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Amelioration of lipophilic compounds in regards to bioavailability as self-emulsifying drug delivery system (SEDDS)

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Abstract

Background: High lipophilicity and poor aqueous solubility are the endemic problems of new drug molecules. Sixty to seventy percent of these drugs are unable to solubilize completely in aqueous media, or have very low permeability. This hampers their oral absorption and further leads to their poor bioavailability. Various researches are in progress to overcome these limitations. Novel technologies like nano-carrier systems have become popular for improving the solubility of drugs.

Main body: Lipid-based formulations, among nano systems, are taking pace for the enhancement of solubility, oral absorption, and hence the bioavailability of drugs. Among the lipid formulations, self-emulsification systems are gaining popularity by offering various advantages to delivery systems. Self-emulsifying drug delivery systems (SEDDS) are isotropic blends of oil and surfactant/co-surfactants. These ingredients upon gentle agitation in aqueous media results in the formation of o/w emulsion. In spite of many works published in SEDDS, the major concerns of this article are to discuss the various approaches to formulate a good lipid-based carrier system for poorly aqueous soluble drugs, role of various polymers, and their categories used in the formulation along-with the modern technologies used for enhancing the stability of liquid SEDDS. This review majorly focuses upon the problems related to the poor aqueous solubility of the newer lipid molecules and the solutions to overcome their solubility and in addition bioavailability.

Conclusion: As per the researches done in formulation and optimization of SEDDS for the enhancement of bioavailability of lipophilic molecules, it can be stated that the aqueous solubility as well as bioavailability can be increased by many folds compared to their marketed or other oral formulations.

Keywords: Dispersion system, Lipophilicity, Self-emulsification, Nano-carrier, Bioavailability

Background

The medications are commonly administered orally; however, around 40% of new drug competitors have poor-water solvency and the oral delivery of such medications is troublesome in view of their low bioavailability, high intra- and inter-subject fluctuation, and an absence of dose proportionality [1, 2]. Low aqueous solvency is the significant issue experienced with development of new chemical compounds [3–5]. Restricted aqueous dissolvability and high lipophilicity confine the remedial result for all medications [1]. It is advisable to broaden the therapeutic efficacy of medications by expanding the bioavailability of the medication and additionally by reducing interpatient changeability in plasma level concentration [4–6]. The most important factor for drugs administered orally is their solubility [2]. The desired concentration of any drug to achieve its pharmacological response is based on this factor majorly and thus it is most challenging for formulation scientists to maintain the pharmacological range of such poorly

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aqueous soluble drugs [1]. Poor aqueous solubility and low dissolution rate are the major cause of inadequate oral bioavailability of lipophilic drugs [4, 5, 7].

To overcome these issues, various strategies are opted including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrin complexation, nanoparticles, and solid dispersions [8, 9]. Various factors influence the oral bioavailability, such as aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms [10]. Lipid soluble drugs require higher doses to reach therapeutic plasma concentrations following oral administration [11]. An enhancement in the solubility and dissolution rate can enhance the oral bioavailability of such compounds, which in addition improves the healing efficacy and patient compliance [12]. This can be beneficial in lowering of frequent dosing of the drugs, required to obtain the identical/extended degree of bioavailability determined with a traditional formula. This would enhance predictability of the remedy and increase uniformity of treatment in patient population [8]. Liposomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), emulsions, and nanoemulsions, are some lipid-based formulations that have been used to improve the performance of poorly water-soluble bioactive compounds [13]. By increasing the solubilization and stability, of the lipid-based drugs, plus providing a sustained, targeted and triggered delivery system they enhance the aqueous solubility [14].

Lipinski's rule of five has gained a valued importance as qualitative predictive model for the estimation of absorption of poorly absorbed drug molecules. In his finding, it was stated that "the rule of 5" predicts that poor absorption or permeation is more probable when there are more than 5H-bond donors, 10H-bond acceptors, the molecular weight is greater than 500, and the calculated Log P is greater than 5. This rule is effective for the drugs that are not substrates for active transporters and efflux mechanisms [15].

