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ENHANCEMENT OF POOR ORAL ABSORPTION DRUG *VIA* LIPID FORMULATION: SELF EMULSIFYING DRUG DELIVERY SYSTEM

Sanket B. Gavhane [1], Shubhrajit Mantry [*1], Sumit A. Joshi [1], Ganesh Y. Dama [2] and Sourav Mohanto [2]

Department of Pharmaceutics [1], SGMSPM's Sharadchandra Pawar College of Pharmacy, Dumbarwadi, Otur, Junnar, Pune - 412409, Maharashtra, India.
Himalayan Pharmacy Institute [2], Majhitar - 737136, East Sikkim, India.

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Correspondence to Author:
Dr. Shubhrajit Mantry

Associate Professor,
Department of Pharmaceutics,
SGMSPM's Sharadchandra Pawar College of Pharmacy, Dumbarwadi,
Otur, Junnar, Pune - 412409,
Maharashtra, India.

E-mail: manu28pharmacy@gmail.com

ABSTRACT: The oral route of drug administration is one of the simplest route of drug administration throughout the world because its patients convenience. The drug administered through orally should possess good aqueous solubility for better oral absorption and thus bioavailability will increase. But it was found that 30-40% of the drug shows low solubility thus bioavailability profile will be affected. Self-emulsifying drug delivery (SEDDS) system is a novel therapeutic drug delivery system of those new drugs whose aqueous solubility is very poor. Thus, by this delivery system the new drugs can be administered to the body *via* oral route and hence therapeutic effect will be desired appropriately. The most unique feature of this delivery system can form oil in water emulsion when diluted in an aqueous phase. Thus, this delivery system enhances the rate and extent of drug or absorption when given by oral route. The cost of this delivery system is affordable as it can consist natural oil and common excipients. Thus, large scale production is also possible for manufacturing unit. In this review we discussed the nature of oils or lipids, surfactant and what should be the criteria for drug selection and also has been discussed the preparation and characterization of self-emulsifying drug delivery systems and their application in modern pharmaceutical dosage form.

INTRODUCTION: Self-emulsifying drug delivery systems are also known as SEDDS. The need for increased folds in the bioavailability of oral lipophilic drugs which led to studies on self-emulsifying drug delivery system. Drugs that have low solubility in aqueous medium but high permeability have given rise to self-emulsifying drug delivery systems, or we can say as SEDDS are used to solve low bioavailability issues of poorly soluble & highly permeable compounds [1].

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Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions (o/w) when introduced into aqueous phase under gentle agitation [2]. The first marketed SEDDS is cyclosporine, and it was found to have higher bioavailability than conventional drug [3]. Hydrophobic drugs can be dissolved in these systems, enabling them to be administered as a unit dosage form for per-oral administration [2, 3]. Self-emulsifying drug delivery systems can be administered orally *via* soft or hard gelatin capsules. When they get diluted in aqueous medium, due to the gentle churning of gastrointestinal fluids they form relatively fine oil-in-water emulsions. This is the process of self-emulsification [3].

When SEDDS formulation is released in the lumen of the gastrointestinal tract, they come in contact with GI fluid and form a fine emulsion (micro/nano) so-called as in situ emulsification or self-emulsification which further leads to solubilisation of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect [1]. Recently, SEDDS has been formulated using medium-chain tri-glyceride oils and non-ionic surfactants, the latter being less toxic. Upon per oral administration, these systems form fine emulsions (or micro-emulsions) in gastrointestinal tract (GIT) with mild agitation provided by gastric mobility [4]. Emulsions are liquid dosage forms which consist of two immiscible phases; where one is a dispersed phase is dispersed into the other phase, dispersion medium, and stability is maintained with the help of an emulsifying agent. The process of self-emulsification can be better explained with the ouzo effect which occurs in anise-flavored liquors where an oil-in-water emulsion is formed when the anise comes in contact with water [3]. The better-absorbed drugs across the gastrointestinal tract (GIT) provide good oral bioavailability but have number of potentially limiting factors. These include appropriate stability and solubility in the GI fluid, reasonable intestinal permeability, and resistance to metabolism both within the enterocyte and the liver.

It has realized that the oral bioavailability of poorly water-soluble, lipophilic drugs may be enhanced when co-administered with a meal rich in fat this has led to increasing recent interest in the formulation of poorly soluble drugs in lipids as a means to enhance drug solubilisation in the GIT [5, 6].

Lipid-based formulations not only improve but normalize drug absorption, which is particularly beneficial for low therapeutic index drugs. These formulations can also enhance drug absorption by a number of ancillary mechanisms [7].

Example:

- **a.** Including inhibition of P-glycoprotein-mediated drug efflux and pre absorptive metabolism by gut membrane-bound cytochrome enzymes.
- **b.** Promotion of lymphatic transport, which delivers the drug directly to the systemic circulation while avoiding hepatic first-pass metabolism and
- **c.** By increasing GI membrane permeability.

2. Physiochemical Properties Affecting Oral Drug Absorption: [8-11]

Physicochemical properties of drug substances such as-

- **2.1.** Drug solubility & dissolution rate
- **2.2.** Particles size & effective surface area
- **2.3.** Polymorphism & amorphism
- **2.4.** Solvates & hydrates
- **2.5.** Salt form of drug
- **2.6.** Ionization state
- **2.7.** Drug pKa & lipophilicity & GI pH ---pH partition hypothesis

Chemical Factors: A variety of chemical options can be used to improve the stability and systemic availability of drugs.

For example, Esters can be prepared for both acids and bases to produce more stable derivatives, which hydrolyze to the active parent once absorbed. The stability and solubility of both acids and bases tend to increase when they are in the form of salts.

Typically, the administration of soluble salts of penicillin gives rise to higher circulating antibiotic levels than the free acid. When the salt of a weak acid dissolves in the stomach, it generates a diffusion layer of relatively high pH which, in turn, promotes further dissolution. The same argument could theoretically be used for basic drugs.

2.1. Drug Solubility and Dissolution Rate: The rate-determining steps in absorption of orally administered drugs are:

- Rate of dissolution.
- Rate of drug permeation through the biomembrane.

2.2. Particle Size and Effective Surface Area:

- Smaller the particle size (by micronization) greater is the effective surface area more intimate contact b/w solid surface and aq solvent higher is the dissolution rate increase in absorption efficiency.

- *E.g.* poorly aqueous soluble non-hydrophobic drugs like Griseofulvin, chloramphenicol whose dissolution is rate limited.
- Particle size reduction has been used to increase the absorption of a large number of poorly soluble drugs, such as bishydroxy-coumarin, digoxin, griseofulvin, nitro-furantoin, and tolbutamide.

2.3. Polymorphism and Amorphism:

- When sub exists in different crystalline forms, *i.e.* in polymorphic form then diff forms are many compounds form crystals with different molecular arrangements or polymorphs. These polymorphs may have different physical properties, such as dissolution rate and solubility.
- *E.g.*, the vitamin riboflavin exists in several polymorphic forms, and these have a 20-fold range in aqueous solubility

2.4. Solvates/Hydrates:

- During their preparation, drug crystals may incorporate one or more solvent molecules to form solvates.
- The most common solvate is water. If water molecules are already present in a crystal structure, the tendency of the crystal to attract additional water to initiate the dissolution process is reduced, and solvated (hydrated) crystals tend to dissolve more slowly than anhydrous forms.
- Significant differences have been reported in the dissolution rate of hydrated and anhydrous forms of ampicillin, caffeine, theophylline, glutethimide, and mercapto-purine.
- The clinical significance of these differences has not been examined but is likely to be slight.
- Solvates have greater solubility than their nonsolvates. *e.g.* Chloroform solvates of Griseofulvin, n-pentanol solvate of fludrocortisone.

