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Approaches to Improve bioavailability and oral absorption of low water-soluble drug by self- emulsifying drug delivery system

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Abstract

Self-emulsifying drug delivery system (SEDDS), a type of lipid-based technology which are isotropic mixtures of oil, surfactant, solvent, and co-solvents generated by the activity of liquid or solid self-emulsifying ingredients onto powders. It shown interest in the recently for enhancement of solubility and bioavailability of poorly water-soluble drugs (BCS-II). With the novelty of research in this field, novel Excipients have been design with novel properties for enhances solubility, Bioavailabity and oral absorption to achieving target response. Self-emulsifying drug delivery systems (SEDDS) emerged as an insightful approach for delivering highly hydrophobic entities to enhance their bioavailability. SEDDS increase drug bioavailability in addition to improving the solubility of poorly soluble drugs by a number of additional potential pathways, such as avoiding the hepatic first-pass effect, blocking P-gp efflux, and overcoming resistance to metabolism by the cytochrome P450 family of enzymes in the gut and liver. Conventional SEDDS were developed in a liquid form which owned numerous overcome like low stability and drug loading efficiency, fewer choices of dosage forms and irreversible precipitation of drug or excipients. To address these curbs solid-SEDDS (S-SEDDS) was introduced as an efficient strategy that combined advantages of solid dosage forms such as increased stability, portability and patient compliance along with substantial improvement in the bioavailability. This review highlights parts of SEDDS, and their characterization evaluation. Which are completely summarized via different techniques.

Keywords: Self-emulsifying drug delivery systems (SEDDS); Lipophilic drugs; lipids; Surfactant; Co-surfactant; Oral absorption; Oral bioavailability; Characterization and evaluation

1. Introduction

SEDDS is a Novel formulation employed to increase solubility and consequently the bioavailability of poorly water soluble drugs such as BCS Class-II drug include Bilastine, Vitamin-E, monoxidil, posoconazole, etoricoxib, safinamide, eltrombopag olamine, brexpiprazole, ketoprofen, indomethacin and hydrocortisone. The BCS Class-II Drugs exhibit poor aqueous solubility, which affects their low bioavailability, variable absorption after oral delivery [1]. There are formulations strategies have been described to increase the dissolution rate of drugs by reducing their particle size (agitation, high energy approach) and salt formation, using excipient such as lipids surfactants, co-surfactant, and cyclodextrins for SEDDS based formulation. A relatively new approach for poorly soluble drugs is lipid-based formulations, particularly self-emulsifying drug delivery systems (SEDDS). SEDDS are isotropic mixtures of oils and surfactants with or without co-surfactants, which act as lipid-based formulations after oral application in aqueous gastrointestinal fluid and upon gentle agitation can form an oil-in-water emulsion [1-3].

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Due to patient compliance and convenience of administration, oral route of administration is the most favored route of administration. Despite the significant benefits of this route, it frequently has low bioavailability either because to poor water solubility, permeability, or medication dissolution rate. A formulator faces a significant hurdle when creating a successful product: improving oral bioavailability [2]. Due to their weak water solubility, class II drugs under the biopharmaceutical classification system frequently have a low oral bioavailability. The development of lipid-based drug delivery systems has become a key formulation approaches to address difficulties with inadequate bioavailability out of the many options that are currently accessible [4].

Moreover, many novelty of technology have been developed to the impact of the self-emulsification process on the drug may result in a shift in droplet size distribution that varies with the drug's concentration. It is important to note that emulsions with smaller oil droplets in more complex preparations are more susceptible to alterations brought on by the addition of drugs substance. Pre-formulation solubility investigations are therefore significant for the creation of an appropriate SEEDS that applies significant sheer stress [5,6]. Turbulence and hydrodynamics are two hypotheses that can account for droplet size. By using this technique, nano-emulsion with droplet sizes under 100 nm can be created (Table-1). The type of homogenizer, the makeup of the sample, and the working conditions of the homogenizer, including time, intensity, and temperature, all have a role in the generation of droplet size of nanoemulsion utilizing high pressure homogenizers. Nanoemulsion production frequently uses high pressure homogenization [1, 3, 6].

