(s) toward specific absorption window in GIT²¹.

Protection of drug(s) from the hostile environment in gut¹⁸.

Protective of sensitive drug substances.

Liquid or solid dosage forms

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. It can be easily stored since it belongs to a thermodynamically stable system.
- Micro emulsions formed by the SMEDDS exhibit good thermodynamic stability and optical transparency. Droplets of micro emulsion formed by the SMEDDS generally range between 2 and 100 nm. 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 can be filled in hard gelatin capsules or soft gelatin capsules or can be formulated into tablets whereas emulsions can only be given as oral solutions.
- Emulsion cannot be autoclaved as they have phase inversion temperature, while SMEDDS can be autoclaved¹⁹.

APPLICATIONS OF SMEDDS

SUPERSATURABLE SMEDDS (S-SMEDDS): S-SMEDDS formulations have been designed and developed to reduce the surfactant side effects and achieve rapid absorption of poorly soluble drugs²⁰.

SOLID SMEDDS: SMEDDS are normally prepared as liquid dosage forms that can be administered in soft gelatin capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SMEDDS has been prepared by the process of extrusion spherulization to provide a good in vitro drug release (100% within 30 min, T50% at 13 min). The same dose of progesterone (16 mg) in pellets and in the SEDDS liquid formulation resulted in similar AUC, C max and T max values²¹.

Applications of SMEEDS are enlisted in Table 1.

Table: 1 Applications of SMEDDS reported in literature²²

Type Of Delivery System	DRUG	OIL	Surfactant	Co-solvent / Cosurfactant	Significance
SMEDDS	Atorvastatin	Labrafil, Estol and Isopropyl myristate	Cremophore EL, Cremophor RH 40	Propylene glycol, PEG 400 and Transcutol	Improves solubility bioavailability and permeability via the mucous membrane. Oral bioavailability increased nearly 1.5 times.
SMEDDS	Simvastatin	Caproyl 90	Cremophore EL	Carbitol	Release rate was higher than conventional tablets. The oral bioavailability of SMEDDS is about 1.5-fold higher than conventional tablets.
SMEDDS	Seocalcitol	Viscoleo (MCT), Sesame oil (LCT)	Cremophore RH40	Akoline	No improvement in bioavailability. After three months of storage at accelerated conditions (40°C/75% RH), a decrease in concentration of 10-11% was found. Simple lipid solutions are better choice compared with the developed SMEDDS due to a slightly higher bioavailability and better chemical stability.
SEDDS	Ontazolast	mixture of mono-and diglycerides of oleic acid	Solid, Polyglycolized mono-di and triglycerides, Tween 80	-	Enhanced bioavailability by 7.5 drug content.
SMEDDS	Silymyrin	Ethyl linoleate	Tween 80	Ethyl alcohol	Release was limited, incomplete and typical of sustained characteristics. Relative bioavailability dramatically enhanced in an average of 1.88 and 48.82 fold that of silymarin PEG 400 solution and suspension respectively.

FORMULATION COMPONENTS OF SMEDDS

- **Drug**
- **Oils/Lipids**
- **Surfactants / Emulsifiers**
- **Co-solvents**

Oils/Lipids:

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 triglyceride²⁹. 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 (1990) 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. Almond oil, Canola oil, Coconut oil, Corn oil, Cottonseed oil, Olive oil, Peanut oil, Safflower oil, Sesame oil, Shark liver oil, Soyabean oil, Wheat germ oil etc are the commercially available triglycerides²³.

Surfactants/Emulsifiers:

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:

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 zwitterionic 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)²³.

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 efflux²³.

Co-solvents:

Organic solvents and additional compounds suitable for oral administration are used in SMEDDS to enhance the solubility of therapeutic agent or triglyceride in the composition²⁴. Examples;

☒ **Alcohols and Polyols:** Such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcitol, dimethyl isosorbide, propylene glycol, polypropylene glycol, hydroxypropyl methyl cellulose and other cellulosic polymers, cyclodextrins and its derivatives.