2.5. Salt form of Drug:

- At given pH, the solubility of the drug, whether acidic/basic or its salt, is a constant.
- While considering the salt form of the drug, the pH of the diffusion layer is imp not the pH of the bulk of the solution.
- *E.g.* of salt of weak acid, which increases the pH of the diffusion layer, which promotes the solubility and dissolution of a weak acid and absorption is bound to be rapid.

2.6. Ionization State:

- Unionized state is imp for passive diffusion through membrane so imp for absorption.
- Ionized state of the drug is very important for solubility.

2.7. Drug pKa & Lipophilicity & GI pH: pH – partition theory states that for drug compounds of molecular weight more than 100, which are primarily transported across the biomembrane by passive diffusion, the process of absorption is governed by-

- pKa of drug
- The lipid solubility of the unionized drug.
- pH at the absorption site.

FIG. 1: CAPSULE CONTAINING LIQUID SELF-EMULSIFYING DRUG DELIVERY SYSTEM

3. Importance of SMEDDS: [12-15]

SMEDDS offer the following advantages such as-

i. Irritation caused by prolonged contact between the drug and the wall of the GIT can be surmounted by the formulation of SEDDS as the microscopic droplets formed

help in the wide distribution of the drug along the GIT and these are transported quickly from the stomach.

ii. Upon dispersion in water, these formulations produce fine droplets with the enormous interfacial area due to which the easy partition of the drug from the oil phase into the aqueous phase is possible which cannot be expected in case of oily solutions of lipophilic drugs.

iii. SMEDDS are advantageous over emulsions in terms of stability because of the low energy consumption, and the manufacturing process does not include critical steps. Simple mixing equipment is enough to formulate SMEDDS and time required for preparation is also less compared to emulsions.

iv. Poor water-soluble drugs that have dissolution rate-limited absorption can be absorbed efficiently by the formulation of SMEDDS with consequent stable plasma-time profile. Constant plasma levels of drug might be due to presentation of the poorly soluble drug is dissolved form that bypasses the critical step in drug absorption, that is, dissolution.

v. Along with the lipids, surfactants that are commonly used in the formulation of SMEDDS like Tween 80, Spans, Cremophors (EL and RH40), and Pluronics are reported to have an inhibitory action on efflux transporters which help in improving bioavailability of the drugs which are substrates to the efflux pumps. Surfactant named d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) produced by esterification of vitamin E succinate and polyethylene glycol 1000 was proved to have inhibitory effect on efflux transporters like P-glycoprotein. The efflux of paclitaxel from the GIT was found to be inhibited with formulation prepared using surfactant named polysorbate 80.

vi. Drugs that have propensity to be degraded by the chemical and enzymatic means in GIT can be protected by the formulation of SMEDDS as the drug will be presented to the body in oil droplets.

vii. Microemulsion preconcentrate is advantageous over microemulsion to dispense in the form of liquid-filled soft gelatin capsules.

viii. SMEDDS are advantageous over SEDDS as the former are less dependent on bile salts for the formation of droplets by which better absorption of the drug is expected compared to SEDDS.

ix. Surfactants of high HLB like Tween 80 are reported to increase the permeability of the drug when administered along with the formulation due to the loosening effect of these on tight junctions.

4. Disadvantages of SEDDS: [16, 17]

a. The high content of surfactant presents in a self-emulsifying drug delivery system, which ranges between 30%- 60% irritates the GIT.

b. *In-vitro* models of self-emulsifying formulations lack good predictive studies on assessment of the formulation.

c. Co-solvents which are volatile in nature can migrate on the soft or hard gelatin capsule shell leading to the precipitation of lipophilic drug.

d. The usual dissolution evaluation tests do not work because SEDDS formulations potentially depend on digestion before the release of the drug.

e. Chemical instabilities are observed in the self-emulsifying drug delivery systems.

f. Production cost is expensive.

g. Self-emulsifying drug delivery system formulations containing a high number of components become difficult to validate.

h. Drug incompatibility is low.

i. Leakage of the drug may occur which leads to lesser drug loading.

5. Mechanism of Self Emulsification: [7] Different approaches are there for the microemulsion formation. Single theory can't explain all aspects of microemulsion formation. Schulman *et al.*, have been studied that due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant the microemulsion droplets were formed spontaneously.

The thermodynamic theory of microemulsion formation explains that emulsification occurs when the entropy changes that favor dispersion is greater than the energy required to increase the surface area of the dispersion and the free energy (ΔG) is negative. The free energy in the microemulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation:

$$\Delta G = \sum N\Pi r2\sigma$$

Where,

- ΔG is the free energy associated with the process (ignoring the free energy of the mixing).
- N is the number of droplets.
- r is radius.
- σ is the interfacial energy.

The two phases of the emulsion tend to separate to reduce the interfacial area with time. The free energy of the system decreases. From aqueous dilution, resulting emulsion is stabilized by emulsifying agents, which forms a monolayer around the emulsion droplets and reduces the interfacial energy, as well as providing a barrier to prevent coalescence.

6. Recent Dosage Form Development in SEDDS: [18]

1. Dry emulsions
2. Self-emulsifying capsules
3. Self-emulsifying sustained/controlled-release tablets
4. Self-emulsifying sustained/controlled-release pellets
5. Self-emulsifying solid dispersions
6. Self-emulsifying beads
7. Self-emulsifying Sustained release microspheres
8. Self-emulsifying nanoparticles
9. Self-emulsifying suppositories
10. Self-emulsifying implant

TABLE 1: MARKETED FORMULATION OF SEDDS

Drug name	Compound	Dosage form	Company	Indication
Neoral	Cyclosporine A/I	Soft gelatin capsules	Novartis	Immune suppressant
Norvir	Ritonavir	Soft gelatin capsules	Abbott laboratories	HIV antiviral
Fortovase	Saquinavir	Soft gelatin capsules	Hoffmann-la Roche Inc.	HIV antiviral
Agenerase	Amprenavir	Soft gelatin capsules	Glaxo Smithkline	HIV antiviral
Convulex	Valproic acid	Soft gelatin capsules	Pharmacia	Antiepileptic
Lipirex	Fenofibrate	Hard gelatin capsules	Genus	Antihyper lipoprotrinrmic
Sandimmune	Cyclosporin A/I	Soft gelatin capsules	Novartis	Immune suppressant
Targretin	Bexarotene	Soft gelatin capsules	Ligand	Antineoplastic

Composition of SMEDDS:

7.1. Lipid (Oils): Oils are the important component of SMEDDS, as solubilization and access of the drug to the lymphatic circulation of poorly water-soluble drugs depend on the type and concentration of oil used for formulation [7]. Digestive lipids such as triglycerides, diglycerides, fatty acids, phospholipids, cholesterol and other lipids based on synthetic origin offer improvement in bioavailability of the drug in contrast to the non-digestible lipids with which reduced bioavailability may occur due to impairment in absorption caused by retention of the fraction of administered drug in the formulation itself [21].

Although edible oils based on natural origin are favored, they are not useful as they do not have sufficient capacity to solubilize large amounts of lipophilic drug and self-emulsification is also problematic with them as they possess a large molecular volume [22, 23, 24].