Table 1 Difference between SEDDS and SNEDDS

Property	**SEDDS**	**SNEDDS**
Mean globule size	>300 nm	< 100 nm
Appearance	Turbid	Optically clear
HLB value	< 12	< 12
Classification as per LFCS	Type II	Type IIIb
Concentration of oil	40–80%	> 20%
Concentration of surfactant	30–40%	40-80%

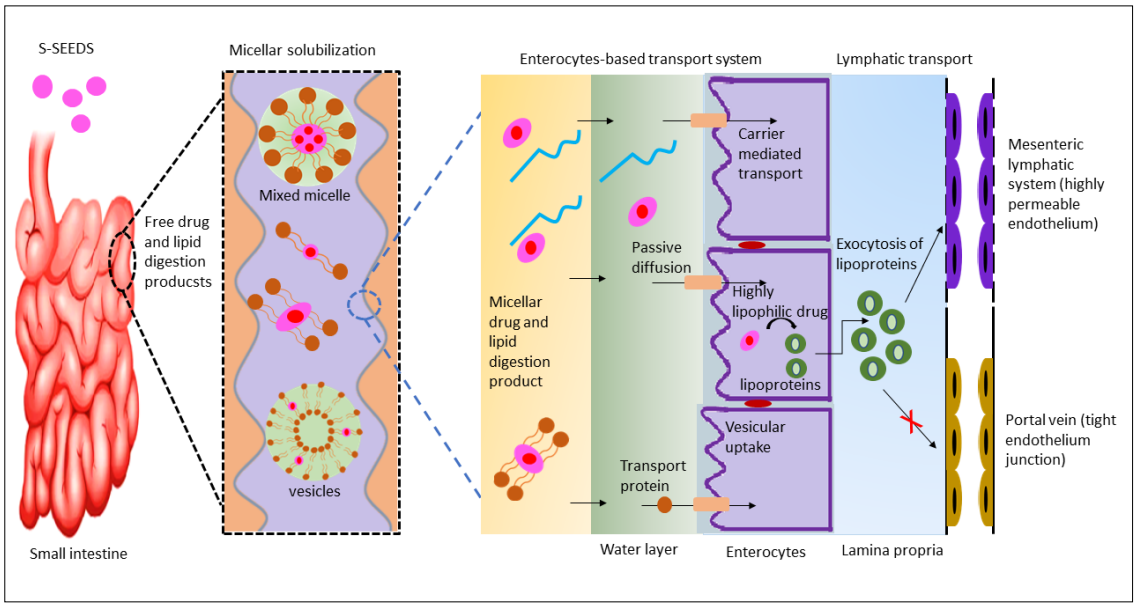


Figure 1 Mechanism of drug absorption from small intestine

SEDDS delivery system enhance the solubilization of active ingredients by creating a lipid Base emulsion and a concentration gradient that directs lipid loaded drug transport to the proper intestinal tissues absorption for site action. The performance of such a delivery system in vivo depends more on how it behaves in the gastrointestinal tract than

on its particle size. Lipid-based formulations provide effects that similar to the consumption of food [8]. The bile salt-lecithin-mixed micelles employed in the system solubilize the digested products of the lipids used in the system, which creates a fine colloidal dispersion that improves absorption [9,10]. For better understanding are shown in figure-1.

2. Significant role of Permeability glycoprotein (P-gp) in permeability, absorption and bioavailability of drug

The multidrug resistance gene (MDR) in humans produces the permeability glycoprotein (P-gp). It is the most widely distributed ATP-binding cassette (ABC) Tran membrane transporter ever discovered and the first [3]. Two homologous nucleotide binding domains and two homologous Tran's membrane domains make up the single polypeptide that makes up P-gp. For substrate binding and efflux, two Tran's membrane domains each made up of six Trans membrane helices combine to produce a single, broad, flexible channel. P-gp is linked to a series of dynamic conformational changes in the transporter, including dimerization of nucleotide binding domains, drug efflux, ATP hydrolysis, and restoration to the initial state. P-gp is expressed in the plasma membranes of the liver, kidney, bladder, blood-brain barrier cells, lungs, and, most importantly for oral drug administration, the esophagus, stomach, jejunum, and colon. P-gp transports molecules from inside cells to the extracellular space, preventing endogenous substances (including lipids, proteins, and metabolic products) and xenobiotics (like medications) from accumulating in cells [11-13]. As a result, P-gp affects absorption, distribution, metabolism, and excretion by pushing drug molecules back into the GI lumen, preventing them from entering organs like the brain, collaborating with cytochrome P450, and altering the function of the biliary and renal tubules, respectively [14].

3. Components of SEDDS

3.1. Drug substance

For the preparations of SEDDS Generally poorly water soluble drugs especially BCS-II Drugs (low solubility and high permeability) are used. It has lipophilic in nature with variable absorption pattern. BCS Class-II drug include Bilastine, vitamin E, monoxidil, posoconazole, etoricoxib, safinamide, eltrombopag olamine, brexpiprazole, etc [11, 14].

