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REVIEW ARTICLE / DERLEME MAKALE

SELF EMULSIFYING DRUG DELIVERY SYSTEMS - AN OVERVIEW

KENDİLİĞİNDEN EMÜLSİFİYE OLABİLEN İLAÇ TAŞIYICI SİSTEMLER

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ABSTRACT

Objective: *Self-Emulsifying Drug Delivery System (SEDDS) has tremendous potential that has yet to be completely realized. They can be used in the formulation of drug compounds that have low water solubility in oral lipid administration and overcome many problems associated with these compounds. The SEDDS can increase the rate and degree of oral absorption by optimizing drug solubility in the intestinal absorption site, attributable to its small particle size, large surface area, high encapsulation efficiency, and high drug load. Furthermore, due to its lipid-based formulation, SEDDS can accelerate and increase pharmaceutical lymphatic transport, bypassing hepatic first-pass metabolism and therefore enhancing bioavailability.*
Result and Discussion: *The quantity of novel therapeutically effective lipophilic molecules that are hydrophobic has steadily increased thanks to innovative drug development approaches. The future of pharmaceutical research may not only pass through the discovery of new molecules but also better exploitation of those already known. The use of SEDDS has been proven to be quite successful in enhancing the oral bioavailability of hydrophobic and lipophilic drug molecules among the strategies to increase the oral bioavailability of these compounds.*
Keywords*:* *Drug solubility, emulsifying dosage forms, lipophilic drugs, self-emulsification, self-emulsifying delivery systems*

ÖZ

Amaç: *Kendiliğinden emülsifiye olan ilaç taşıyıcı sistemler (SEDDS), henüz tamamen aydınlatılmamış olan muazzam bir potansiyele sahiptir. Oral lipid uygulamasında suda çözünürlüğü düşük olan ilaç bileşiklerinin formülasyonunda kullanılabilirler ve bu bileşiklerle ilişkilendirilen birçok problemin üstesinden gelebilirler. SEDDS, küçük parçacık boyutuna, geniş yüzey alanına, yüksek kapsülleme etkinliğine ve yüksek ilaç yüküne atfedilebilen bağırsak emilim bölgesindeki ilaç çözünürlüğünü optimize ederek oral emilim oranını ve derecesini artırabilir. Ayrıca, lipit bazlı*

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formülasyonu nedeniyle SEDDS, hepatik ilk geçiş metabolizmasını atlayarak ve dolayısıyla biyoyararlanımı artırarak farmasötik lenfatik taşınmayı hızlandırabilir ve artırabilir.
Sonuç ve Tartışma: *Terapötik açıdan etkili olan yeni lipofilik hidrofobik moleküllerin miktarı, yenilikçi ilaç geliştirme yaklaşımları sayesinde istikrarlı bir şekilde artmıştır. Farmasötik araştırmaların geleceği, yalnızca yeni moleküllerin keşfedilmesinden değil, aynı zamanda halihazırda bilinenlerin daha iyi kullanılmasından da geçebilir. Bu bileşiklerin oral biyoyararlanımını artırma stratejilerinden hidrofobik ve lipofilik ilaç moleküllerinin oral biyoyararlanımını artırmada SEDDS kullanımının oldukça başarılı olduğu kanıtlanmıştır.*
Anahtar Kelimeler: *Emülsifiye dozaj formları, ilaç çözünürlüğü, kendiliğinden emülsifikasyon, kendiliğinden emülsifiye olabilen ilaç taşıyıcı sistemler, lipofilik ilaçlar*

INTRODUCTION

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].

The desired concentration of any drug to achieve its pharmacological response is based on its solubility majorly and thus it is very challenging for formulation scientists to maintain the pharmacological range of lipophilic drugs [1,2].

Classification of Lipid-Based Delivery Systems

The Biopharmaceutics Classification System (BCS) divides medications into four categories entrenched in their solubility and intestinal permeability, as determined by the United States Food and Drug Administration's (US FDA) statistics on intestinal drug absorption as described in table 1. In the formulation of SEDDS, class II medications that have great permeability and limited solubility are employed [3,4].