Main text

It is possible to enhance the oral bioavailability and reduce the probable side effects of an active pharmaceutical ingredient with lipid-based carrier systems. Lipid-based carriers are less toxic compared to other delivery systems, as they are biocompatible and biodegradable [16].

Solubility

Enhancement of solubility thereby oral bioavailability of such drug molecule remains one of the most difficult aspects of the drug development process especially for oral-drug delivery system [17]. Various approaches are stated in literatures and are available for the enhancement of solubility of poorly aqueous soluble drugs, especially when administered orally. These approaches are opted based on certain aspects, such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. In addition, modification of crystal habit, reduction of particle size, solid dispersions, solid solutions, salt formation, and miscellaneous methods, including supercritical fluid process and use of surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients as adjuvant to increase solubility are considered [18]. In practice, the occurrence of spontaneous emulsification is difficult to establish because when mechanical agitation is absent gravitational force provides a small quantity of energy for emulsification. The ratio and overall concentration of oils and surfactants in each formulation will determine the rate and extent of the absorption of any drug [19]. To enhance the rate of absorption, digestibility of oil and partition of the drug between the two phases should be optimized. The principal concept of lipid-based drug delivery system is to bring the drug in its dissolved state, by the formation of its colloidal dispersion in the gastrointestinal tract. This dispersion helps to enhance the solubility and absorption of lipophilic drugs in aqueous system. Various forms of lipid-based delivery systems are present, namely solutions, suspensions, emulsions, microemulsions, SEDDS, or dry emulsions [20].

Theory of Pouton

In the year 2000, Pouton introduced one useful lipid formulation classification system (LFCS). LFCS was recreated in the year 2006 by Pouton himself. As per the LFCS, SEDDS (type II) is an isotropic mixture of oil or mixture of oils and surfactant/s and on exposure to the gastric media; it gets emulsified [21]. Therefore, it can be said that the self-emulsifying systems improves the absorption and distribution of drug by avoiding the slow dissolution and gastric irritation, leading to improved bioavailability of lipid-soluble drugs. Ability to dissolve the poorly aqueous drugs in suitable solvents, thereby enhancing their absorption and bioavailability, is the major reason behind the growing demand of lipidic excipients [22].

Lipid-based drug delivery system classification by Pouton

Pouton classified the lipid-based delivery system for poor aqueous soluble drugs into four categories, as described in the table below (Table 1).

Various in-vivo properties of lipid-based delivery systems associated with their bioavailability enhancing property include the following:

Table 1 Classification of LBDDS by Pouton

Category	OIL (lipophilic)	Surfactant (lipophilic)	Surfactant (hydrophilic)	Co-solvents	Formulations
Category I	100 %	0%	0%	0%	Simple oily solutions
Category II	40-80%	20-60%	0%	0%	SEDDS
Category III	0%	20-40%	20-40%	20-50%	SMEDDS
Category IV	0%	0-20%	20-80%	0-80%	Colloidal micellar dispersions

SEDDS self-emulsifying drug delivery systems, *SMEDDS* self-micro-emulsifying drug delivery systems [23]

1. Prevention of drug precipitation and recrystallization by the formation of fine dispersion and micellar suspension
2. Improved drug absorption by implying certain changes in GIT by the lipid compounds and its metabolites
3. This system has the ability to inhibit the efflux system, which fluctuates the distribution of drug. Controlled efflux system controls the drug circulation in the cellular system.
4. Helps reduce the first-pass drug metabolism by the mechanism of drug uptake directly into the lymphatic transport [24].

Digestion and absorption are the two complex mechanisms, which are yet to be understood well by the scientists. However, lipid excipients provide a safe and effective way of formulating a lipophilic drug with enhanced solubility and bioavailability. In addition to the solubility and bioavailability, this system introduces various improved chemical and mechanical technologies to deal with such problems [1, 4, 5].