3.2. Lipids (Oil)

Table 2 Components of self-emulsifying drug delivery systems (SEDDS)

Component	Role	Example
Lipid (oil)	Solublizationand GI transit Increase Intestinal permeability Protect drug from degradation Lymphatic transport and Reduce food effect Inter-intra subject variability	Oleinacid, Caster oil, capryol 90, ethyl oleate, labrafil and capmul PG-8NF, Crodamol oil, , peceol, rose oil,
Surfactant	Solublization and emulsification Regulation the droplet sizeand release rate Inhibits of Pgp efflux CYP3A4, Help in opening of tight junction	Labrasol ALF, labraf IF, Tween 80,20,60, labrasol, span 80, 85, cremophore and kolliphore.
Co-surfactant	Solublization and emulsification Help in dispersion and make flexibility to interface Reduce the amount of surfactant	Cappryol, plurol oleique, Ethanol, isopropyl alcohol, 1-butanol, propylene glycol, transcutol HP
Drug	For the preparations of SEDDS Generally Poorly water soluble drugs Specially BCS-II Drugs are used.	BCS Class-II drug include Bilastine, vitamin E, monoxidil, posoconazole, etoricoxib, safinamide, eltrombopag olamine, brexpiprazole,

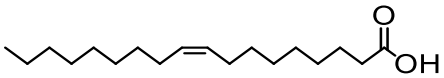
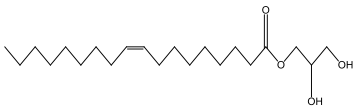
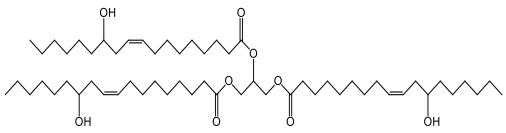
Oils are the most crucial excipients playing vital role in the SEDDS formulation to their ability to dissolve large amounts of lipophilic drugs. It improves transport through the lymphatic system. Moreover, lipidic parts cause secretion of bile and pancreatic juices resulting in the formation of mixed micelles comprising of bile salts, phospholipids and cholesterol [11, 15]. By virtue of such micelles formation, solubility of poorly soluble components is remarkably increased and increases the solubilization capacity of poorly soluble drugs in the GIT. Lipids exist in solid, semi-solid and liquid states and as described with examples in Triglycerides are commonly classified based on carbon chain length into short chain (SCT) composed of less than 5 carbon atoms, medium chain (MCT) consisting of 6–12 and long chain (LCT) consisting of 12–22 carbon atoms. Due to the short length of the carbon chain, MCTs directly diffuse through the gastrointestinal tract by the mechanism of passive diffusion into the portal system without undergo any molecular modifications. Lipids enable faster absorption from of the gastrointestinal tract compared to long-chain triglycerides and are preferred due to their greater capacity for drug dissolution and higher resistance to oxidation [16, 17]. Triglyceride vegetable oils are well absorbed and digested. Due to their safety profile resulting from their source of origin, are mostly preferred. They are a mixture of triglycerides from different chain lengths and saturation rates. But they find limited applications due to low content solubility of lipophilic drugs and poor self-dispersion properties (N) [18].

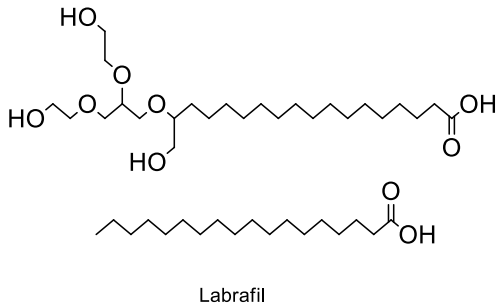
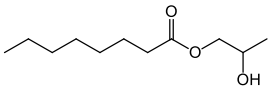
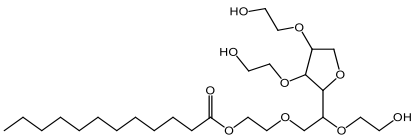
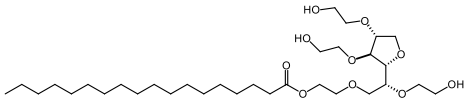
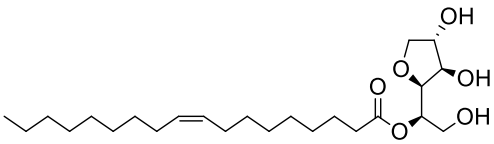
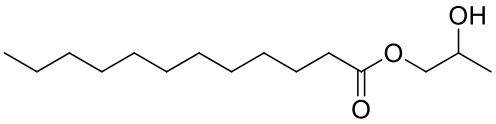
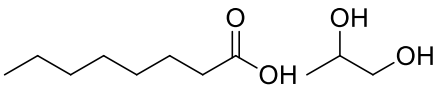
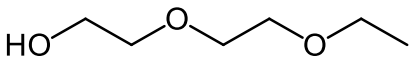
3.3. Surfactants