Table 1. Classification of lipid-based delivery systems

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 dispersion

Solubility Enhancement Techniques

To improve the therapeutic effectiveness of lipophilic drugs, researchers are working to improve their oral bioavailability.

To prevail drug solubility related problems, numerous formulation methods are practised such as the use of permeation enhancers, surfactants, lipids, salt formation, micronization, cyclodextrins, supercritical fluid process, and solid dispersions [5].

Some of the lipid-based formulations that have been utilized to increase the efficacy of weakly water-soluble bioactive compounds are liposomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), emulsions, and nanoemulsions. They improve water solubility by enhancing the solubilization and stability of lipid-based drugs, as well as offering a sustained, targeted, and triggered delivery mechanism [2,4]. Increased drug solubility can also be achieved using formulation approaches such as self-emulsifying formulations [6]. Some of these strategies are represented in Figure 1 [6,7].

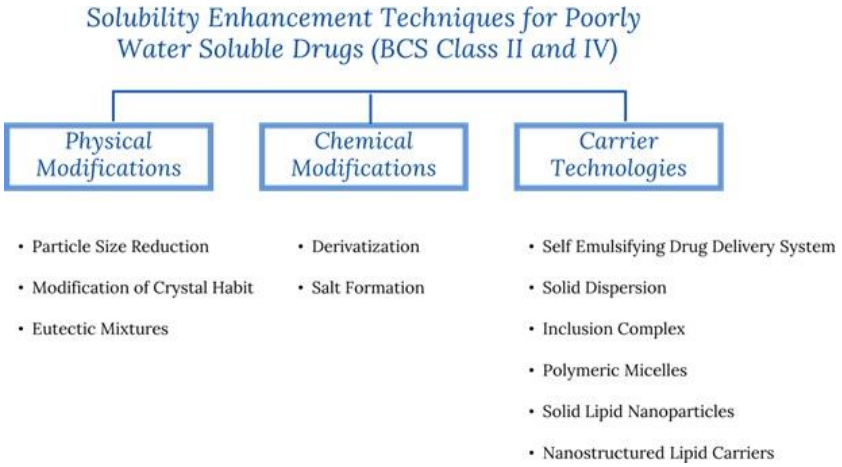

Figure 1. Several solubility improvement techniques for weakly water-soluble drugs

Self-Emulsifying Drug Delivery Systems (SEDDS)

"SEDDS are isotropic and thermodynamically stable systems consisting of oil, surfactant, co-solvent/co-surfactant, and drug components, which can form an oil/water microemulsion when mixed with water at low speed" [8].

The spontaneous formation of the emulsion in the gastrointestinal tract with slight agitation produced by stomach motility is the principle underlying SEDDS improving dissolving rate. The drug is delivered in a solubilized state, and the droplet's small size offers a large interfacial surface area for drug absorption [8,9].

The SEDDS can affect drug absorption in a variety of ways, including enhancing drug solubility, permeability, and lymphatic uptake [8,10]. When a SEDDS is taken orally (Figure 2), it is released into the GIT's (gastrointestinal tract) lumen and interacts with the GI fluid to generate micro or nano-emulsions. Oil droplets can quickly move through the stomach, increasing drug distribution throughout the GIT, and absorption by lymphatic way permits the drug to evade first-pass metabolism, enhancing drug oral bioavailability [10].