Oil can increase the fraction of lipophilic drugs that pass through the intestinal lymphatic system, thereby increasing absorption from the gastrointestinal tract, depending on the nature of triglyceride. Different degrees of saturation of long and medium-chain triglyceride (LCT and MCT) both oils have been used to design the SEDDS

formulation. But medium-chain triglycerides are considered as a great compound for the formulation. They show hydrophilic and lipophilic properties as well as surfactant properties also [24].

By increasing the intestinal lymphatic permeability, solubility in gastric and intestinal fluids, protecting the drug from metabolism, and increasing the rate of dissolution oils can develop the oral bioavailability of the lipophilic drug. The concentration of oil should be 40-80% to get a good SEDDS formulation. Natural and synthetic oils can be used in self-emulsifying drug delivery systems [23, 25, 28].

Polyglycolized glycerides of varying HLB attributed to the difference in fatty acid chain length and PEG chain length are used along with vegetable oils for the improvement in the bioavailability of drugs and are used for the reason of better tolerability by the human body. Triglycerides with long and medium-chain length containing different degrees of saturation are commonly used in the preparation of SMEDDS [26]. Medium-chain triglycerides have the capacity to get digested efficiently compared to the long-chain triglycerides and also exhibit greater fluidity, improved solubility properties, and good ability to self-emulsify along with the reduced tendency towards oxidation due to which they contribute to the increase of drug absorption and in turn have positive effects on bioavailability [24]. These attractive properties made them more commonly used compared to LCTs.

Prajapati *et al.* performed a study for microemulsion area in phase diagram and concluded that the mixture of lipids (medium-chain fatty acids) composed of monoglyceride: diglyceride or triglyceride in 1:1 ratio produced expanded microemulsion phase and reduced gel phase which is suitable for oral administration. Though medium-chain triglycerides have superior properties to long-chain triglycerides, the drug access to lymph is not possible with them, and it is possible only with lipids composed of LCTs. Oils like cottonseed oil and soybean oil composed of LCTs are reported to enhance the bioavailability of highly lipophilic drugs by stimulation of lymphatic transport of drugs. Mepitiostane (prodrug of epitiostanol) and Mepitiostaneolefin with octanol: water partition coefficients of 6 and 5.1 were proved to undergo significant lymphatic transport when given along with lipids like long-chain triglycerides.

Not only the type of lipid but also the concentration of lipid has an effect on drug transfer into lymphatics and this was investigated with sirolimus SMEDDS where enhanced lymphatic transfer of drug was achieved with formulation containing ≥25% of oil content. The lipids with high instauration tend to get oxidized, and the resultant peroxide may lead to detrimental effect on drug release due to the delay in capsule disintegration. This problem can be addressed by various means like including antioxidants in the formulation, by controlling the utilization of highly unsaturated lipids and by employing sealed hard gelatin capsules that possess impermeability to oxygen [27, 28].

7.2. Surfactants: A surfactant is needed to adopt self-emulsification property by SMEDDS, which is the prime process to form microemulsion, and it is also helpful to solubilize the hydrophobic drug; in turn the dissolution rate can be improved. The solubilization behavior of surfactant for the drug gained popularity due to its inhibitory effect on drug precipitation *in-vivo* [25]. Permeability barrier that is intestinal cell membrane comprised of lipids can be disrupted by surfactant partition; thereby permeability will be enhanced. The opening of tight junctions by the surfactants also contributes to the improvement in permeability, and this was explored with the study conducted by Sha *et al.*, where enhanced permeability of the drug was observed with surfactant labrasol due to opening of tight junctions. The inhibitory effect of surfactants on p-glycoprotein helps in the improvement of overall bioavailability of many drugs that are substrates to p-glycoprotein transporter.

Although natural surfactants are less toxic, the efficiency of self-emulsification is limited. For spontaneous emulsification, the surfactants are required to be selected with attention to attain ultralow interfacial tension. The selection of surfactants is based on HLB value [28]. The surfactants with high HLB facilitate the formation of O/W microemulsion. Surfactants with hydrophilic nature, that is, HLB value of greater

than 12, along with water-soluble co-solvents, are used for drugs with relatively low octanol: water partition coefficient to increase the solvent capacity of the formulation and these systems produce very fine droplets of size less than 100 nm with high surfactant concentration [25]. The less toxicity offered by nonionic surfactants like oleates, polysorbates, polyoxyls, and so forth compared to ionic surfactants allows them to be used more commonly in the formulation of SMEDDS. With commonly used lipids in the formulation of SMEDDS like medium and long-chain triglycerides, the nonionic surfactants like oleates of HLB 11 having unsaturated acyl side chains are more suitable excipients for efficient self-emulsification [24, 25, 29].

Most of the surfactants have an impact on lipid digestion that is catalyzed by lipase in various ways like the formation of complexes with the enzyme at interface, by preventing the adsorption of enzyme at interface or by the interaction with the lipase itself. Inhibition of lipid digestion may also occur as the surfactant has the tendency to interact with other components like bile salts and phospholipids. When different surfactants are compared in this aspect, little impact on lipid digestion is observed in case of non-ionic surfactants, promoting effects on lipid digestion with the use of cationic surfactants and inhibitory effects with anionic surfactants [24, 25].

Care should be exercised to minimize the concentration of surfactant as minimum as possible because the use of high concentration of surfactants has disadvantages like GI irritation, decrease in self-emulsification efficiency, and dehydrating effect on soft and hard gelatin capsules (caused by some of the nonionic surfactants like polysorbates and polyoxyls) with consequent brittleness. At high concentrations of surfactant, GI irritation occurs due to tissue damage and the efficiency of self-emulsification capacity decreases which may be due to the formation of liquid crystalline phase at the interface which in turn is due to viscous nature.

Although there is an indirect relationship between droplet size and surfactant concentration, it exists only to about a certain range due to stabilization effect caused by surfactant on oil droplets by its accumulation at oil/water interface [29]. Above the range, the opposite effect is observed due to the disruption of interface with the surfactant of high concentration that leads to entry of water into oil droplets co-solvent. Co-solvents facilitate the dissolution of surfactant and hydrophobic drugs in oil phase because of their ability to access the entry of water into the formulation. These excipients play the role of cosurfactant in microemulsion system. Some of the commonly used cosolvents are short-chain alcohols like ethanol, n-butanol, propylene glycol, and polyethylene glycol. The addition of cosolvents such as short-chain alcohols imparts flexibility to the interface that is helpful for the free movement of the hydrophobic tails of surfactant at interface which in turn imparts dynamic behavior to microemulsions. Alcoholic, low molecular weight cosolvents may cause precipitation of the drug when the formulation is filled in gelatin capsules since they are absorbed onto the capsule shells. Along with nature, the concentration of cosurfactant also has an impact on drug precipitation [30].

Due to their high polarity, they tend to migrate towards aqueous phase upon dispersion into aqueous media leading to drug precipitation. Hence, it is advisable to formulate SMEDDS in minimum concentration. The selection of suitable surfactant and cosurfactant should be done by considering the efficacy, irritancy, change in efficacy caused by repeated administration of formulation, their interaction with the proteins and lipids of the mucosa, and metabolic pathway followed by them [25, 30].