Surfactant is one of the essential components in the formulation, as they promote the emulsification properties (during the preparation of SEDDS, SEDDS able to lower the interfacial tension to a very small value which facilitates dispersion process). Surfactants, being amphiphilic in nature, can dissolve (or solubilize) relatively high amounts of hydrophobic drug compounds [12, 19]. The type and concentration of the surfactant showing effect on droplet size of micro- or nanoemulsion. Therefore, two significant factors that are hydrophilic-lipophilic balance (HLB) value and concentration of the surfactants. The mostly utilized emulsifiers include Tween 80, 20, 60, labrasol, cremophore and kolliphore Sorbitan mono oleate (Span 80), Polyoxy-40-hydrogenated castor oil (Cremophor RH40), and Polyoxyethylated glycerides. In selection of a surfactant, safety is an important factor. Surfactants which are obtained from natural origin are more safety to use the Synthetic surfactants emulsifiers [20]. Moreover, these surfactants have a limited capacity for self-emulsification. Emulsifiers from natural sources are seldom employed for the formulation of SEDDS. Ionic surfactants are shown to be more harmful than non-ionic surfactants but may induce reversible improvements in intestinal lumen permeability. Normally, to form stable formulations, the surfactant concentration varies from 30-40% w/w for SEDDS [21,22].

3.4. Co-surfactant

Table 3 Structure and Chemical Constituent

S.n	Excipient structure	Chemical constituent	HLB value
1	 Olein acid	Octaic-9-enoic acid or cis-9-octadecenoic acid	1-2
2	 Peceol	Glyceryl monooleate 40	1-2
3	 castor oil	Fatty acid and neutral lipids (triglycerides)	15

5	 Labrafil	Oleoyl macrogol glycerides	4
6	 capryol 90	Propylene glycol monocaprylate (type ii)	9-12
7	 Tween 20	Polyoxyethylene sorbitan monolaurate	16-17
8	 Tween 60	Polyoxyethylene sorbitan monostearate	14-15
	 Span 80	Sorbitan monooleate	4-5
7	 Lauroglycol 90	Propylene glycol mono- and di-esters of lauric acid(type ii)	4-5
9	 Capryol PGMC	Propylene glycol monocaprylate (type i)	4-5
10	 Transcutol HP	Diethylene glycol monoethyl ether	4-5

Whenever Low interfacial tension can sporadically be achieved with a single surfactant consequently, the addition of a co solvent or additional surfactant (co surfactant) is typically required. They can work together with surfactants to make the oil more soluble for the drug and more dispersible for the surfactant, making the nano-emulsion more stable and homogeneous [23]. By enhancing interfacial fluidity, the use of co surfactants or co solvents can lessen the surfactant's local irritancy and formulation dose variability. It has also been reported that the size distribution and the size of the

nano-emulsion area are significantly influenced by the weight ratio of the surfactant to the co surfactant or co solvent. Propylene glycol, ethanol, poly (ethylene glycol) (PEG), as well as more recent co solvents like Transcutol® HP, are all common co solvents. Co solvents, on the other hand, can improve drug solubilization in the formulation, but due to their polarity, their quantity should be kept to a minimum. Following aqueous dispersion, co solvents readily migrate toward the water phase, resulting in drug precipitation [1,3,24]. In addition, drug precipitation can occur when alcohols and other volatile co solvents evaporate into capsule shells. In addition to the components that have already been presented, additional components, such as antioxidants, viscosity enhancers, and components for modified drug release, may be utilized in the SEDDS and SNEDDS formulation are shown in table-2 [25].

4. Method of preparations of SEDDS

4.1. High pressure homogenizer

An homogenizer primarily comprises of a pump and a homogenizing valve from a technical perspective. For the preparation of nano-formulation The High pressure is required to fluid forced into the valve where the homogenization occurs using a pump. Fine emulsion is formed depending upon the application of high sheer stress. Turbulence and hydrodynamic are two theories that might be used to explain the droplet size. By using this technique, nano-emulsion with droplet sizes under 100 nm can be created [26]. The type of homogenizer, sample position, and operating settings of the homogenizer, such as time, intensity, and temperature, are all elements that affect the generation of droplet size of nanoemulsion utilizing high pressure homogenizers. The process of high pressure homogenization is frequently used to create nanoemulsion of components for food, medicine, and biotechnology [1,27].

4.2. High energy approach

The high energy technique, which results in the preparation of nanoemulsion by combining isotropic mixture of surfactants, oil, and co-solvent, calls for high mechanical energy. High energy techniques are used extensively during nanoemulsion formulation. High mechanical energies are utilized to break up big droplets into nanosized droplets, creating nanoemulsion with high kinetic energies. These form strong disruptive forces. Basically, SNEDDS rely on the phenomenon of self-emulsification and have low energy requirements [28,29].

4.3. Micro-fluidization

A device called a micro-fluidizer is necessary for the micro-fluidization process. The positive displacement pump forces the product towards the direction of the interaction chamber. A tiny droplet channel called a micro channel can be seen in this system. Following the formation of the product, it is transported by micro channels to the impingement area, where a nanoemulsion of incredibly small droplets is created. When the mixture of the aqueous phase and the oil phase is put to the homogenizer, a coarse emulsion is then created. The formation of a transparent and uniformly stable nanoemulsion results from additional processing [3,28,30].