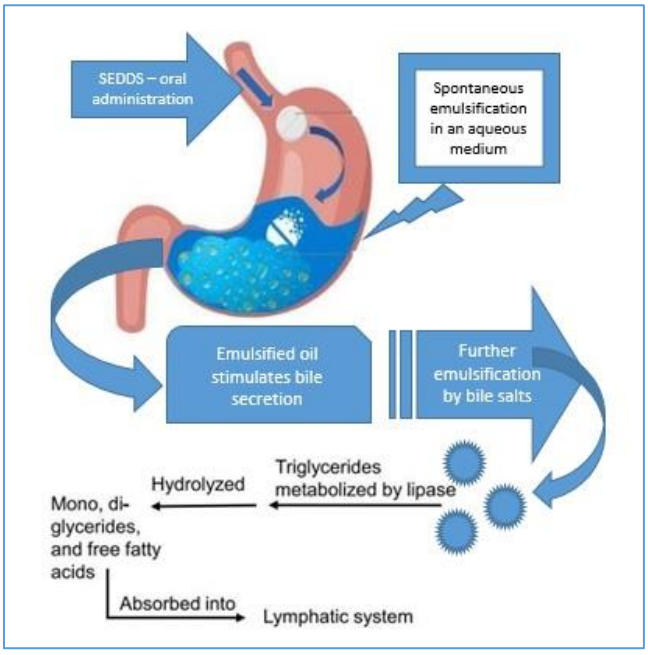

Figure 2. Oral absorption procedure of SEDDS

Self Nano-Emulsifying Drug Delivery System (SNEDDS)

SNEDDs are heterogeneous dispersions of two immiscible liquids with mean droplet sizes in the nanometer range (less than 100nm). Regardless of the method used to prepare it, this is especially important for medications that increase solubility, such as simvastatin and atorvastatin [11].

Self Micro-Emulsifying Drug Delivery System (SMEDDS)

When they encounter water, they make microemulsions (Figure 3). SMEDDS' emulsions have a mean droplet size that ranges from 100-250nm on a micrometric range. The fundamental distinction between traditional emulsions and microemulsions is the mean droplet size. Thermodynamically, SMEDDS are stable [3,8,11]. They produce optically clear emulsions. The surface area for absorption and dispersion is considerably improved due to the very small droplet size, and it quickly penetrates the gastrointestinal system and could be absorbed [3].

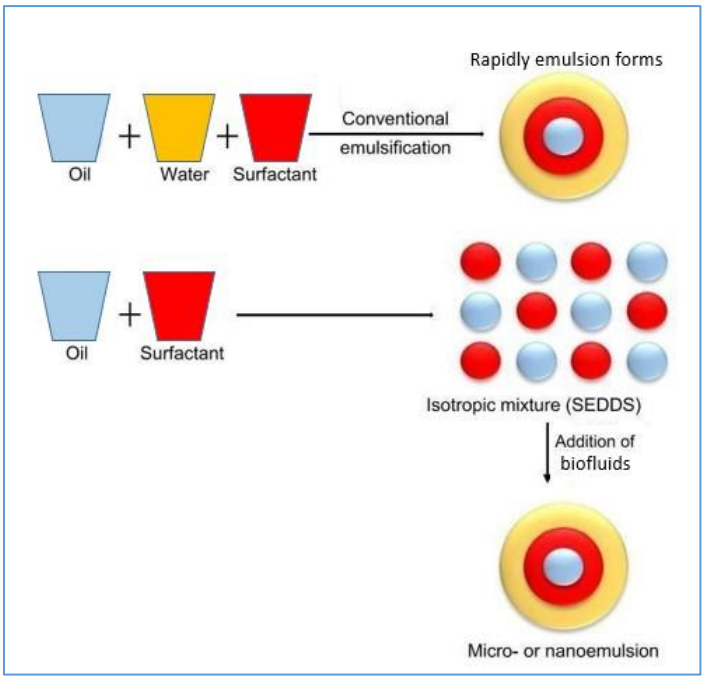

Figure 3. Illustration of the self-emulsification mechanism

Self-emulsification is a complicated process that is still being studied. On the other hand, as attested by some theories, self-emulsification happens at the time of the entropy shift, it promotes dispersion that is larger than the requisite energy to expand the dispersion surface area. The free energy of a traditional emulsion formation is proportional to the energy needed to produce a new surface between the two phases, and can be expressed using the following equation:

$$\Delta G = \sum N i \pi r 2 \, \sigma$$

Where ΔG represents the process's free energy (reckon without the mixing free energy), N indicates the number of droplets of Radius. The interfacial energy is represented by r and σ.

Throughout time intervals, separation of the emulsion's two phases will occur, lowering the area of the interface, so that, as a result, the system's free energy. Consequently, traditional emulsifying agents stabilize aqueous dilution emulsions by forming emulsion droplets surrounded by monolayer. As a result, the energy of the interface is lowered, and coalescence is prevented. Before the emulsification occurs spontaneously, in self-emulsifying systems, the free energy necessary to generate the emulsion is either extremely low but also positive or quite low and negative [12].