Self-emulsifying drug delivery systems

As per the known definitions, SEDDS are isotropic mixtures of natural/synthetic oils, solid/ liquid surfactants, and/or one or more hydrophilic solvents and co-solvents/surfactants [25]. Again, as stated earlier, with a mild agitation they dilute the drug in the system (aqueous media), such as GI fluids, and forms fine oil-in-water (o/w) emulsions (0.1-100 μm) or microemulsions (10-300 nm), spreading readily into the GIT where agitation is provided by the movement of the stomach and intestinal fluid forming a self-emulsified system [26].

Figure 1 represents an illustrative diagram explaining the mechanism of self-emulsification.

SEDDS are modified further as self-micro emulsifying drug delivery systems (SMEDDS) or self-nanoemulsifying drug delivery systems (SNEDDS) drug delivery systems, classified as type IIIa or IIIb, respectively [27]. This modified form additionally contains one or more co-surfactant or co-solvents (hydrophilic) [28]. By the application of ternary phase diagram, and modifying the rations of oil/ surfactant, SEDDS can be prepared experimentally, using the "trial–error" method [29].

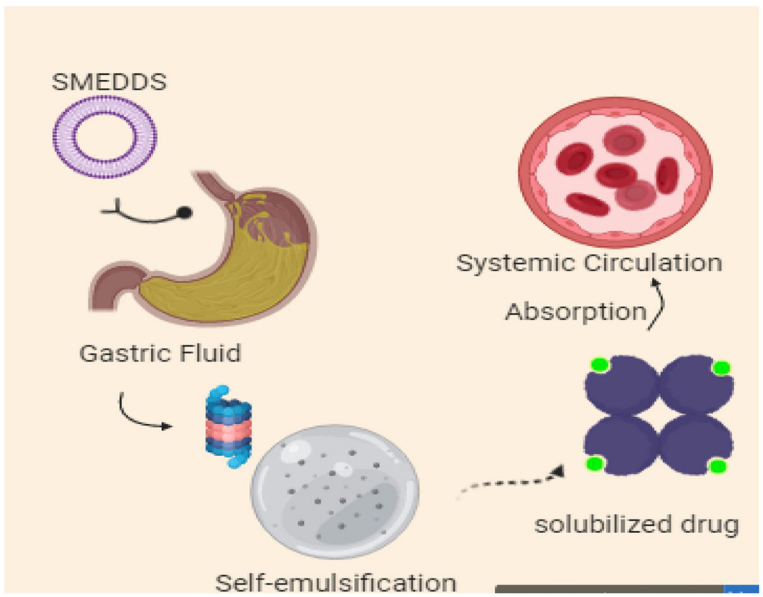

Fig. 1 Mechanism of self-emulsification

Advantages

Potential advantages of these systems (SEDDS) include the following:

1. Dose reduction by ability to improve the solubility
2. More steady chronological profiles of drug absorption
3. Specific absorption from targeted area
4. Drug protection from the unstable GIT surroundings
5. Control of delivery profiles
6. Reduction in variable drug action
7. Protection of susceptible drug substances
8. Enhanced drug potential
9. Available in both liquid and solid dosage forms
10. No/less, influence of lipid digestion on SEDDS
11. Drug dose can be reduced by these formulations.
12. Easy manufacturing and scaling up technique is used.
13. This formulation provides quick onset of action [29, 30].

Suitable drug candidates for SEDDS

Although SEDDS is suitable for all the four categories of BCS classification system, but the candidates that are required to be formulated as SEDDS fall under BCS class II and IV categories [31].

Application of SEDDS in drug solubility and dissolution

1. SEDDS aids in the incorporation of active pharmaceutical ingredients (API's) in a lipid vehicle imparting improved drug dissolution in an aqueous medium.
2. Improved drug dissolution affects the drug release and GI-absorption.
3. In addition, drug can easily penetrate into the surfactant interfacial layer, which enhances its penetration through membrane barriers and its efficacy [32].

