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RECENT APPROACHES IN SELF EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Self emulsifying is a topic of current interest for overcoming the formulation difficulties of drugs with poor aqueous solubility. SEDDS are isotropic mixture of oil, surfactant and co-surfactant with a unique ability to form fine oil-in-water (o/w) emulsions or micro emulsions upon mild agitation in the gastrointestinal tract which present the drug in a solubilized form, and the small size of formed droplet provides a large interfacial surface area for drug absorption. It is a promising strategy to improve the rate and extent of oral absorption. The SEDDS were characterized for robustness to dilution, globule size, polydispersity index and zeta potential.

INTRODUCTION: Oral route is the most easiest and convenient way of non-invasive administration. Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery. A rate limiting step for absorption of these drugs is often their Solubilization in the GIT. These drugs are classified in class II drug by Biopharmaceutical classification system (BCS), drugs with poor aqueous solubility and high permeability. Different formulation approaches like micronization, solid dispersion, and complexation with cyclodextrin have come up [1].

Indeed in some cases these approaches have been successful but they often many have disadvantages. The main problem with micronization is chemical /thermal stability; many drugs may degrade and lose bioactivity when they are micronized by conventional method. For solid dispersion the amount of carrier use is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. Moreover, since the carriers used are usually expensive and freeze drying or spray –drying methods requires particular facilities and processes leading to high production cost."

Though traditional solvent method can be adopted instead, it is difficult to deal with co-precipitation with high viscosity. Complexation with cyclodextrin technique is not application for drug substances which are not soluble in both aqueous and organic solvents.

Realization that the oral bioavailability of poorly water soluble drugs may be enhanced when co- administered with meal rich in fat has led to increasing recent interest in the formulation of poorly water soluble drugs in lipids.

Lipid based drug delivery have gained considerable interest after the commercial success of Sandimmiune Neoral (Cyclosporin A) [2], Forovase (Saquinavir), Norvir (Rotonavir) [3].

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Self-emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of lipid/oil, surfactant, co-surfactant and drug substance that rapidly form a fine oil-in-water micro (SMEDDS) and nano (SNEDDS)-emulsions, when exposed to aqueous media under conditions of gentle agitation or digestive motility that would be encountered in the GIT. The spontaneous formation of emulsion advantageously presents the drug in a dissolved form, and the resultant small droplet size provides a large interfacial surface area. These characteristics result in faster drug release from emulsion in a reproducible manner, which can be designed further to make the release characteristics independent of the gastrointestinal physiology and the fed/fasted state of the patient [4, 5].

Recently, SEDDS have been formulated using medium chain triglyceride oils and non-ionic surfactants, the latter being less toxic [6]. Both SEDDS and SMEDDS have distinct features associated with improved drug delivery properties. SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SMEDDS requires the use of a co surfactant to generate a micro-emulsion. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm-5 mm and the dispersion has a turbid appearance. SMEDDS, however, have a smaller lipid droplet size (<100 nm) and the dispersion has an optically clear-to-translucent appearance. Both systems are associated with the generation of large surface area dispersions that provide optimum conditions for the increased absorption of poorly soluble drugs.

TABLE 1: CHARACTERIZATION OF SEDDS AND SMEDDS

SEDDS	SMEDDS
Can be a simple binary formulation with the drug and lipidic excipient able to self-emulsify in contact with gastrointestinal fluids (or) A system comprising drug, surfactant, oil (also referred to as lipid phase.	Are composed of the drug compound, surfactant, co-surfactant and oil (or lipid phase)
Lipid droplet size in the dispersion ranges from 200 nm-5µm providing a large surface area for absorption. The dispersion has a turbid appearance.	Lipid droplet size in the dispersion is <200 nm providing a large surface area for absorption. The dispersion has an optically clear to translucent appearance.
SEDDS systems are not thermodynamically stable in water or physiological conditions.	SMEDDS systems are thermodynamically stable in water or physiological conditions.
Development/optimization of SEDDS may require the development of ternary phase diagrams.	Pseudo-ternary phase diagrams are required to optimize SMEDDS.
SEDDS and SMEDDS forms a fine oil-in-water dispersion in contact with gastrointestinal fluids	
SEDDS and SMEDDS formulations can be prepared as liquids and semi-solid for capsule dosage forms and solid forms	

Composition of SEDDS:

The self-emulsifying depends on [7]:

i. The nature of oil surfactant pair.

ii. The surfactant concentration.

iii. The temperature at which self-emulsification occur.