4.4. Sonication method

Sonication method Sonication is one of the useful techniques for forming SNEDDS. Compared to other high-energy methods, ultra-sonication is superior in terms of cleaning and operation. The cavitations forces generated by ultrasonic waves break down macro emulsions into nanoemulsion during ultrasonic emulsifications. The emulsion shrinks to the size of Nanoparticles as a result of this process. The reduction in droplet size is caused by the sonication mechanism [3,29,31].

5. Material and methods

5.1. Materials

Pure drug API used in the study were purchased from different pharmaceutical/ chemical industrial/research laboratory [8,32]. The solvents and excipient were used for analytical calibration curve and preparation of SEDDS purchased from following pharmaceutical/ chemical industrial/research laboratory which are mention in below Table-4.

Table 4 Different drug substance and analytical grade Material

Material				Ref. no
Chemical	**Supplier laboratory**	**Solvent**	**Supplier laboratory**	
Chlorpromazine	Global Pharmaceutical Pvt. Ltd. Islamabad, Pakistan	Methanol	Sigma-Aldrich (Munich, Germany)	[8]
Ceftriaxone sodium	Avonchem, New Hampshire, UK) United Kingdom	Analytical grade	Sigma-Aldrich (Munich, Germany)	[18]
Resveratrol	Xian Lukee Bio-Tech Co., Ltd., (Xi'an, Shaanxi Sheng, People's Republic of China)	Analytical grade	Loba Chemie, Mumbai, India	
Itraconazol	Matrix Laboratories Ltd. (Hyderabad, India)	Analytical grade	Spectrochem (Mumbai, India).	[19]

5.2. Methods

5.2.1. Solubility studies

The solubility of gifted pure drug sample was determined in various natural oils (cotton seed oil, sunflower seed oil, and soybean oil), synthetic/semi synthetic oils (Capmul MCM EP, Labrafil 1944 CS, Labrail M2125 CS, Labrafil M2130 CS, ethyl oleate), and surfactants/co surfactants (Tween 20, Tween 80, PEG 400, Labrasol, Solutol HS 15, Carbitol, and Span 80). Adequate amounts of pure drug sample were added to 1 ml of each oil/surfactant and vortexes until completely dispersed (around 10 mints) [6, 32]. Then, the mixtures were kept in a isothermal shaking at 50 rpm and 37 ± 0.5 °C for 24 h, followed by homogenate centrifugation at 3000 rpm for 10 min or 5000rpm for 5 mint. The supernatants were collected and filtered through a 0.45 µm syringe filter and Dilute in mixed solvent system (dimethyl sulfoxide (DMSO) and Acetonitrile (ACN) (50:50, v/v)). The filtrates were assay by using UV-Visible spectrophotometer or high-performance liquid chromatography (HPLC) with a detector [30,33].

5.2.2. Selection of Surfactant and co surfactant:

According to the previously described procedure, the selection of surfactant was based on its emulsifying property. The number of inversions necessary to emulsify the lipid phase in water was examined to assess the emulsification capability of surfactants. Chosen oil (300 mg) was combined with an equal amount of different surfactants, and then heated to between 45 and 50 °C. Following the addition of the mixture to 30 ml of distilled water, the number of inversions necessary to emulsify the oil in aqueous medium was counted [34]. The resulting mixture may be left out for two hours, and a UV-vis spectrophotometer was used to measure the % transmittance at λmax nm while using distilled water as a control [35,36].

Furthermore, the selection of co-surfactant was made based on how well it would improve the surfactant's capacity for emulsification. The appropriate co-surfactant was chosen using a turbidimetric approach from a variety of co-surfactants. In order to achieve a chosen surfactant was combined in a 2:1 ratio with several co-surfactants, resulting in a mixture known as "S-mix." Oil was added to the S-mix in a 1:1 ratio after the mixtures were heated at 45–50 °C to homogenize the contents. Each resulting mixture (300 mg) might produce nano-emulsions by emulsifying with 30 ml of distilled water. Transparent nano-emulsions were tested for relative turbidity, let to stand for 2 hours, and then their percent transmittance was measured in accordance with the guidelines for surfactant screening [37,38].