Applications of self-nanoemulsifying drug delivery system and its novel approaches

1. Various novel advancements in SNEDDS include solid SNEDDS, super saturated SNEDDS, self-double emulsions (w/o/w), controlled release SNEDDS, SNEDDS for overcoming mucus gel barrier, delivery of biomolecules, and even drug targeting.
2. Super saturated SNEDDS include hydrophobic precipitation inhibitors that control drug precipitation, during storage, hence improving its stability.
3. Solidification of liquid SNEDDS (L-SNEDDS) inhibits the interaction of drug and excipients, interaction of liquid dosage with the capsule shell, etc.
4. Biomolecules with low bioavailability can be designed easily using SNEDDS, as they provide small droplet size and maximum surface area for the better penetration of molecules.
5. Other advancements like targeted SNEDDS, self-double SNEDDS have also gained popularity in increasing the solubility, bioavailability, and stability of molecules [33].

Dosage forms of SEDDS

Various dosage forms, such as capsules, sustained release, and controlled release tablets/pellets, dispersion systems can be easily formulated using self-emulsified dosage design. SEDDS is also suitable for other routes other than oral, like topical, ocular, pulmonary, and parenteral route [34].

Composition of self-emulsifying drug delivery systems

Self-emulsification process depends upon the following:

1. Nature and ratio of oils and surfactants
2. Concentration of surfactant
3. Temperature and time of self-emulsification [35]

Excipients used in the formulation of SEDDS

Oils

The most important and basic ingredient of SEDDS are oils, as they have the ability to dissolve lipid molecules and improve their solubility [36]. Depending upon the nature of triglycerides, drug transportation of the lipid drug is increased, via the lymphatic system. In addition, GIT absorption of the drug is also increased [37]. Generally, long and medium-chain triglycerides (LCT and MCT) are preferred for the formulation of SEDDS. The LCT and MCT are used with different degrees of saturation [38]. Dietary lipids undergo lipolysis, and are converted to monoglycerides and free fatty acids. Short-chain triglycerides (SCT) and MCT get absorbed quickly and reach the systemic circulation as soluble fatty acids. Whereas a different absorption is found for the LCT, as they get absorbed they esterify and forms chylomicrons. Triglycerides, apoproteins, cholesterol, and cholesterol ester comprises the chylomicrons. They are absorbed through the lymphatic uptake. This serves as a vehicle system here, for various lipophilic molecules, bypassing the liver [39].

List of oils used in the formulation of SEDDS/SMEDDS/SNEDDS:

1. Glyceryl monolinoleate

2. Maisine 35-1
3. Neobee M5
4. Miglyol 840
5. Labrafac lipophile WL139
6. Kolliphore RH 40
7. Oleic acid
8. Captex 200
9. Captex 355 EP/NF
10. Other vegetable ad edible oils (castor, sesame, olive, coconut, etc.)

Surfactants

Surfactants are having amphiphilic character. They help in the solubilization of lipophilic drug compounds. In the gastro intestinal lumen, this prevents precipitation of drug [40]. Hence, drug sustains in the GIL for a definitely longer time [32]. For the formulation of SEDDS, various compounds having surfactant properties can be used, but those having oral acceptance should be chosen [41]. Surfactants are of four types, namely cationic (quaternary ammonium halide), anionic (potassium laureate, sodium lauryl sulfate), ampholytic (sulfobetaines), and non-ionic surfactants [sorbitan esters (spans), polysorbates (tweens)] [42]. Among all the surfactants, the most preferable ones are the non-ionic surfactants, having relatively high hydrophilic-lipophilic balance (HLB) [43]. Optimum concentration of surfactants, for the formulation of a stable SEDDS is 30-60% [35, 44–46].

Surfactants are grouped as follows:

- Anionic surfactants
- Cationic surfactant
- Ampholytic surfactants
- Non-ionic surfactants
  (a) Anionic surfactants—in this class, the hydrophilic group carries a negative charge, for example, carboxyl (RCOO-), sulfonate (RSO3-), or sulfate (ROSO3-).
  (b) Cationic surfactants—in this class, the hydrophilic group carries a positive charge.
  (c) Ampholytic surfactants—(also called zwitterionic surfactants) contain both a negative and a positive charge.
  (d) Non-ionic surfactants—in this class, the hydrophilic group carries no charge but imparts water solubility from its polar groups such as hydroxyl or polyoxyethylene (Tweens) [44].