Oils: Both long- and medium-chain triglyceride (MCT) oils with different degrees of saturation have been used for the design of self-dispersing formulations. Unmodified edible oils provide the most `natural' basis for lipid vehicles, but their poor ability to dissolve large amounts of hydrophobic drugs and their relative difficulty in efficient self-emulsification markedly reduce their use in SEDDS.

In contrast, modified or hydrolyzed vegetable oils have contributed widely to the success of the above systems [8, 9, 10]. Since, they exhibit formulative and physiological advantages, these excipients form good emulsification systems, with a large number of non-ionic surfactants approved for oral administration, while their degradation products resemble the end products of intestinal digestion. MCTs were preferred in the earlier self-emulsifying formulations [11, 12]. Because of higher Fluidity, better solubility properties and self-emulsification ability, but evidently, they are considered less attractive compared to the novel semi-synthetic medium chain derivatives [13] which can be defined rather as amphiphilic compounds exhibiting surfactant properties. In such cases, the more lipophilic surfactant may play the role of the hydrophilic oil in the formulation [14, 15].

Solvent capacity for less hydrophobic drugs can be improved by blending triglycerides with mono- and di-glycerides [16].

Surfactants: Non-ionic surfactants with a relatively high hydrophilic lipophilic balance (HLB) were advocated for the design of self-dispersing systems, where the various liquid or solid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80); are the most frequently used excipients.

Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SDLF (self-dispersed lipid formulation) use [17, 18, 19] despite their limited ability to self-emulsify. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents, but they may cause moderate reversible changes in intestinal wall permeability [20, 21].

Amemiya et al. proposed a new vehicle based on a fine emulsion using minimal surfactant content (3%) to avoid the potential toxicological problems associated with high surfactant concentration [22].

The usual surfactant concentration in self-emulsifying formulations required to form and maintain an emulsion state in the GI tract ranged from 30 to 60% w/w of the formulation. A large quantity of surfactant may irritate the GI tract. Thus, the safety aspect of the surfactant vehicle should be carefully considered in each case. The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/selfemulsifying performance. The surface active agents are amphiphilic by nature, and they are therefore usually able to dissolve and even solubilize relatively high quantities of the hydrophobic drug.

The latter is of prime importance for preventing precipitation within the GI lumen and for the prolonged existence of the drug molecules in soluble form, which is vital for effective absorption [23]. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of self-micro emulsifying formulations.

Co-solvents: Relatively high surfactant concentrations (usually more than 30% w/w) are needed in order to produce an effective self-emulsifying system. Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base. These solvents sometime play the role of the co-surfactant in the micro emulsion systems, although alcohol- free self-emulsifying microemulsions have also been described in the literature [20].

Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile cosolvents comprised in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin, or hard, sealed gelatin capsules, resulting in the precipitation of the lipophilic drug. On the other hand, the lipophilic drug dissolution ability of the alcohol free formulation may be limited. Drug release from the formulation increased with increasing amount of cosurfactant.

TABLE 2: EXAMPLES OF EXCIPIENTS USED IN SELF EMULISFYING DRUG DELIVERY

oils	Surfactant	Co-surfactant/co-solvent
Cotton seed oil	Polysorbate 20(Tween20)	Span 20
Soyabean oil	Polysorbate 80(Tween 80)	Span 80
Corn oil	D-alphaTocopheryl polyethylene Glycol 1000	Caproyl90
Sunflower oil	succinate(TPGS)	Lauroglycol
Castor oil	Polyoxy-35-castor-oil(CremophorRH 40)	Transcutol
Sesame oil	Polyoxy-40-hydrogenatedcastor-oil(Cremophor	Capmul
Peanut oil	RH 40)	Ethanol
Labrafac, Labrafil	Labrasol	Polyethylene Glycol

Mechanism of Self Emulsification: In emulsification process the free energy (ΔG) associated is given by the equation [24];

$$\Delta G = \Sigma N_i \pi r_i^2 \sigma$$

In which "N" is number of droplets with radius "r" and "σ" is interfacial energy. It is apparent from equation that the spontaneous formation of the interface between the oil and water phase is energetically not favored. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in the thermodynamic sense. The process of self-emulsification was observed using light microscopy. The emulsification process may be associated with the ease with water penetrates the oil-water interface with the formation of liquid crystalline phases resulting in swelling at the interface thereby resulting in greater ease of emulsification.