7.3. Co-solvents: Co-solvents are solvents that help in dissolving immiscible phases (oil/aqueous) in a formulation. They dissolve either large amounts of hydrophilic surfactants or the hydrophobic drug in oil phase. One or more hydrophilic solvents may be used. Co-solvents can also be referred as co-surfactants depending on their use in a formulation. Because high concentration of surfactants is required in SEDDS formulations, usually above 30%, which causes irritation in the gastrointestinal tract, co-surfactants are employed to reduce the concentration of surfactants. Both surfactants and co-surfactants work together to reduce the interfacial tension to a negligible negative value [7, 24].

When this value is achieved, the interface expands to form droplets that are finely dispersed, surfactants and co-surfactants are later adsorbed until the bulk condition is exhausted enough to make a positive interfacial tension. This is called spontaneous emulsification, and it forms the emulsions [15].

In a self-emulsifying drug delivery system, organic solvents that are approved for oral administration such as polyethylene glycol, ethanol, and propylene glycol can act as co-surfactants dissolving large quantities of either the drug in oil base or the hydrophilic surfactant. Studies show that there are alcohol-free self–emulsifying emulsions. These alcohol-free SEDDS systems have advantages over the other formulations because, in capsule dosage forms, alcohol and volatile solvents migrate to the soft or hard [13].

7.4. Drug/Active Pharmaceutical Ingredient: According to the Biopharmaceutical classification system (BCS), there are four classes of drugs based on solubility (the ability of a solute dissolve in a solvent) and permeability (contact between a solute and solvent to form a solution). These classes include-

- **a. Class I:** High solubility and high permeability
- **b. Class II:** Low solubility and high permeability
- **c. Class III:** High solubility and low permeability
- **d. Class IV:** Low solubility and low permeability

The class II drugs which have low solubility and high permeability are used in the formulation of SEDDS [5].

When poor solubility is the major reason for insufficient absorption of the drug, lipid-based formulations are preferred. Apart from poor water solubility, appreciable solubility of the drug in oil phase is important in the selection of suitable drug candidates for the formulation of lipid-based delivery systems like SMEDDS. The drug should be sufficiently hydrophobic to be soluble in the lipid component of the formulation; that is, octanol: water partition coefficient should be high ($\log P > 5$) to incorporate the whole required dose of the drug in one dosage unit [5]. Most of the hydrophobic drugs have good solubility in synthetic oils and Surfactants compared to that in oils from natural sources the greater bioavailability from the SMEDDS can be achieved when the dose is very low, especially for the drugs with high octanol: water partition coefficient. The absorption of the drug from SMEDDS is primarily dependent on its solubility in water and lipid phase. Drugs that have poor bioavailability because of presystemic metabolism can be formulated as SMEDDS provided that the drug should have high solubility in long chain triglycerides (>50mg/mL) and octanol: water partition coefficient of greater than five [7].

8. Effect of Drug Addition on SMEDDS: [7] Optimal drug incorporation can be achieved if good compatibility exists between the added drug and the system with respect to physical and chemical properties. The drug may cause changes in the behavior of the system by reacting with the formulation components or by entering into the interfacial surface where surfactant molecules exist. This problem is more pronounced in case of SMEDDS where the droplet size is much smaller than other self-emulsifying formulations. Preformulation studies like determination of solubility of drug in various components of formulation and construction of phase diagram to know the exact emulsification area can help in resolving the problem of unwanted effects of drug incorporation on optimal SMEDDS. The drug loading also has influence on the droplet size. Bandivadeka *et al.,* studied the effect of drug addition on droplet size and concluded that increased amount of drug addition leads to the increase in particle size and this may be due to the decreased availability of surfactant to reduce the particle size. If the drug has propensity to form H-bonds with ethoxy chains of surfactant, it can affect the performance of SMEDDS. If the drug is highly lipophilic and does not have the ability to form H-bonds, there will not be any effect of drug addition even in high concentrations. The construction of phase diagrams in the presence of drug is helpful for the determination of the effect of drug addition on the existence of microemulsion area.

9. Formulation Design of SEDDS: Formulation of SMEDDS involves the following steps-

9.1. Screening of excipients.
9.2. Construction of pseudo ternary phase diagram.
9.3. Preparation of SMEDDS.
9.4. Characterization of SMEDDS.

9.1. Screening of Excipients:

9.1.1. Solubility Studies: These are mainly useful for the selection of the most suitable excipients that can be used in the preparation of SMEDDS and helps in the prediction of drug precipitation *in-vivo*. The solubility of the drug in various oils, surfactants, and cosurfactants should be tested [25, 31]. These studies are generally performed by shake flask method in which the drug is usually added to the excipient in excess amount and then shaken for 48 hours in water bath shaker or air oscillator at room temperature. Then, the samples should be subjected to centrifugation followed by filtration through 0.45 µm filters, and drug content should be determined [32]. These solubility studies are generally performed with the objective of choosing oil that shows maximum solubility for the drug and surfactant/cosurfactant which have maximum capacity to solubilize the drug. The other objective is achievement of optimum drug loading with minimized total volume of the formulation.

Drug precipitation may occur from diluted SMEDDS which is dependent on octanol: water partition coefficient of the drug and also on the level of involvement of surfactant in the solubilization of the drug [33].

9.1.2. Screening of Surfactants and Cosurfactants for their Self-Emulsification Ability: The emulsification ability of surfactants can be known by mixing the equal proportions of selected oil and surfactant which is followed by homogenization. When this mixture is added to the double-distilled water, the number of flask inversions required to form homogenous emulsion is noted and this gives indication about ease of emulsification [34]. Then, the resultant micro-emulsion should be tested for clarity, turbidity, and percentage transmittance. The surfactants that show highest emulsification efficiency, that is, that show high percentage transmittance and that require low flask inversions, should be selected. Similarly, the cosurfactants should be screened with the same procedure by mixing selected surfactant and oil phase with cosurfactant [35].

9.2. Construction of Pseudoternary Phase Diagram: These are the diagrams that represent change in phase behavior of the system according to the change in composition. The ternary phase diagram is used to study the phase behavior of three components. In SEDDS, this represents the system with three components like oil, water, and surfactant. But in case of SMEDDS, [36] the additional component like cosurfactant/cosolvent addition is most common. The ternary diagram contains three corners that correspond to 100% of the particular component. In case of addition of fourth component, the ternary diagram can be called pseudo ternary phase diagram as one of the corners corresponds to the mixture of two components like surfactant and cosurfactant [37].

For the construction of pseudo ternary phase diagram, mixtures containing different compositions of microemulsion components should be evaluated for emulsification efficiency. At different compositions, different structures may be formed like emulsions, microemulsions, micelles, inverted micellar forms, and so forth, and the extent of formation of these structures can be known with the construction of phase diagram. This phase diagram helps in the determination of dilute ability of formulation and in getting information about the different compositions that form monophasic clear solutions [36]. Pseudo ternary diagrams are constructed by keeping the ratio of any two of the four components as constant and this ratio along with the remaining two components generally forms three corners of the phase diagram.

This fixed (mixture) ratio is generally formed by the combination of surfactant and cosurfactant and sometimes it may be the mixture of oil and surfactant. This is mixed with the required volume of the third phase like oil or cosurfactant then the other component, which is usually water is added in incremental amount and for every addition of fourth component, the solution should be tested for the clarity, flowability, time for self-emulsification, and dispersibility. The total percent concentration of all components in each mixture should be 100%. Then pseudo ternary diagram should be plotted with the help of suitable software.

The samples which formed clear solution should be denoted by suitable symbols in the phase diagram.