Biosurfactants

Surfactants may alter the therapeutic efficacy of the drug molecule, as its concentration may vary and as a result may hamper the availability of the rug at the absorption site. It may also produce some toxicity at various concentrations. This can be overcome by the use of biosurfactants in place of normal surfactants. Biosurfactants increase the safety and decrease toxicity associated with the gastric irritation caused by the surfactants [47].

Co-solvents

Organic solvents are one of the best options to be used as co-solvents for SEDDS, such as ethanol, propylene glycol, and polyethylene glycol, this aid in the increased solubility of lipid drugs [5]. Higher concentrations of surfactant are required for the optimum formulation of SEDDS, but this higher concentration may lead to the drug precipitation [48]. Therefore, co-solvents are added to lower the surfactant concentration and maintain the uniformity of the formulation [4, 49].

Co-surfactant

In addition to co-surfactant, the concentration of surfactants can be decreased, as it increases the loading capacity of the active pharmaceutical compound. Co-surfactants increase the interfacial fluidity and hence reduce the chances of variability and local irritation caused by surfactants also enhancing the process of dispersion in the medium [50]. Ethanol, propylene glycol, and other newer co-surfactants such as transcutol P and Glycofurol are a few of common excipients used as co-surfactants [51].

Some examples of co-surfactants and co-solvents:

1. Mixture of glycerol an ethanol
2. Transcutol
3. Capmul MCM
4. Glycerol
5. Polyethylene glycol
6. PEG 400
7. Glycofurol

Newer components of formulation in SEDDS and SMEDDS

SEDDS and SMEDDS have gained popularity among other nanoparticle dosage forms in many ways. Further modifications on SEDDS and SMEDDS are done by including some more new components that can enhance drug absorption. However, the selection of these components largely depends on the proper ratio of the mixture of oil and surfactant along with the co-surfactant and co-solvents. Still, some modifications have been made for the enhancement and stability of such formulations. These include the inclusion of adsorbents like silica gel and neusilin to solidify the liquid formulation. Grafted polymers are being use as modifiers such as, aeroperl and soluplus. Along with the components, various techniques are being adopted for improving the stability and efficacy of these dosage forms [52].

Role of polymers in SEDDS and SMEDDS formulation

The below Table 2 summarizes a few of polymers along with few excipients which plays different roles in the design and optimization of SEDDS and SMEDDS.

Importance of emulsion droplet size on drug absorption

Globule size of the particles in microemulsion is the factor affecting the bioavailability at different levels [55]. It has been stated that dispersion at nano-scale affects the rate of drug absorption, but it cannot be said exactly that lower droplet size will enhance the bioavailability of the drugs [56]. Yap and Yuen stated that bioavailability of tocotrienol SEDDS from two microemulsions, one of which is very prone to lipolysis while another with minor emulsion globule range, showed similar results, regardless of the droplet size [57].

Challenges of using S-SMEDS in food and pharmaceutical industries

In order to lower the surface tension between the two phases, higher concentrations of surfactant and co-surfactant are required, this may lead to the increase in toxicity [58]. Although the cytotoxicity of surfactants, which are, generally used in food and pharmaceutical systems, has been widely studied, little is known about the toxicity of surfactants in microemulsions and especially in solid self-emulsifying drug delivery systems (S-SMEDDS). Some studies reported that the toxicity of a surfactant would change in these systems [59]. For example, Warisnoicharoen et al. established a fact that using Brij97 (polyoxyethylene-10-oleyl ether) alone or in a combined form with low molecular weight (LMW) oils was toxic over a range above its critical aggregation concentration [60]. However, a combination of Brij97 with high molecular weight oils (e.g., Miglyol 812 and soybean oil) was observed to be toxic only at levels higher than the critical aggregation concentration [5, 61]. The formation of a distinct oil core in the aggregates, which resulted in lowering the ability of the system to solubilize the cell membrane components, was suggested to be the reason of reducing the toxicity of the high molecular weight oil microemulsions. Some researchers and scientists found that the cell toxicity of single components of vitamin E microemulsions (e.g., El-35 and ethyl butyrate) was higher than that of the microemulsions [62]. Some researchers and scientists evaluated the cytotoxicity of β-carotene microemulsions prepared from Tween 80 and medium-chain triglycerides (Capmul MCM) [46]. An increase in toxicity was observed at concentration higher than 0.0313% when Tween 80 interacted with the cell culture monolayer [63]. According to the recent research, it was found that microemulsions and SEDDS formulation of atrovastatin was cytotoxic, with the use of isopropyl myristate, a combination of 2 biocompatible surfactants: lecithin/D-α-tocopheryl polyethylene glycol succinate (TPGS) and ethanol as co-surfactant [64]. The S-SMEDDS formulations prepared with lecithin-20 had highest in vitro cytotoxicity and lowest IC50 than those prepared with lecithin-100 [65]