The additional mechanisms by which lipid based delivery systems enhance the absorption of lipophilic drugs are:

- **Enhanced dissolution/Solubilization:** The presence of lipids in the GI tract stimulates gallbladder contractions and biliary and pancreatic secretions, including bile salts (BS), phospholipids (PL) and cholesterol. These products, along with the gastric shear movement, form a crude emulsion which promotes the solubilization of the coadministered lipophilic drug [25].
- **Prolongation of gastric residence time:** Lipids in the GI tract provoke delay in gastric emptying, i.e. gastric transit time is increased. As a result, the residence time of the co-administered lipophilic drug in the small intestine increases.thi enables better dissolution of the drug at the absorptive site, and thereby improves absorption.
- **Stimulation of lymphatic transport:** Bioavailability of lipophilic drugs may be enhanced also by the stimulation of the intestinal lymphatic transport pathway.
- **Affecting intestinal permeability:** A variety of lipids have been shown to change the physical barrier function of the gut wall, and hence permeability.
- **Reduced metabolism and efflux activity:** Recently, certain lipids and surfactants have been shown to reduce the activity of efflux transporters in the GI wall, and hence, to increase the fraction of drug absorbed, because of the interplay between P-gp and CYP3A4 activity this mechanism may reduce intra-enterocyte metabolism as wall.

Potential advantages of SEDDS:

- Potential advantages of these systems (SEDDS) include
- Enhanced oral bioavailability enabling reduction in dose.
- More consistent temporal profiles of drug absorption.
- Selective targeting of drug(s) toward specific absorption window in GIT
- Protection of drug(s) from the hostile environment in gut.
- Control of delivery profiles.
- Reduced variability including food effects.
- Protection of sensitive drug substances.
- High drug payloads.
- Liquid or solid dosage forms [26, 27].

Disadvantages of SEDDS:

- Chemical instabilities of drugs and high surfactant concentrations [28]
- The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered.
- Volatile co solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- Lack of in vitro model for the assessment of the formulations.

Biopharmaceutical aspects: The ability of lipids and/or food to enhance the bioavailability of poorly water soluble drugs has been comprehensively reviewed and the interested reader is directed to these references for further details. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms including the following [29];

- Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution [30]
- Increases in effective luminal drug solubility: The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures, either directly (if sufficiently polar) or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity [31]
- Stimulation of intestinal lymphatic transport: For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism.
- Changes in the biochemical barrier function of the GI tract: It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism.
- Changes in the physical barrier function of the GI tract: Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water soluble, and in particular, lipophilic drugs [8]

Factors affecting SMEDDS formulation:

- Drugs which are administered at very high dose are not suitable for SMEDDS, unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs exhibit limited solubility in water and lipids are most difficult to deliver by SMEDDS [9].
- The polarity of lipid phase is one of the factors that govern the release from drug from the microemulsion. HLB, chain length degree or unsaturation of the fatty acid, molecular weight of the hydrophilic portion and concentration of the emulsifier govern polarity of the droplets. In fact, the polarity reflects the type of forces involved. The high polarity will promote rapid rate of release of the drug into the aqueous phase. Sang-Cheol Chi *et al*., who observed that the rate of release of idebenone from SMEDDS is dependent upon the polarity of the oil phase used. The highest release was obtained with the formulation that had oily phase with highest polarity [10].
- The ability of SMEDDS to maintain the drug in solubilized of the drug in oily phase. If the surfactant or co-surfactant is contributing to greater extent for drug solubilization, here could be a risk of precipitation, as dilution of SMEEDS will lead to lowering of solvent capacity of surfactant or co-surfactant [11].

Table 3: SELF EMULSIFYING DRUG DELIVERY SYSTEM OF DIFFERENT API

Drug	Category	Name of researcher	Work done
lacidipine	Antihypertensive	**Emad et al., 2010**	Prepared the SNEDDS containing bioenhancers for improvement of dissolution and oral absorption of lacidipine
Ibuprofen	NSAID	**Wang et al., 2009**	Designed and optimized self nanoemulsifying drug delivery system of a poorly water soluble drug Ibuprofen.
Vinpocetin	Vasodilator	**2008**	Designed and optimized self micremulsifying drug delivery system of a poorly water soluble drug Vinpocetin
Oridonin	Anti-inflammatory	**Liu et al.., 2008**	Released rate of oridonin is enhanced by SMEED formulation