The area that is formed when these points are joined indicates the monophasic microemulsion existing area and wide area indicates the good emulsification efficiency [38].

9.3. Preparation of SMEDDS: The preparation involves the addition of the drug to the mixture of oil, surfactant, and cosurfactant and then it should be subjected to vortexing. In some cases, drug is dissolved in any one of the excipients and the remaining excipients are added to the drug solution. Then, the solution should be properly mixed and tested for the signs of turbidity. After equilibration at ambient temperature for 48 h, the solution should be heated for the formation of clear solution, if required. Depending on the final volume, the formulation should be stored in capsules of suitable size [32, 33].

9.4. Characterization of SMEDDS:

9.4.1. Visual Evaluation: The assessment of self-emulsification is possible by visual evaluation. After dilution of SMEDDS with water, the opaque and milky white appearance indicates the formation of macro emulsion whereas the clear, isotropic, transparent solution indicates the formation of microemulsion [32]. Assessment of precipitation of drug in diluted SMEDDS is also possible by visual evaluation [33]. The formulations can be considered as stable when drug precipitation is not evident. Precipitation is common if the formulation contains water-soluble co-solvents and can be avoided by increasing the concentration of surfactant [39].

9.4.2. Droplet Size Analysis: The droplet size is mainly dependent on the nature and concentration of surfactant. Microemulsion formed upon dilution with water produces droplets of very narrow size and size distribution for effective drug release, in vivo absorption, and also stability [39]. Spectroscopic techniques like photon correlation spectroscopy and microscopic techniques are used for droplet size analysis.

Dynamic light scattering techniques employing Zeta sizer can also be used for droplet size analysis. Samples should be diluted suitably before analyzing for size evaluation [40]. The determination of polydispersity index (PDI) gives suitable information about size distribution. The low value of PDI indicates the uniform and narrow size distribution [41].

9.4.3. Zeta Potential Measurement: Zeta potential is generally measured by zeta potential analyzer or zeta meter system. The value of zeta potential indicates the stability of emulsion after appropriate dilution. Higher zeta potential indicates the good stability of formulation. Usually the value of zeta potential is negative due to the presence of free fatty acids but when cationic lipid such as oleylamine is used, the positive charge gets developed [42]. The droplets of positive charge have the property of interacting efficiently with the mucosal surface of the GIT and these interactions are of electrostatic nature due to which strong adhesion can be expected with increased absorption time for emulsification. The time needed for self-emulsification for different formulations can be assessed generally using dissolution apparatus USP type II in which the formulation is added dropwise to the basket containing water and observing the formation of clear solution under agitation provided by paddle at 50 rpm [43]. Assessment of self-emulsification helps to determine the efficiency of self-emulsification of the formulation. The rate of emulsification is found to be dependent on nature of oil phase and oil/surfactant ratio. The rapid rate of emulsification is observed with higher surfactant concentration because of rapid ejection of oil droplets by penetration of water into interface. The emulsification time can also be determined by visual evaluation after placing the formulation in 0.1N HCl under stirring at body temperature by which the GI conditions can be simulated [43].

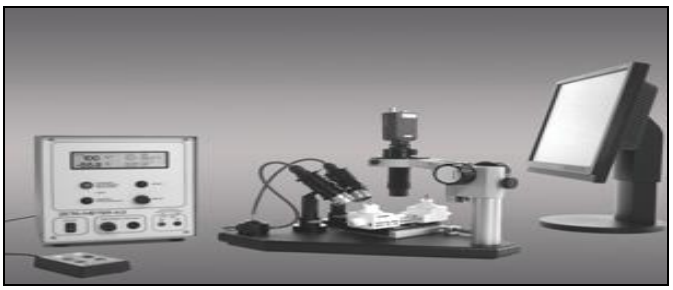

FIG. 2: ZETA POTENTIAL ANALYZER OR ZETAMETER SYSTEM [62]

9.4.4. Cloud Point Determination: Cloud point is generally determined by gradually increasing the temperature of the water bath in which the formulation is placed and measured spectro-photometrically. The point where % transmittance decreases signifies the cloud point that is the temperature above which the transparent solution changes to cloudy solution.

As the body temperature is 37 ºC, formulations to retain its self-emulsification property. Phase separation and decrease in drug solubilization are commonly observed at higher temperatures than the cloud points due to the susceptibility of surfactant to dehydration. Cloud point is influenced by drug lipophilicity and other components of the formulation [25, 44].

9.4.5. Viscosity Measurements: Viscosity of diluted SMEDDS formulation that is microemulsion is generally determined by rheometers like Brookfield cone and plate rheometer fitted with cone spindle or rotating spindle Brookfield viscometer. During titration, the initial increase in viscosity with subsequent decrease, with the increase in water volume attributed to water percolation threshold, indicates the formation of o/w microemulsion from w/o microemulsion with intermediate bicontinuous phase. The rheology of microemulsion can be determined by the graph plotted between shear stress and shear rate. The Newtonian behavior indicates the presence of droplets of small and spherical shape [45, 46, 47].

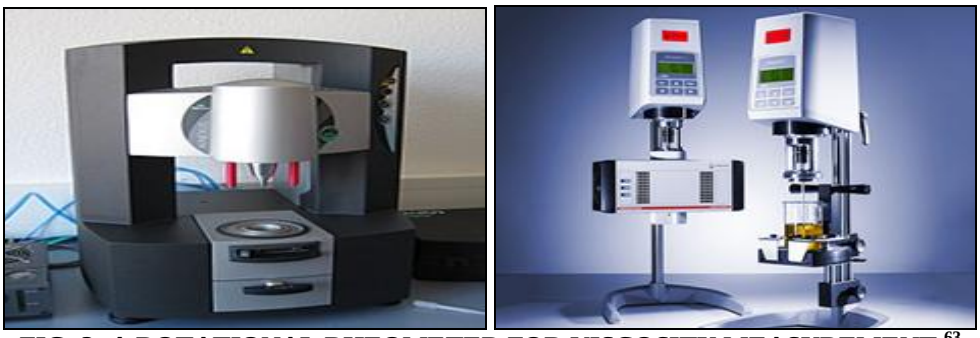

FIG. 3: A ROTATIONAL RHEOMETER FOR VISCOSITY MEASUREMENT [63]

9.4.6. Dilution Studies: The effect of dilution on microemulsion clarity can be evaluated by performing the dilution of microemulsion preconcentrate to various dilutions that simulate the gastric conditions and in various diluents like double distilled water, simulated gastric fluid (SGF), and simulated intestinal fluid (SIF). If clarity is maintained on increased dilution and also in case of change in type of diluents, this indicates absence of drug precipitation. The extent of dilution of SMEDDS to 100 times with all the above diluents can simulate the conditions in vivo. Effect of pH of dilution medium can be investigated by the dilution of SMEDDS with different solvents like Buffer pH1.2, Buffer pH 6.8, and so forth along with the distilled water and should be observed for transparency and efficiency of self-emulsification [48, 49, 50].

9.4.7. Refractive Index: Refractive index is the property by which the isotropic nature of diluted SMEDDS that is microemulsion can be determined. Karamustafa and Celebi *et al.*, performed refractive index measurements of optimized formulation at 4 ºC and 25 ºC up to 6 h at different time intervals and concluded that there is no significant change in refractive index indicating the constant micro-emulsion structure. The constant refractive index also indicates the thermodynamic stability of the formulation. Usually, the refractive index measurements are carried out using refractometers. The refractive index is mainly dependent on two factors, that is, amount of the cosurfactant and globule size. Refractive index decreases with increase in cosurfactant concentration attributed to decrease in the rigidity of microemulsion structure and it increases with the increase in globule size [51, 52, 53].