☒ **Esters of propylene glycols** having average molecular weight of about 200 to 6000 such as tetrahydrofuryl alcohol, PEG ether (glycofural) or methoxy PEG

MECHANISM OF SELF-EMULSIFICATION

Conventional emulsions are formed by mixing two immiscible liquids, water and oil stabilized by an emulsifying agent. When an emulsion is formed surface area expansion is created between the two phases, which cause formation of excess surface free energy. The excess surface free energy is dependent on the droplet size and the interfacial tension.²⁵

The thermodynamic relationship for the net free energy change is described by following equation:

$$\Delta G = \sum N_i 4\pi r_i^2 \sigma$$

Where,

ΔG = Free Energy associated with the process r_i = Radius of the droplets N_i = Number of droplets σ = Interfacial energy

The two phases of the emulsion tend to separate with time to reduce the interfacial area and thus minimize the free energy of the system(s). The emulsion is stabilized by emulsifying agent that form a monolayer around the emulsion droplets, reduce the interfacial energy and form a barrier to coalescence.

In case of SMEDDS, the free energy of formation is very low and positive or even negative which results in thermodynamic spontaneous emulsification. It has been suggested that self-emulsification occurs due to penetration of water into the Liquid Crystalline (LC) phase that is formed at the oil/surfactant-water interface into which water can penetrate assisted by gentle agitation during self-emulsification. After water penetrates to a certain extent, there is disruption of the interface and a droplet formation. This LC phase is considered to be responsible for the high stability of the resulting micro-emulsion against coalescence.^{26,}

FORMULATION OF SMEDDS

The novel synthetic hydrophilic oils and surfactants usually dissolve hydrophobic drugs to a greater extent than conventional vegetable oils. The addition of solvents, such as ethanol, PG and PEG may also contribute to the improvement of drug solubility in the lipid vehicle²⁷. With a large variety of liquid or waxy excipients available ranging from oils through lipids, hydrophobic and hydrophilic surfactant to water soluble co solvent, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixture which disperse to give fine colloidal emulsions. The following should be considered in the formulation of a SMEDDS.

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

The selection of oil, surfactant and co solvent based on the solubility of the drug

Preparation of the phase diagram.

The preparation of SMEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co solvent²⁸.

TERNARY PHASE DIAGRAMS

Phase diagrams are useful tools to determine the number and types of phases, the wt% of each phase and the composition of each phase at a given temperature and composition of the system. These diagrams are three-dimensional but are illustrated in two-dimensions for ease of drawing and interpretation.

Each corner will typically represent a binary mixture of two components such as surfactant/co-surfactant, water/drug or oil/drug. The number of different phases present for a particular mixture can be visually assessed. Microstructural features can also be investigated with the aid of a wide variety of techniques. Figure shows a hypothetical pseudo-ternary phase diagram of an oil/surfactant/water system with emphasis on micro-emulsion and emulsion phases.

Within the phase diagram, existence fields are shown where conventional micelles, reverse micelles or water-in-oil (w/o) micro-emulsions and oil-in-water micro-emulsions are formed along with the bi-continuous micro-emulsions. At very high surfactant concentrations two phase systems are observed²⁹. It should be noted that not every combination of components produce micro-emulsions over the whole range of possible compositions, in some instances the extent of micro-emulsion formation may be very limited.

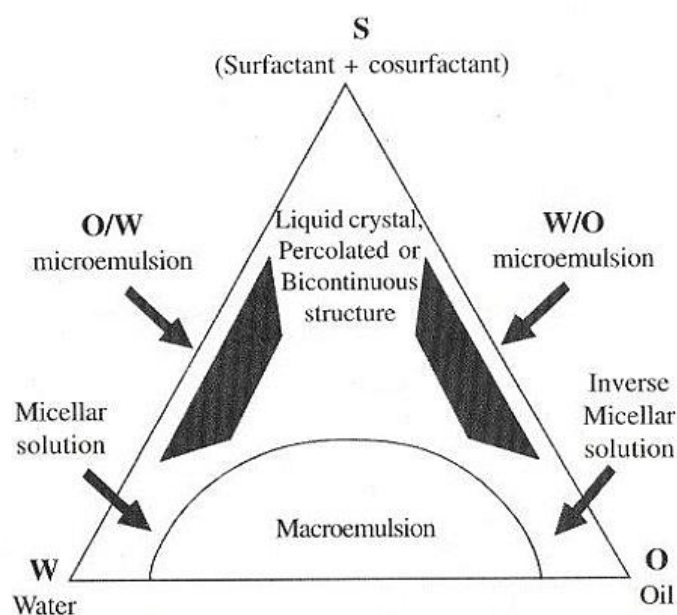


Figure: A hypothetical ternary phase diagram

CHARACTERIZATION OF SMEDDS

Particle size: The droplet size of the emulsion is a crucial factor because it determines the rate and extent of drug release as well as absorption. Photon correlation spectroscopy (PCS) is a useful method for determination of emulsion droplet size especially when the emulsion properties do not change upon infinite aqueous dilution, a necessary step in this method³⁰.