Application of SEDDS/SMEDDS Formulation

Improvement of Oral Absorption:

SEDDS partially eliminates the need for a second drug dissolving stage before absorption in the GIT. They improve drug absorption by increasing the quantity of solubilized drug in the intestinal liquids. Furthermore, incorporating lipid-based ingredients in the formulation may aid in medication absorption [9,13].

Retardation of Gastric Emptying Time:

Surfactants are thought to slow down gastric transit time, allowing the active pharmaceutical ingredient to be dissolved and absorbed more quickly. Surfactants can pace down gastric emptying for a while in the intestinal and gastric lumen by forming a viscous mass and enhancing the bioavailability of an investigational drug.

Increase in Effective Drug Solubility in Lumen:

Oral lipid-based formulations' biopharmaceutical characteristics and effective preparation development are strongly dependent on the lipidic transport route from the GI lumen to the systemic circulation. SEDDS passes through the digestive, absorptive, and circulatory stages after being taken orally [11,13].

Lymphatic Pathway:

Most of the drug delivery of SEDDS are absorbed systematically via the portal vein. The lymphatic system is a massive drainage system that runs across the whole body. It is located behind the blood flow system and is accountable for returning liquid that has seeped into the tissue space to the blood. Intestinal lymphatics are especially important for the absorption of lipid-digested substances, like longchain fatty acids and lipid-soluble vitamins [7,13].

Effect of P-glycoprotein (P-gp) Inhibition:

Reduction in P-gp drug efflux might contribute to an increase in the intake of SEDDS from the GIT. Moreover, to be a multidrug efflux pump, phase I metabolism by intestine cytochrome P450s has a substantial influence over oral bioavailability. In some cases, excipients in SEDDS/SMEDDS have been shown to block both pre-systemic drug metabolism and P-gp-mediated intestinal efflux, resulting in enhanced oral absorption of cytotoxic drugs [13].

Properties of SEDDS

SEDDS has the following properties:

1. They can self-emulsify fast in GI biofluids and create a fine o/w emulsion under theinfluence of peristaltic and other GIT motions [1,5,14].
2. Drugs (hydrophobic or hydrophilic) can be efficiently incorporated into the oilsurfactant mixture.
3. Suspension, emulsion, pills, pellets, and suppositories are all examples of liquid andsolid dose forms of SEDDs.
4. In comparison to traditional dosage forms, they require a lower drug dose [11-15].

Advantages

- The principal advantage is improving the oral bioavailability of lipid soluble medicines.
- They enable more steady drug absorption patterns, selective drug targeting to a particular absorption window in the GIT, and drug protection from the gastrointestinal tracts' hostile conditions, as well as protection of sensitive drugs.
- SEDDS' fine oil droplets are likely to move quickly and stimulate extensive drug dispersion down through GIT, reducing the discomfort commonly seen during prolonged contact between the gut wall and bulk medicine material.
- Variability reduction, including dietary effects.

- SEDDS has a greater drug loading capability than other lipid/oil-based formulations.
- SEDDS is unaffected by the lipid digesting process.
- The method is simple to manufacture and scale up.
- SEDDS can be applicable for both liquid and solid dosage types.
- SEDDS has a rapid onset of effect.
- Dose reduction by the ability to improve the solubility [9,14-17].

Disadvantages

- Traditional dissolution methods do not work because these formulations are potentially dependent on digestion prior to the release of the drug.
- This *in vitro* model needs further development and validation before its strength can be evaluated.
- Further development will be based on *in vitro – in vivo* correlations and therefore different prototype lipid-based formulations needs to be developed and tested *in vivo* in a suitable animal model.
- Chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) [13-17].

Composition of Self-Emulsifying Drug Delivery Systems

When selecting excipients, it is critical to evaluate the pharmacological acceptance of the excipientsas well as the toxicological problems of the ingredients.