5.2.3. Construction of Pseudo-Ternary Phase Diagrams

The ternary phase diagram was built using olive oil, Tween 80 (a surfactant), and propylene glycol (a co surfactant), which were chosen based on the findings of the saturation solubility investigations. In order to create a variety of formulations, different oil concentrations (10%, 15%, 20%, and 30%) were used [29]. Different weight ratios of surfactant and co surfactant (Smix) were combined at each oil percentage (1:1, 2:1, 3:1, 4:1, 1:2, 1:3, and 1:4, respectively). By combining the specified weight of each component in small glass vials, and then vortex mixing the mixture until a clear solution was obtained, these Smix ratios were chosen in increasing concentration of surfactant with respect to co surfactant and vice versa formulation were obtained and prepared. Up until usage, the mixes were kept at room temperature [29,39]. Visual analysis was used to examine the self-emulsifying abilities of SEDDS formulations. A magnetic stir bar was used to gently combine the contents of each formulation after an exact measured 0.2 ml of each formulation was added to 100 ml of water in a glass beaker at 37°C. On the basis of the emulsion's

apparent stability, clarity, and speed of emulsification, various formulations were grouped. The formulations were then given a "good" or "bad" rating depending on how easily the oil droplets dispersed in the water without further coalescence within a minute of addition and produced a clear emulsion with a bluish tint or if there was little to no emulsion formation and the oil droplets immediately coalesced.Phase diagram was constructed by identifying the good self-emulsifying region using custom design software [40]. The Common SEDDS formulation availabe in market, excipient used and their outcome are shown in table-5.

Table 5 Common SEDDS formulation, excipient and their outcome

Drug substance	Excipient	Outcome	Ref. No.
Chlorpromazine	Oil (captex, triacetin, linseed oil, and olive oil), surfactants (Tween 85), and ethanol.	1.5-fold increased elimination half-life ($p < 0.01$), up to 6-fold increased oral bioavailability, and 1.7-fold decreased plasma clearance rate ($p < 0.01$) compared to a drug suspension.	[8]
Clofazimine	Oils: olive oil Surfactants: Tween 80, co-surfactants (peg 400, peg 200, peg 600, span 60)	Clofazimine delivery could not be directly related to droplet size, size distribution and zeta-potential; where a reduced droplet size and increased zeta-potential normally meaningfully enhance rapid and increased drug permeation during dermal drug delivery	[18]
Itraconazole	Capryol 90, Labrasol, Tween 20 and Transcutol P	Ratios of oil's/CoS mixture in an attempt to increase its release rate and bioavailability.	[19]
Calcimimetic Cinacalcet HCl	Oil: peceol, capmul mcm, labrafac wl1349, triacetin, labrafac pg, captex 200p and captex 355 Surfactant: labrasol, kolliphor rh40, tween 80 and tween20 Co-solvent: lauroglycol 90, pleurol olique cc 497cg, peg 300, peg 400	Better dissolution profile with nearly 2.5 times cumulative % drug release than the pure drug in 30 min. In vivo studies showed threefold augmentations in oral bioavailability with increased Cmax and decreased Tmax for optimized formulation in comparison with aqueous suspension of pure drug	[36]
Rosuvastatin calcium	Oil: olive oil and cinnamon oil, (oleoyl polyoxyl-6 glycerides), labrafac® lipophile wl 1349 (caprylic capric triglyceride), labrasol® (caprylocaproyl macrogol-8 glycerides), peceol® (glyceryl monoloeate), Tween® 80 (polysorbate 80) and hydrochloric acid	Overcome its poor solubility, and augment its anticancer activity) % transmittance: 99.05±0.09% and highest drug solubility:80.52±2.57 mg/ml, globule size of 17.53±0.89 nm, a zeta potential of − 10.2±0.21 mv, and a cloud point of 88.5±0.54 °c	[37]
Senicapoc (potent antisickling agent)	Oil: capryol pgmc®, castor oil Surfactants: cremophor-el® and Tween® 80 Co-surfactants (transcutol hp® and peg 400) Surfactant: co surfactant in a 2:1 (w/w) ratio).	Investigations showed the potential of SNEDDSs to enhance the solubility and permeation of insoluble drugs such as SEN, although further preclinical studies are required before clinical trials can be conducted.	[40]
Ceftriaxone sodium (lower permeability and gastric instability)	Oil: cinnamon oil (43.33% w/w), soya bean oil, nutmeg oil, coconut oil, cinnamon oil, Surfactant:Tween 80 (30% w/w)	it was not be delivered orally due to its lower permeabilityso SNEDD formulation efficiently permeated across cell membrane and increase the drug oral bioavailability in animals	[42]

	Co-surfactant: propylene glycol (26.77% w/w), polyethylene glycol 400, polyethylene glycol 200 (peg 200)		
Curcumin (improved anti-cancer activity)	Tween 80, peg 200 and cinnamon oil were selected as surfactant (30%), co-surfactant (30%), and oil (40%).	Efficiently enhance CMN bioavailability, prevent its pre-mature metabolism and increase its intracellular delivery, Absorption and anticancer activity was high.	[44]
Candesartan (loaded self-nanoemulsifying drug delivery)	Oil: capmul Surfactant: pg-8 Co- solvent: kolliphor el	In vitro drug release study indicated up to 1.99- and 1.10-fold enhancement in dissolution rate from SNEDDS	[45]
Fexofenadine	Maisine 35-1 (monoglyceride/ diglyceride mixture) and Labrasol (HLB = 14) Propylene Glycol Dicaprylocaprate), and Capmul	Bioenhancer excipients were promising strategies for enhancing dissolution rate and thereby oral bioavailability of the fexofenadine	[49]