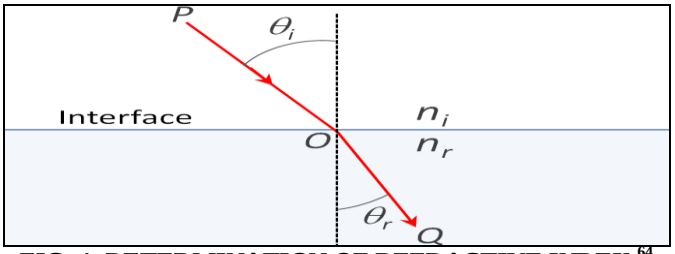

FIG. 4: DETERMINATION OF REFRACTIVE INDEX [64]

9.4.8. Percentage Transmittance: This test gives the indication of transparency of diluted SMEDDS formulation. It is determined spectrophotometrically after dilution of formulation with water, keeping water as blank. The percentage transmittance value near to 100% indicates clear and transparent microemulsion formation [33].

9.4.9. Transmission Electron Microscopy (TEM) Study: It is mainly used to investigate the structure and morphology of microemulsions that are formed by dilution of SMEDDS. These studies are performed by the combination of bright field imaging at increasing magnification and diffraction modes. The diluted SMEDDS is placed on holey film grid and morphology can be determined. Basalious *et al.*, and Elnaggar *et al.*, performed TEM studies by staining the samples. In both experiments, the drop of diluted formulation was placed on copper grid, and after staining with suitable stains like uranyl acetate it was dried and then the droplets were visualized for the detection of morphology like size and shape of the droplets. Some other stains like 1% phosphor tungstic acid solution and 1% methylamine vanadate can also be used. By TEM studies, the uniformity in droplet size can also be known [33, 54, 48].

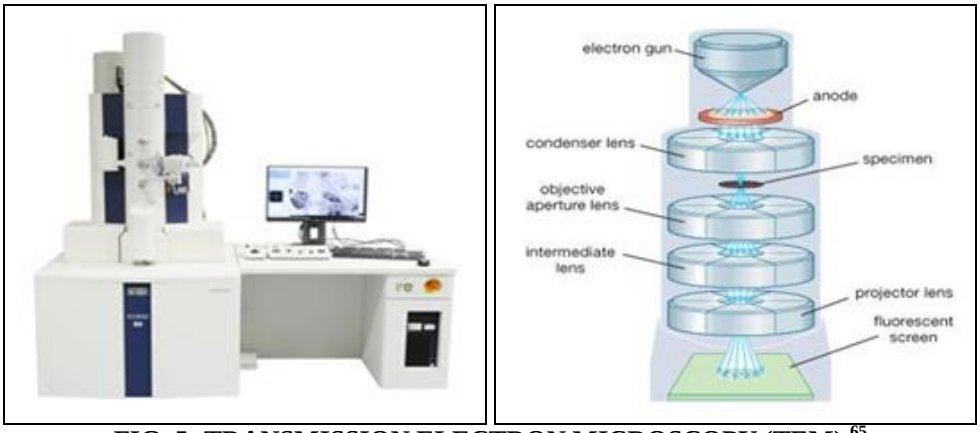

FIG. 5: TRANSMISSION ELECTRON MICROSCOPY (TEM) [65]

9.4.10. Differential Scanning Colorimetry: This is mainly used for the characterization of microemulsions that are formed by dilution of SMEDDS in terms of peaks corresponding to water. The peaks give information about the condition of water like bound state or free state. Pure water is used as reference which shows large, sharp peak approximately at −17 ºC that indicates the freezing point. Podlogar *et al.*, conducted DSC experiments on microemulsions of water- Tween 40/Imwitor 308-isopropyl myristate system and identified peaks corresponding to the water at lower temperature than the pure water (approximately at −45 ºC at 15% w/w) indicating the presence of water in the bound state in micro-emulsions preferably bound to surfactants. The more increased concentration of water than this leads to the shift to higher temperatures. From the observations of thermal behavior of water, they concluded that the high concentration of water (>35% w/w) produced O/W microemulsions. Thermodynamic Stability Studies. These studies are useful to evaluate the consequence of temperature change on formulation. The formulation is diluted with aqueous phase and subjected to centrifugation at 15,000 rpm for 15 min or at 3500 rpm for 30 min. The samples in which the phase separation is not observed are subjected to freeze-thaw cycles (−20 ºC and 40 ºC temperature, resp.) and observed visually. The thermodynamically stable formulations will not show any change in visual description [55, 56].

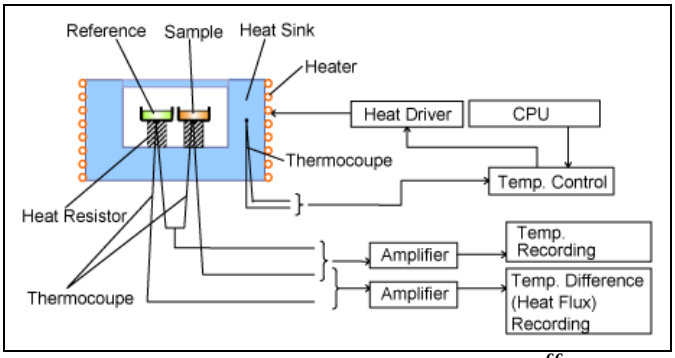

FIG. 6: BLOCK DIAGRAM OF DSC [66]

9.4.11. *In-vitro* Drug Release from Formulation: It can be evaluated after filling the formulation in a hard gelatin capsule using USP XXIII apparatus I at 100 rpm or USPXXIII apparatus II at 50 rpm or with dialysis method at 37 ± 0.5 ºC. Samples at regular intervals should be withdrawn from the medium, and drug content is estimated and compared with the control. The polarity of oil droplets has impact on drug release from the diluted SMEDDS. The higher the polarity, the

faster the drug release from the oil droplet into the aqueous phase. Polarity is mainly dependent on the HLB of surfactant, molecular weight of hydrophilic part of the surfactant, and its concentration along with the degree of unsaturation of fatty acid of lipid phase.

In a study performed by Jantratid *et al.*, comparison is made between the drug release profile using paddle-type apparatus and that of reciprocating cylinder and it was found that the use of USP apparatus 3 (reciprocating cylinder, Bio-Dis) for the evaluation of drug release from the liquid lipid dosage forms like SMEDDS is more suitable than the paddle method and produced reproducible results compared to the paddle method and concluded that this type of behavior is attributed to the uniform break-up of oil layer by the movement of inner cylinder with mesh inserts compared to the paddle method [57, 47].

9.4.12. Stability Assessment: Stability studies are performed as per the ICH guidelines on the formulation which is filled in gelatin capsules. According to the ICH guideline Stability study of the microspheres was checked for any changes in physical stability, size, shape, drug content and release profile. Selected formulations were subjected to exhaustive stability testing at 25 ± 2 °C 60 ± 5% RH for 1st & 2nd month and 40 ± 2 °C 75 ± 5% RH for 3rd months. Samples were withdrawn at 1, 2 and 3 months period according to ICH guidelines. If there is no change in all these properties during storage conditions, formulation can be concluded as stable formulation [31, 58, 59].