Enhancement of stability through SEDDS and SMEDDS

With the formulation of SEDDS and SMEDDS, researchers have found that the formulation design is optimum for the lipophilic drugs. Enhancement of oral solubility and bioavailability is proven parameters for these systems. However, there are some drawbacks like physical stability and pharmacokinetics of the formulation system, which has to be overcome. Certain modifications have been made regarding the issues raised. One of which is the formation of the liquid preconcentrate to its solid form. Liquid solid compacts are one such modifications, these are a mixture of liquid preconcentrate

Table 2 Role of polymers

S. no	Polymer used	Role of polymer	Reference
1.	Polyvinyl caprolactam-polyvinyl acetatepolyethylene glycol graft copolymer (Soluplus®) and Aeroperl® 300 Pharma	Formation of spray-dried solid dispersion	[52]
2.	Stearic acid phosphotyrosine	Zeta potential modifier in SEDDS	[53]
3.	Polyvinylpyrrolidone (PVP) VA64 and sodiumdodecyl sulfate (SDS)	Combined stabilizers	[16]
4.	Soluplus® mixed with D-α-tocopheryl polyethylene glycol-1000-succinate (TPGS)	Formation of micelles for improved stability and bioavailability	[14]
5.	Soluplus	Supersaturation stabilizer	[27]
6.	Neusilin US2® - (excipient)	Solidification	[43]
7.	Precipitated papain	Mucus permeation enhancer	[42]
8.	Fujicalin (dibasic calcium phosphate) - (excipient)	Porous carrier as adsorbent	[54]

Table 3 List of drugs formulated as solid/liquid self-micro emulsified drug delivery systems (SMEDDS)