5.3. Preparation solid SEDDS

The formulations were prepared by dissolving a quantity of drug substance in the mixture of oil, surfactant and co-surfactant, at 40 ^{0}C in a water bath. This mixture was mixed by vertaxing until a transparent preparation was obtained. The formulation was equilibrated at ambient temperature for at least 48 hours to examine for any sign of turbidity or phase separation [29, 32]. The General Method of Preparation Solid SEDDS are shown in figure-2.

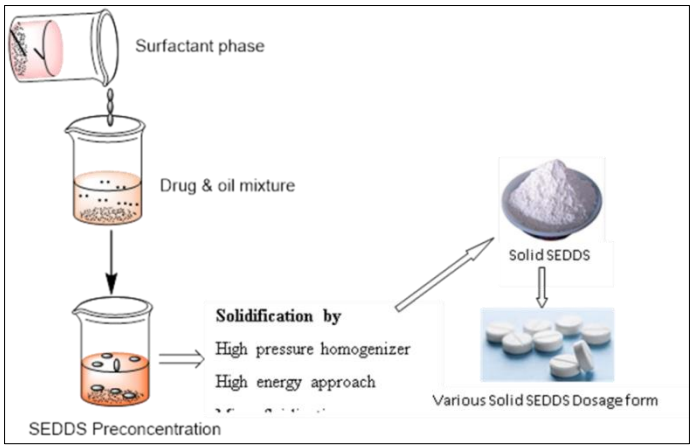


Figure 2 General Method of Preparation Solid SEDDS

5.4. Evaluation of SEDDS

Table 6 Common parameter and techniques used for SEDDS Characterization

S.N	Parameter	Evaluation of SEDDS Using following Techniques
Physicochemical Characterization		
1.	Droplet Size and Zeta Potential Analysis	Dynamic light scattering (DLS)
2.	Solid state characterization	Differential scanning Calorimetry (DSC), X-ray diffractometer
3.	Morphological characterization	Scanning electron microscopy
***In vitro* evaluation**		

4.	*In-vitro* studies	Dissolution apparatus
5.	*In vitro* permeation studies	Parallel artificial membrane permeability assay
6.	*In- vitro* lipolysis	pH stat model
7.	In-vivo pharmacokinetic study	*In-vivo* evaluation
8.	Clinical trials in Humans	Pharmacokinetic, bioequivalence toxicity, pharmacodynamic

Evaluation of the final SEDDS for various criteria is always significant. The following is a summary of the common parameter and techniques used for SEDDS characterization in Table-6 [2,33,50]:

5.4.1. Drug content

The required quantity of SEDDS formulation was taken and diluted in methanol. Volume was made up to 25 ml with methanol (1 mg/ml). 0.1 ml (100 ug) was withdrawn from the above solution and diluted up to 10 ml with methanol (10 ug/ml). Aliquots of 40ppm were injected into HPLC system, to analyze at given λmax [3,51].

5.4.2. Visual Assessment

Self-emulsification assessment is aided by visual observation. After water dilution of SEDDS, the presence of a clear, isotropic, transparent solution supports Microemulsion creation, but an opaque, milky white appearance shows macro emulsion evolution. Lack of precipitation and/or phase separation indicates the stability of the formulation [52].

5.4.3. Investigation of droplet size

The kind and concentration of the surfactant determine the size of the droplet. Optimal drug release, in vivo absorption, and stability depend on the micro emulsion's narrow droplet size distribution, which is created when SMEDDS is diluted with water. DLS techniques are used for droplet size analysis [53,54].

5.4.4. Determination Zeta Potential

Zeta potential determines the surface charge of the produced droplets in the dispersion liquid and informs the stability of the droplets. The electrophoretic mobility of the droplets is measured to find out. Although in the case of SEDDS, zeta potential is not more critical for evaluating the stability of the emulsion; the charge on the droplet plays a crucial role in enhancing drug absorption. This occurs because positively charged droplets interact with the negatively charged membrane in an efficient manner [55-57].

5.4.5. Time Required For Emulsification

The oil/surfactant and oil phase ratios influence how long it takes to emulsify a mixture [58]. This is determined using a basket dissolution apparatus, which monitors the generation of a clear solution as it is being stirred after formulation is added drop by drop to a water-filled basket.

5.4.6. Determination of cloud point

The temperature at which a homogeneous solution loses its transparency is known as the cloud point. The surfactant typically loses its capacity to produce micelles above the cloud point. It is discovered by gradually increasing the formulation's temperature and monitoring the turbidity spectrophotometrically [33,58]. The temperature at which the % transmittance starts to decline is known as the surfactant's cloud point. The cloud point of formulations should be greater than 37.5^{o}C to preserve self-emulsification [59].