Carvedilol	β-adrenergic blocker	**Mahmoud et al., 2010**	Prepared super porous hydro gel of self nanoemulsifying drug delivery system of carvediol
Cefpodoxime proxetil	Anti-microbial	**Date et al ., 2006**	Developed the SNEDDS of Cefpodoxime proxetil, a poorly bioavailable high dose antibiotic
Fenofibrate[30]	Hypolipidimic drug	**Patel et al., 2007**	SMEDDS formulation significantly reduced serum level in Triton test as compared with lain fenofibrate
Acyclovir	Antiviral	**Patel et al., 2007**	BA enhanced to 3.5 fold
Silymarin		**Woo et al., 2007**	BA enhanced to 2.5 fold
Carvedilol[31]	β-adrenergic blocker	**Wei et al., 2005**	BA enhanced to 415%
Celecoxib	NSAID	**Subraminium et al., 2004**	BA enhanced to 49.5%
Simvastatin[32]	Hypolipidimic drug	**kang et al., 2004**	The release rate of Simvastatin as well as bioavailability was higher than conventional tablet
Ubiquinone	Congestive heart failure	**Nazzal et, al., 2002**	Studied about the effect of microcrystalline cellulose on compaction, surface roughness, and in-vitro dissolutionof self-nano emulsified solid dosage form of Ubiquinone
Lovastatin[33]	Hypolipidimic drug	**Yoon et al., 2002**	BA enhanced to 40%
Itraconazole[34]	Antifungal drug	**Hong and Kim et al., 2006**	To enhance the dissolution and oral absorption of poorly water-soluble Itraconazole, self-emulsifying drug delivery system (SEDDS

Recent Techniques in Self Emulsifying Drug Delivery:

- **Supersaturable SEDDS(S-SEDDS):** The high surfactant level typically present in SEDDS formulations can lead to GI side effects and a new class of supersaturable formulations, including supersaturable SEDDS(S-SEDDS) formulations, have been designed and developed to reduce the surfactant side effect and achieve rapid absorption of poorly soluble drugs. The S-SEDDS approach is to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium.Supersaturation is intended to increase the thermodynamic activity to the drug beyond its solubility limit and therefore, to result in an increased driving force for transit into and across biological barrier [35, 36].

- **Solid SEDDS:** SEDDS are normally prepared as liquid dosage form that can be administered in soft gelatine capsule, which have some disadvantages especially in the manufacturing process. An alternative approach is to incorporate of liquid self-emulsify ingredients into a powder in order to create a solid dosage form [37].

Solidification technique for converting Liquid/ Semisolid SEDDS to solid-SEDDS:

- **Capsule filling with liquid and semisolid self-emulsifying formulation**: Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid self emulsifying formulation for the oral route. For semisolid formulations, it is a four step process:1)heating of the semisolid excipients to at least 20c above its melting point 2)incorporation of active substance with continues stirring 3)capsule filling with the molten mixture and 4)cool at room temperature. For liquid formulation it involves two-step process;1)filling of the formulation into capsule 2)sealing of the body and cap of the capsule either by banding or by microspray sealing.

- **Melt granulation:** Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or soften at relatively low temperature. As a one-step operation, melt granulation offers several advantage compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Wide range of solid and semisolid lipids can be applied as metastble binders [38].

- **Melt extrusion:** Melt extrusion is a solvent free process that allows high drug loading approximately 60%.Extrusion is a procedure for

converting a raw material with plastic properties into a product of uniform shape and density, by forcing through a die under controlled temperature, product flow, and pressure conditions. The size of the extrude aperture will determine approximately size of resolution spheroids [39].

- **Spray drying:** This technique involves the preparation of a formulation by mixing lipids, surfactant, drug, solid carrier and solubilisation of the mixture before spray drying. The solubilised liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase evaporates, and forming dry particles under controlled temperature and airflow condition. Such particles can be further prepared into tablets or capsules.

- **Adsorption to Solid Carriers:** The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resultant powder may then be filled directly into capsule or alternatively, mixed with suitable excipient before compression into tablets. The major advantage of using this technique is good content uniformity. SEDDS can be absorbed at higher level (upto 70%) onto suitable carriers. Solid carrier can be micro porous substances, high surface area colloidal inorganic adsorbent substances, cross linked polymer or nano particles adsorbent, for example silica, silicates, magnesium trisilicate, talcum, crosspovidone.