Drug	Oils	Surfactant/co-surfactant	Formualtion type	Therapeutic outcome	Ref.
Silybin	Labrafac	Cremophore RH40/transcutol	Supersaturatable self-emulsifying drug delivery system (S-SEDDS)	Enhanced oral bioavailability	[6]
Fenofibrate	Medium-chain triglyceride oil (Myritol 318),	TPGS (D-a-tocopheryl polyethylene glycol 1000 succinate) and polysorbate (Tween 80 or Tween 20)	Self-microemulsifying drug delivery system (SMEDDS)	Increased oral bioavailability	[13]
Rosuvastatin calcium	Capmul MCM	Cremophore ELP/Propylene Glycol	Solid self-emulsifying drug delivery system	Improved bioavailability	[19]
Celastrol	Corn oil, soybean oil, ethyl oleate, GTCC, IPM, castor oil, masine-1, olive oil, IPP	Labrafil M1944, Labrasol, OP-10/ Transcutol P	Solid self-microemulsifying dispersible tablets	Increased bioavailability	[26]
Alginate and curcuin	Cremophor EL, Larafac PG, Capryol 90	Labrasol, Sodium CMC (absorbent), Aerosil 200	Curcumin loaded solid SMEDDS designed by freeze-drying technique	Enhance the release profile of drug	[28]
Dutasteride	Capryol 90	Cremophore EL/transcutol HP	Gelatin micropatrticles of a self-emulsified system	Enhanced oral bioavailability of dutasteride	[34]
Dutasteride	Capryol 90	Cremophore EL/ Transcutol HP	Soluplus-based supersaturable self-emulsifying drug delivery system	Improved oral absorption of dutasteride	[35]
Carbamazepine	Caprylic/ Capric triglycerides	Polysorbate 80/cremophore-RH 40	Solid self-microemulsifying drug delivery systems	Improved drug release and increase bioavailability	[45]
ELQ – 331 (antimalarial prodrug)	Tween-20, Span® 85, PEG 400 and sodium lauryl sulfate	Tween-20, Span® 85, PEG 400 and sodium lauryl sulfate	Preparation of spray dried dispersions and its comparison	Described the effect on the solubility and bioavailability of prodrug	[52]
Glyburide	Capryol 90, Lauroglycol 90, Labrafac Hydro WL 1219, polyglyceryl-3 dioleate	Labrasol, Tween 20/glycofurol, transcutol, PEG 400	fast-dissolving solid self-microemulsifying tablets	Improve dissolution and technological properties	[58]
Ritonavir	Imwitor 988	Cremophore EL and cremophore RH 40 (1:1)/capmul GMS K-50	Solid self-microemulsifying drug delivery system	Enhance dissolution and oral bioavailability of drug	[67]
Simvastatin	Capryol 90	Kolliphor EL/transcutol P	Self-emulsifying drug delivery system	Improved drug release	[68]
Carbamazepine	Mygliol 812	Cremophor EL/macrogol 400	Solid self-microemulsifying drug delivery systems (S-SMEDDS)	Increase in dissolution rate compared to pure Carbamazepine	[69]
Naproxen	Miglyol 812	Gelucire 44/14	Tablets and mini-tablets of spray dried SMEDDS	Lowered dissolution profile of naproxen from tablets and minitablets	[70]
Atrovastatin	Oleic acid and capryol 90	Caprol MPGO, Kolliphor RH40, Labrasol and Tween 80/PEG 400 and 1,2-propylene glycol	Liquid and solid Self-Emulsifying Drug Delivery Systems	better solubilization properties exhibited by solid formulation	[71]
Atorvastatin	Isopropyl myristate	lecithin/D-a-tocopheryl polyethylene glycol succinate/ethanol	Spray-dried self-microemulsifying drug delivery systems	Enhanced the cytotoxic activity on lung cancer cells	[72]
Paprika Oleoresin (carotenoid)	Limonene	Tween 80/ethanol	Solid self-microemulsifying system	Enhanced bioavailability and pigmentation	[73]
Naproxen	Miglyol 812	Gelucire 44/14/glycerin	Solid SMEDDS	Preserved the self-microemulsifying properties of liquid SMEDDS & exhibited dissolution profiles similar to liquid SMEDDS	[74]
Atorvastatin	Coconut oil and Isopropyl myristate	Tween 80/PEG 400 and glycerin	Solid self-micro emulsification system	Improve bioavailability	[75]

Table 3 List of drugs formulated as solid/liquid self-micro emulsified drug delivery systems (SMEDDS) *(Continued)*

Drug	Oils	Surfactant/co-surfactant	Formualtion type	Therapeutic outcome	Ref.
Mefanamic Acid	clove oil, olive oil and rice bran oil, Imwitor 742	Tween 60, cremophore El/transcutol HP	Self-emulsifying formulation	Enhance solubility	[76]
Atrovastatin calcium	Capmul® MCM	Tween® 20/tetraglycol	Solidified self-microemulsifying drug delivery system	Improve dissolution and bioavailability	[77]
Mebendazole	Labrafil 2125 CS	Tween 20/maisine 35-1	Self-microemulsifying drug delivery System	Improve dissolution and bioavailability	[78]
Huperzin	CremophorRH40	Propylene glycol	Self-microemusifying drug delivery system	Enhancing bioavailability and lymphatic uptake of the drug	[79]
Curcumin	Caprylic acid, cremophor RH 40, cremophor EL	Tween 80 and PEG 200	Vaginal self-emulsifying delivery system	Enhancement of drug penetration	[80]
Cathepsin K inhibitor (HL235)	Capmul MCM EP	Tween 20 (surfactant) and 20.0% carbitol (cosurfactant)	SEDDS were prepared by applying D-optimal mixture design	Improve drug solubility and drug loading. Increase bioavailability	[81]
Ferulic acid	Glyceryl triacetate, OP-10, Labrasol combination	PEG 400	Preparation of SMEDDS for	Enhancement of oral solubility of drug with improved hypnotic activity	[82]
Kaempferol and quercetin from plant Moringa oliefera	CrodamolTM P C (propylene glycol dicaprylocaprate)	Tween® 80 and polyethylene glycol 400	SMEDDS	Enhancement of solubility of the flavonoids	[83]
Nilotinib	Capryol 90	Transcutol HP and Tween 80	SMEDDS	Enhancement of solubility of the drug	[84]