5.4.7. Viscosity measurement

The required quantity of SEDDS was weighed and transferred to beaker and the viscosity of formulation was determined with the help of Brookfield Viscometer at 10 rpm for 5 min and the corresponding dial reading on the viscometer was noted [29, 60].

5.4.8. Liquefaction time

This analysis is done to find out how long Solid SEDDS take to melt in a GI environment that is simulative without moving. Transparent polyethylene film is used to cover the dose form, which is attached via thread to a thermometer's

bulb. After that, the thermometer should be kept at 37^{0}C while being submerged in a round-bottomed flask filled with 250 mL of simulated stomach juice devoid of pepsin. The time it takes for the liquefaction to occur is then recorded [30,61].

5.4.9. Test of thermodynamic stability

The Performance of a formulation depends on physical stability since chemical precipitation in the excipient matrix could be harmful. Excipient step separation can be caused by poor formulation physical stability, decreased bioavailability, and diminished therapeutic efficacy [62]. When the formulation and the gelatin shell of the capsule are incompatible, brittleness, softness, and delayed or partial medication release may result. These studies are conducted using the ensuing cycles [63].

5.4.10. Test for Transmittance

Transmittance is a quantifiable feature that can be used to calculate self-emulsification time and droplet size. A turbidity meter is used to measure the turbidity after a certain amount of SEDDS has been added to a set amount of acceptable medium while it has been continuously stirred at 50 rpm on a magnetic stirrer at the right temperature [47,64]. The rate of turbidity shift, or rate of emulsification, cannot be measured because the amount of time needed for full emulsification is too short. Following emulsification, the growth of droplets is monitored by turbidimetric analysis.

5.4.11. Dissolution Studies

Dissolution studies of SEDDS was carried out using USP Dissolution apparatus I (basket type) at speed of 50 rpm in 900 mL 0.1 N HCl at 37 ± 0.5^{o}C. In the experiment, one marketed capsule (100 mg) and four SEDDS filled were used for the dissolution studies. Aliquots of 5 mL were removed at 2, 5, 10, 15, 30, 45, 60, 75 and 120 min. Volume of aliquots was replaced with fresh dialyzing medium each time [65]. These samples were analyzed quantitatively for amount of Drug released at corresponding time by using UV–Visible spectrophotometer (Shimadzu UV-18000, at given λmax [12,30,66].

5.4.12. Release kinetics

To study the release kinetics, in vitro dissolution study was fitted in various data obtained from kinetic models: Zero order as cumulative percent of drug released versus time, first order as log cumulative percentage of drug remaining versus time and Higuchi's model as cumulative percent drug released versus square root of time, Hixon crowel describes the release from systems when there is a change in a surface area and diameter of particles respectively [12, 23]. To determine the mechanism of drug release, the data was fitted into Korsmeyer and Peppas equation as log cumulative percentage of drug released versus log time and the exponent n was calculated from slope of the straight line. For slab matrix, if exponent is 0.5, then diffusion mechanism is Fickian; if $0.5 < n < 1.0$, then it is anomalous transport. If n is 1.0, it is case II transport and if $n > 1.0$, then it is super case II transport [44,51,66].

6. Conclusion

After review of various self-emulsifying drug delivery system, SEDDS formulations increase solubility and consequently the bioavailability of poorly water soluble drugs, which allow better formulation versatility and characterization of lipidic excipients, offer a viable alternative to serve the desired purpose through physicochemical and physiological mechanisms controlling drug absorption. SEDDS increase drug bioavailability in addition to improving the solubility of poorly soluble drugs by a number of additional potential pathways, such as avoiding the hepatic first-pass effect, blocking P-gp efflux, and overcoming resistance to metabolism by the cytochrome P450 family of enzymes in the gut and liver.

SEDDS's tiny globule size and surface activity make it possible for drugs to pass through the intestinal boundary layer and absorptive brush border membranes more effectively, ultimately leading to a faster start and longer duration of therapeutic action. The heterogeneity in bioavailability is additionally decreased by SEDDS' reduced vulnerability to gastric emptying delays and GI tract lipolysis, as well as by their high thermodynamic stability and resistance to dilution, which keeps the drug in a solubilized state during the absorption phase.

The authors of this review paper study make an effort to give a comprehensive overview of all the component, method of preparation, and significant characterization and evaluation features of these self-emulsifying formulations. Its anticipate that this will give us the motivation we need scientists working on product development, enabling future development of the SEDDS research product.

Compliance with ethical standards

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Disclosure of conflict of interest

All the authors declare no conflict of interest.

Authors' contributions

Authors read and agreed with the final manuscript.

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