- **Novel self-emulsifying controlled floating drug delivery system (SEFDDS)** of tetrahydrocurcumin (THC) using silicon as an adsorbent. The release rate and extent of release of THC liquid SEDDS (80% within 2h) and self-emulsifying floating pellet formulation (80% within 8h) were significantly higher than that of unformulated THC (only 30% within 8 h) [39].

- **Sustained-release microspheres with self-emulsifying** capability containing zedoary turmeric oil (ZTO) were prepared by the quasi-emulsion-solvent-diffusion method. it increased the bioavailability to 135.6% as compared to conventional drug [40].

- Novel gelled sustained release self-emulsifying drug delivery system (SEDDS) of ketoprofen prepared using Captex 200 (an oil), Tween 80 (a surfactant), and Capmul MCM (a cosurfactant). Silicon dioxide as a gelling agent, which may aid in solidification and retardation of drug release [41].

Table 4: EXAMPLES OF PHARMACEUTICAL PRODUCT FORMULATED AS SELF EMULISFYING DRUG DELIEVERY [42]

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
Convulex®	Valproic acid	Soft gelatin capsule	Pharmacia	Antiepileptic
Lipirex®	Fenofibrate	Hard gelatin capsule	Genus	Antihyper-lipoproteinemic
Sandimmune®	Cyclosporine A/II	Soft gelatin capsule	Novartis	Immuno suppressant
Targretin®	Bexarotene	Soft gelatin capsule	Ligand	Antineoplastic
Rocaltrol®	Calcitriol	Soft gelatin capsule	Roche	Calcium regulator
Gengraf®	Cyclosporine A/III	Hard gelatin capsule	Abbott Laboratories	Immuno suppressnat

TABLE 5: PATENT ON SMEDDS [43]

Patent no.	Patent name	Inventor
US 2007/0104740	Self-micro emulsifying drug delivery of HIV protease	Jody firmin Marceline
US 1999/5,993,858 Amidon	Method and formulation for increasing the bioavailability of poorly soluble drug	Crison, John R
US 2006/0275358 Enzyme Q10	Self-micro emulsifying dosage form of low Solubility active ingredients	Lin, zing
US 2001/6309665 micro emulsion	Composition with sustained release of Active principle, capable of forming	Barthelmy, Philippe
US 2004/0248901	composition containing itraconazole and Their preparation method	Leo beom jin, Choonyoung
US 2010/0331356	Self microemulsifying drug delivery system	Igor,Legen,Janez,Kerc

Characterization of SEDDS: The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements [44].

- **Visual assessment:** This may provide important information about the self-emulsifying and micro emulsifying property of the mixture and about the resulting dispersion [45].

- **Turbidity Measurement:** This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time [46].

- **Droplet Size:** This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size. The reduction of the droplet size to values below 50 µm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions [47].

- **Zeta Potential Measurement:** This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.

- **Dispersibility test:** The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2.One milliliter of each formulation was added to 500 ml of water at 37±0.5^{o}C. A standard stainless steel dissolution paddle rotating at 50rpm provided gentle agitation. The *in vitro* performance of the formulation is visually assessed using the following grading system [48].

Grade A: Rapidly forming (within 1 min) Nanoemulsion, having a clear or bluish appearance.
Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
Grade C: Fine milky emulsion that formed within 2 min
Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).
Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globule present on the surface.

- **Drug content**: Drug from preweighed SEDDS 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 [49].

Application: SEDDS formulation is composed of lipids, surfactants, and cosolvents. The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation. SEDDSs present drugs in a small droplet size and well-proportioned distribution, and increase the dissolution and permeability.

Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism [50].

TABLE 6: APPLICATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM [51, 52, 53, 54]

DRUG	OIL	SURFACTANT	COSOLVENT	IMPROVEMNET
Ketoprofen	Captex 200	Tween 80	Capmul MCM	Silicon dioxide was used as for gelling agent, as the concentration increase, it causes an increase in the droplet size of emulsion and slows the drug diffusion
Carvedilol	Labrasol	labrafil M 1944CS	Transcutol p	it improves the oral bioavailability of Carvedilol upto 413%when compared to conventional tablet
Simvastation	Caproyl 90	Cremophore EL	Carbotol	The release rate of simvastatin from SMEDDS was higher than conventional tablet. The oral bioavailability of SMEDDS is about 1.5 fold higher than conventional tablet
Diclofenac sodium	goat fat	Tween 65		SEDDS tablets were formulated by pour molding using plastic mold, the tablet contain higher tween 65:goat fat content ratio give better release rate

CONCLUSION: Self-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 SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

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