CONCLUSION: Self-emulsifying drug delivery systems are a recent and effective approach for the augmentation of oral bioavailability of many poorly water-soluble drugs provided that the drug should be potent with high lipid solubility. It is well demonstrated that SEDDS promotes lymphatic delivery of extremely hydrophobic drugs (with high octanol: water partition coefficient) with good solubility (>50mg/mL) in triglycerides. Thus, for poor absorption drug which needs to be administered *via* oral route can be delivered by this drug delivery system and efficient bioavailability can be achieved. There are so many marketed formulations of SEDDS which most of the capsule dosage form but solid SEDDS are preferable because ease of manufacturing, stability issues and transportation cost. It can also achieve controlled, and sustained release of the drug thus drugs with low biological half-life and poor aqueous solubility can be delivered by SEDDS. The major problem is there is no such model for dissolution study of SEDDS. Further, with solid SEDDS, compatibility and interaction studies between the excipients such as adsorbent, capsule shell & formulation components can be carried out in order to effectively harness its potential for the benefit of mankind. Definitely it can be used to improve the bioavailability of BCS class II and IV drugs in future.

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REFERENCES:

1. Chakraborty S, Shukla D, Mishra B and Singh S: Lipid- an emerging platform for oral delivery of drugs with poor bioavailability. European Journal of Pharmaceutics and Biopharmaceutics 2009; 73(1): 1-15.
2. Gursoy RN and Benita S: Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomedicine and Pharmacotherapy 2004; 58(3): 173-82,
3. Mistry R and Sheth NS: Self-emulsifying drug delivery system. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3(2): 23-28.
4. Chouksey R: Preparation and evaluation of the self-emulsifying drug delivery system containing atorvastatin HMGCOA inhibiter. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3(3): 147-52.
5. Ajay K, Surabh S and Ravindra K: Self-emulsifying drug delivery systems (SEDDS): Future aspects. International Journal of Pharmacy and Pharmaceutical Sciences 2012; 2(4): 7-13.
6. Pouton CW: Formulation of poorly water soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci 2006; 29(3-4): 278-87.
7. Gershanik T and Benita S: Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. European Journal of Pharmaceutics and Biopharmaceutics 2000; 50(1): 179-88.
8. Brahmankar DM and Jaiswal SB: Absorption of Drugs. Biopharmaceutics and Pharmacokinetics – A treatise, VallabhPrakashan, Delhi First edition, 1995; 5-75.
9. Shargel L, Andrew BC: Physiologic factors related to drug absorption Applied Biopharmaceutics and Pharmaco-kinetics, Prentice Hall International, INC., Stanford Fourth edition 1999; 99-128.

10. Aulton ME: Pharmaceutics, the Science of Dosage form Design, Edinburgh New YorK, Churchill Livingstone, Second edition, 2002.
11. Swarbrick J and Boylan JC: "Absorption" Encyclopedia of Pharmaceutical Technology, Marcel Dekker, INC., New York 1988; 1: 1-32.
12. Tang JL, Sun J and He ZG: Self-emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs. Current Drug Therapy 2007; 2(1): 85-93.
13. Gohel MC, Parikh RK, Modi SC, Vyas KG and Sheth KM: Novel drug delivery approaches to bypass P-glycoprotein efflux pump. Pharmainfo.net 2011; 9(1). http://www.pharmainfo.net/reviews/novel-drug-delivery-approaches-bypass-p-glycoprotein-efflux-pump.
14. Constantinides PP, Scalart JP and Lancaster C: Formulation and intestinal absorption enhancement evaluation of water-in-oil microemulsions incorporating medium-chain glycerides. Pharmaceutical Research 1994; 11(10): 1385-90.
15. Narang AS, Delmarre D and Gao D: Stable drug encapsulation in micelles and microemulsions. International Journal of Pharmaceutics 2007; 345(1-2): 9-25.
16. Kim HJ, Yoon KA, Hahn M, Park ES and Chi SC: Preparation and *in-vitro* evaluation of self-microemulsifying drug delivery systems containing idebenone. Drug Development and Industrial Pharmacy 2000; 26(5): 523-29.
17. Rahul S, Chukwunedu CF, Richa S, Shweta. Review on Self Emulsifying Drug Delivery System for Delivery of Drugs. Mod Appl Pharm Pharmacol. 2018; 1(5): MAPP.000524.
18. Thakare P Mogal V, Borase P, Dusane J and Kshirsaga S: A review on self-emulsified drug delivery system. Journal of Pharmaceutical and Biological Evaluations 2016; 3(2): 140-53.
19. Dahan A and Hoffman A: Rationalizing the selection of oral lipid based drug delivery systems by an *in-vitro* dynamic lipolysismodel for improved oral bioavailability of poorly water soluble drugs. Journal of Controlled Release 2008; 129(1): 1-10.
20. Gursoy RN and Benita S: Self-emulsifying drug deliverysystems (SEDDS) for improved oral delivery of lipophilic drugs. Biomedicine and Pharmacotherapy 2004; 58(3): 173-82.
21. Djekic L and Primorac M: The influence of cosurfactants and oils on the formation of pharmaceutical microemulsions based on PEG-8 caprylic/capric glycerides. International Journal of Pharmaceutics 2008; 352(1-2): 231-39.
22. Gershanik T and Benita S: Self-dispersing lipid formulations for improving oral absorption of lipophilic drugs. European Journal of Pharmaceutics and Biopharmaceutics 2000; 50(1): 179-88.
23. Porter CJH, Pouton CW, Cuine JF and Charman WN: Enhancing intestinal drug solubilisation using lipid-based delivery systems. Advanced Drug Delivery Reviews 2008; 60(6): 673-91.
24. Nawale RB, Salunke PB and Jadhav AB: Self emulsifying drug delivery system: a review. Int J Pharm Sci Res 2015; 6(8): 3198-08.
25. Constantinides PP, Scalart JP, Lancaster C: Formulation and intestinal absorption enhancement evaluation of water-in-oil microemulsions incorporating medium-chain glycerides. Pharmaceutical Research 1994; 11(10): 1385-90.
26. Pouton CW and Porter CJH: Formulation of lipid-baseddelivery systems for oral administration: materials, methods and strategies. Advanced Drug Delivery Reviews 2008; 60(6): 625-37.
27. Nankervis R, Davis SS, Day NH and Shaw PN: Effect of lipid vehicle on the intestinal lymphatic transport of isotretinoinin the rat. International Journal of Pharmaceutics 1995; 119(2): 173-81.
28. Khedekar K and Mittal S: Self-emulsifying drug delivery system: a review. Int J Pharm Sci Res 2013; 4(12): 4494-07.
29. Y´a˜nez JA, Wang SWJ, Knemeyer, IW Wirth MA and Alton KB: Intestinal lymphatic transport for drug delivery. Advanced Drug Delivery Reviews 2011; 63(10-11): 923-42.
30. Hauss DJ: Oral lipid-based formulations. Advanced Drug Delivery Reviews 2007; 59(7): 667-76.
31. Kohli K, Chopra S, Dhar D, Arora S and Khar RK: Selfemulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discovery Today 2010; 15(21-22): 958-65.
32. Bagwe RP, Kanicky JR, Palla BJ, Patanjali PK and Shah DO: Improved drugdelivery using microemulsions: rationale, recent progress, and new horizons. Critical Reviewsin Therapeutic Drug Carrier Systems 2001; 18(1): 77-140.
33. Borhade V, Nair H and Hegde D: Design and evaluation of self-micro emulsifying drug delivery system (SMEDDS) of tacrolimus. AAPS Pharm Sci Tech 2008; 9(1): 13-21.
34. Wang Y, Sun J, Zhang T, Liu H, He F and He Z: Enhanced oral bioavailability of tacrolimus in rats by self-microemulsifyingdrug delivery systems. Drug Development and Industrial Pharmacy 2011; 37(10): 1225-30.
35. Singh AK, Chaurasiya A and Awasthi A: Oral bioavailability enhancement of exemestane from self-micro emulsifying drug delivery system (SMEDDS). AAPS Pharm Sci Tech 2009; 10(3): 906-16.
36. Basalious EB, Shawky N and Badr-Eldin SM: SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of lacidipine. I. Development and optimization. International Journal of Pharmaceutics 2010; 391(1-2): 203-11.
37. Elnaggar YSR, El-Massik MA and Abdallah OY: Selfnanoemulsifying drug delivery systems of tamoxifen citrate: design and optimization. International Journal of Pharmaceutics 2009; 380(1-2): 133-41.
38. Lawrence MJ and Rees GD: Microemulsion-based media as novel drug delivery systems. Advanced Drug Delivery Reviews 2000; 45(1): 89-121.
39. Cui SX, Nie SF, Li L, Wang CG, Pan WS and Sun JP: Preparation and evaluation of self-microemulsifying drug delivery system containing vinpocetine. Drug Development and Industrial Pharmacy 2009; 35(5): 603-11.
40. Hu L, Wu H, Niu F, Yan C, Yang X and Jia Y: Design of fenofibrate microemulsion for improved bioavailability. International Journal of Pharmaceutics 2011; 420(2): 251-55.
41. Balakrishnan P, Lee BJ and Oh DH: Enhanced oral bioavailability of Coenzyme Q10 by self-emulsifying drug delivery systems. International Journal of Pharmaceutics 2009; 374(1-2): 66-72.
42. Sharma G, Wilson K, van derWalle CF, Sattar N, Petrie JR and Kumar MNVR: Microemulsions for oral delivery of insulin: design, development and evaluation in