with a non-volatile solvent, further converted to a solid form by adsorption to a solid carrier. This is a simple and advanced technique to enhance the stability of liquid SEDDS, bypassing its instability in liquid state [66].

Table 3 includes a detailed study of drugs formulated as liquid/solid SMEDDS and their therapeutic outcomes, and Table 4 includes a detailed study of drugs formulated as liquid/solid SNEDDS and their therapeutic outcomes.

Conclusion

As stated in the literature and with a brief review, it can be now said that SEDDS is a better approach for the formulation and development of delivery systems for low solubility and/or low permeability drugs, to facilitate their dissolution and absorption. The process of manufacturing is excellent and simple and with the use of conventional and commonly available equipments.

Table 4 List of drugs formulated as solid/liquid self-nano emulsified drug delivery systems (SNEDDS)

Drug	Oils	Surfactant/co-surfactant	Formualtion type	Therapeutic outcome	Ref.
Naringenin	Triacetin	Tween 80/transcutol P	Self-nanoemulsifying drug delivery system	Improve oral bioavailability	[1]
Talinolol	Triacetin, Miglyol 812, castor oil, isopropyl myristate, soybean oil, and olive oil	Span 20, Span 80, Labrafac PG, Plurol Oleique, and Lauroglycol 90/ethanol, PEG 200, PEG 400, propylene glycol	Self-nanoemulsifying drug delivery system (SNEDDS)	Improved permeability of drug	[7]
Glyburide	Miglyol 812, Ethyl oleate	Tween 80, Cremophore RH 40/1,2-pranpanediol, PEG 400	Self-nanoemulsifying drug delivery system	Improved oral bioavailability	[20]
Atazanavir	Maisine 35-1	Transcutol P and Span 20	Self-nanoemulsifying drug delivery system	Enhance oral bioavailability	[29]
β-carotene	Corn oil, orange oil	Tween 80	Nanoemulsion-based delivery systems formed by spontaneous emulsification	β-carotene bioaccessibility increased due to greater solubilization in mixed micelles	[85]
Resveratrol	Imwitor	Transcutol, Tween 80	Nanoemulsion-based delivery systems formed by spontaneous emulsification	Developed a method which can measure the emulsification of SEDDS	[86]

Abbreviations

SEDDS: Self-emulsifying drug delivery systems; GIT: Gastrointestinal tract; LFCS: Lipid formulation classification; SMEDDS: Self-microemulsifying drug delivery systems; SNEDDS: Self-nanoemulsifying drug delivery systems; BCS: Biopharmaceutical classification system; LCT: Long chain triglycerides; MCT: Medium chain triglycerides; S-SMEDDS: Solid self-emulsifying drug delivery systems; LMW: Low molecular weight; TPGS: Tocopheryl polyethylene glycol succinate; SLN: Solid lipid Nanoparticles; NLC: Nanostructured lipid carriers; HLB: Hydrophilic lipophilic balance

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Authors' contributions

PB complied and designed the final manuscript data. She collected the basic informations by literature survey and formatted the blinded manuscript as review of self-emulsifying drug delivery systems. AR checked the initially manuscript format and grammatically corrected the blinded manuscript. SV did the final editing of the manuscript. TS contribute in the designing the conclusion part of the manuscript. SB contributed in the designing and final editing of collected manuscript data. He also checked for the plagiarism of the manuscript and edited the final manuscript accordingly. All authors have read and approved the manuscript.

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