Polarity: Emulsion droplet polarity is also a very important factor in characterizing emulsification efficiency. The HLB, chain length, degree of unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration

of the emulsifier have an impact on the polarity of the oil droplets. Polarity represents the affinity of the drug compound for oil and/or water and the type of forces formed. Rapid release of the drug into the aqueous phase is promoted by polarity³⁰.

Zeta potential: The charge of the oil droplets in conventional SMEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1.0-3%, will yield cationic SMEDDS. Thus, such systems have a positive z-potential value of about 35-45 mV¹⁵. This positive z-potential value is preserved following the incorporation of the drug compounds³⁰.

Drug precipitation /stability on dilution: The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. If the surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant, hence it is very important to determine stability of the system after dilution. This is usually done by diluting a single dose of SMEDDS in 250ml of 0.1N HCl solution. This solution is observed for drug precipitation if any. Ideally SMEDDS should keep the drug solubilized for four to six hours assuming the gastric retention time of two hours³⁰.

EVALUATION OF SMEDDS

Thermodynamic stability studies: The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. Furthermore, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug³¹.

Heating Cooling Cycle: Six cycles between refrigerator temperature (4°C) and 45 °C with storage at each temperature 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.

Dispersibility test: The efficiency is assessed using a standard USP XXII dissolution apparatus 2. One mL of each formulation was added to 500 mL of water at 37 ± 0.5 °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The *in vitro* performance of the formulations is visually assessed using the following grading system³¹:

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 forms within 2 min.

Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

Turbidimetric Evaluation: Nepheloturbidimetric evaluation is done to monitor growth of emulsification. Fixed quantity of Selfemulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it isn't possible to monitor the rate of change of turbidity (rate of emulsification)³².

Viscosity Determination: The SMEDDS 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 viscometer³³.

Droplet Size Analysis Particle Size Measurements: The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads³³.

Refractive Index and Percent Transmittance: Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (Refractive index of water 1.333). The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water and formulation have percent transmittance > 99 %, then formulation has transparent nature.

Electro conductivity Study: The SEDD system contains ionic or non-ionic surfactant, oil, and water. So, this test is used to measure the electroconductive nature of system. The electro conductivity of resultant system is measured by electroconductometer.

In vitro Diffusion Study: *In vitro* diffusion studies are performed to study the release behavior of formulation from liquid crystalline phase around the droplet using dialysis technique³³.

Drug content: Drug from pre-weighed SMEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

Droplet polarity: Droplet polarity and droplet size are important emulsion characteristics. Polarity of oil droplets is governed by the HLB value of oil, chain length and degree of unsaturation of the fatty acids, the molecular weight of the hydrophilic portion and concentration of the emulsifier. A combination of small droplets and their appropriate polarity (lower partition coefficient o/w of the drug) permit acceptable rate of release of the drug. Polarity of the oil droplets is also estimated by the oil/water partition coefficient of the lipophilic drug.⁹

Sustained release: For this, dissolution study is carried out for SMEDDS. Drugs known to be insoluble at acidic pH can be made fully available when it is incorporated in SMEDDS³⁴.

CONCLUSION

Self-micro emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SMEDDSs, which have been shown to substantially improve oral bioavailability and thus the dose of the drug can be reduced. With future development of this technology, SMEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

MARKETED FORMULATIONS

Table 2: Examples of marketed SMEDDS formulations³⁵

DRUG NAME	COMPOUND	DOSAGE FORM	COMPANY	INDICATION
Neoral®	Cyclosporine A/I	Soft gelatin capsule	Novartis	Immune suppressant
Norvir	Ritonavir®	Soft gelatin capsule	Abbott Laboratories	HIV antiviral
Fortovase®	Saquinavir	Soft gelatin capsule	Hoffmann-La Roche inc.	HIV antiviral
Agenerase®	Amprenavir	Soft gelatin capsule	Glaxo Smithkline	HIV antiviral
Targretin®	Bexarotene	Soft gelatin capsule	Ligand	Antineoplastic
Rocaltrol®	Calcitriol	Soft gelatin capsule	Roche	Calcium Regulator
Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Lipirex®	Fenofibrate	Hard gelatin Capsule	Genus	Antihyperlipoprotein
Sandimmune®	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immuno Suppressant
Gengraf®	Cyclosporine A/III	Hard gelatin Capsule	Abbott Laboratories	Immuno Suppressant

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