streptozotocin induced diabetic rats. European Journal of Pharmaceutics and Biopharmaceutics 2010; 76(2): 159-69.
43. Bali V, Ali M and Ali J: Nanocarrier for the enhanced bioavailability of a cardiovascular agent: *in-vitro*, pharmacodynamics, pharmacokinetics and stability assessment. International Journal of Pharmaceutics 2011; 403(1-2): 45-56.
44. Tang JL, Sun J and He ZG: Self-emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs. Current Drug Therapy 2007; 2(1): 85-93.
45. Atef E and Belmonte AA: Formulation and *in-vitro* and *in-vivo* characterization of a phenytoin self-emulsifying drug delivery system (SEDDS). European Journal of Pharmaceutical Sciences 2008; 35(4): 257-63.
46. Elnaggar YSR, El-Massik MA and Abdallah OY: "Selfnanoemulsifying drug delivery systems of tamoxifen citrate: design and optimization. International Journal of Pharmaceutics 2009; 380(1-2): 133-41.
47. Boonme P, Krauel K, Graf A, Rades T and Junyaprasert VB: Characterization of microemulsion structures in the pseudoternary phase diagram of isopropyl palmitate/ water/Brij 97:1- butanol. AAPS Pharm Sci Tech 2006; 7(2): E45.
48. Karamustafa F and Celebi N: Development of an oral microemulsion formulation of alendronate: Effects of oil & cosurfactant type on phase behavior. Journal of Microencapsulation 2008; 25(5): 315-23.
49. de Campos Ara´ujo LMP, Thomazine JA and Lopez RFV: Development of microemulsions to topically deliver 5-aminolevulinic acid in photodynamic therapy. European Journal of Pharmaceutics and Biopharmaceutics 2010; 75(1): 48-55.
50. Bandivadeka MM, Pancholi SS, Kaul-Ghanekar R, Choudhari A and Koppikar S: Self-microemulsifying smaller molecular volume oil (Capmul MCM) using non-ionic surfactants: a delivery system for poorly water-soluble drug. Drug Development and Industrial Pharmacy 38(7): 883-92.
51. Li P, Ghosh A, Wagner RF, Krill S, Joshi YM and Serajuddin ATM: Effect of combined use of nonionic surfactant on formation of oil-in-water microemulsions. International Journal of Pharmaceutics 2005; 288(1): 27-34.
52. Borhade V, Nair H and Hegde D: Design and evaluation of self-microemulsifying drug delivery system (SMEDDS) of tacrolimus. AAPS Pharm Sci Tech 2008; 9(1): 13-21.
53. Parveen R, Baboota S, Ali J, Ahuja A, Vasudev SS and Ahmad S: Oil based nanocarrier for improved oral delivery of silymarin: *in-vitro* & *in-vivo* studies. International Journal of Pharmaceutics 2011; 413(1-2): 245-53.
54. de Campos Ara´ujo LMP, Thomazine JA and Lopez RFV: Development of microemulsions to topically deliver 5-aminolevulinic acid in photodynamic therapy. European Journal of Pharmaceutics and Biopharmaceutics 2010; 75(1): 48-55.
55. Shafiq-un-Nabi S, Shakeel F and Talegaonkar S: Formulation development and optimization using nanoemulsion technique: a technical note. AAPS Pharm Sci Tech 2007; 8(2): E12–E17.
56. Sharma G, Wilson K, van derWalle CF, Sattar N, Petrie JR and Kumar MNVR: Microemulsions for oral delivery of insulin: design, development and evaluation in streptozotocin induced diabetic rats. European Journal of Pharmaceutics and Biopharmaceutics 2010; 76(2): 159-69.
57. Podlogar F, Gaˇsperlin M, Tomˇsiˇc M, Jamnik A and Rogaˇc MB: Structural characterisation of water-Tween 40/Imwitor308-isopropyl myristatemicroemulsions using different experimental methods. International Journal of Pharmaceutics 2004; 276(1-2) 115-28.
58. Kim HJ, Yoon KA, Hahn M, Park ES and Chi SC: Preparation and *in-vitro* evaluation of self-microemulsifying drug delivery systems containing idebenone. Drug Development and Industrial Pharmacy 2000; 26(5): 523-29.
59. Jantratid E, Janssen N, Chokshi H, Tang K and Dressman JB: Designing biorelevant dissolution tests for lipid formulations: case example-lipid suspension of RZ-50. European Journal of Pharmaceutics and Biopharmaceutics 2008; 69(2): 776-85.
60. Atef E and Belmonte AA: Formulation and *in-vitro* and *in-vivo* characterization of a phenytoin self-emulsifying drug delivery system (SEDDS). European Journal of Pharmaceutical Sciences 2008; 35(4): 257-63.
61. Kale AA and Patravale VB: Design and evaluation of self-emulsifying drug delivery systems (SEDDS) of nimodipine. AAPS Pharm SciTech 2008; 9(1): 191-96.
62. http://www.orbitresearch.in/zeta-meter-system-4-0-unit--1459323.html
63. https://en.wikipedia.org/wiki/Rheometer#/media/File:Rheometer
64. http://www.hotelsrate.org/refractive-index-equation-organic-chemistry/
65. https://www.alamy.com/stock-photo-the-components-of-a-transmission-electron-microscope-tem-24898253.html
66. https://www.hitachihightech.com/global/products/science/tech/ana/thermal/descriptions/dsc.html

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