Self-emulsification is based on:

- The type of oil and surfactant used
- The quantity of surfactant used
- The temperature at which self-emulsification occurs [17].

Components of SEDDS are depicted in Figure 4.

Active pharmaceutical ingredient (API)

They have the following characteristics:

- Drugs undergo significant hepatic metabolism.
- Drugs with sufficient half-life.
- Low dosage.
- A greater log P number shows that the drug has a high lipophilicity.
- Drugs in the BCS Class II (poor water solubility).
- The drug's bioavailability should be limited [6,11,17].

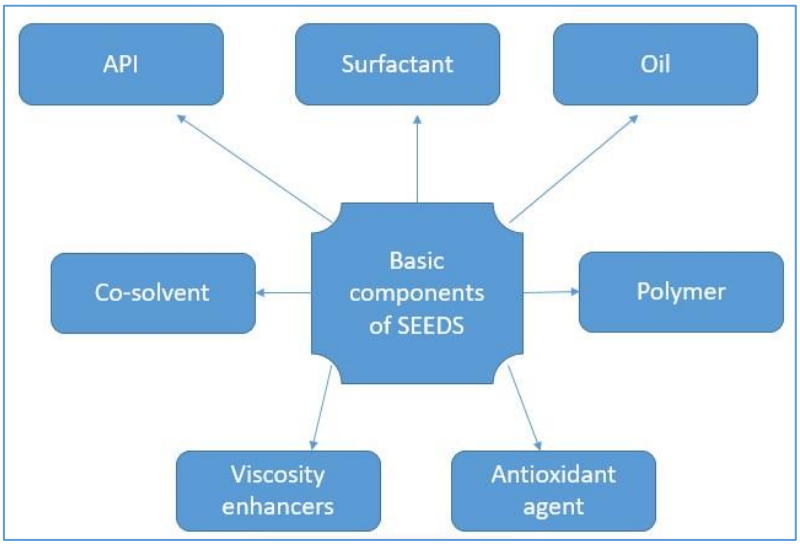

Figure 4. Basic components of SEDDS

Oil

Since oil solubilizes the needed amount of the lipophilic drug, it is the most critical excipient in SEDDS composition. It also serves to make self-emulsification easier. SEDDS are also known as self-emulsifying oil formulations due to the role of oil in them. In a SEDDS, natural or synthetic oils can be employed.

Oils improve lymphatic permeability in the intestines, solubility in the stomach and liquids in the intestines, shield the medicine from biotransformation, and increase the dissolution rate, these together enhance the bioavailability of oral lipophilic drugs [3,8,18].

Surfactants

"In the composition of SEDDS, nonionic surfactants having large HLB value are employed. Because non-ionic surfactants are not toxic, they are recommended over cationic and anionic surfactants in SEDDS" [3].

Many compounds with surfactant qualities may be useful in the development of SEDDSs, but the options are restricted since only surfactants appropriate for oral administration are applicable. One of the most crucial aspects while choosing a surfactant seems to be safety. Natural emulsifiers are favored over synthetic surfactants whereas they are thought to be safer. Non-ionic surfactants having a HLB (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.) are the most widely recommended [19].

For the development of stable SEDDS, the surfactant concentration normally varies between 30-60% w/w of the formula's composition. This high concentration of surfactants causes gastrointestinal distress, which is a disadvantage of SEDDS.

Surfactants included in the SEDDS formulation enhance bioavailability through a variety of methods, including increased intestinal epithelial permeability, decreased or blocked drug efflux of p-glycoprotein, improved active pharmaceutical ingredient solubility.

Co-solvent

Co-solvents aid in the dissolution of phases that are immiscible in a formulation (o/w). In the oil phase, co-solvents dissolve significant quantities of hydrophilic surfactants or hydrophobic drug. One or more hydrophilic solvents can be employed.

In order to develop an efficient self-emulsifying system, comparatively large concentrations of surfactants (typically bigger than 30% w/w) are needed, which tends to produce GI irritation [16]. As a result, co-solvents are utilized to decrease the surfactant amount. When combined with surfactants, they lower interfacial tension to an extravagantly small, even temporarily negative value. When this number is reached, the interface extends to form finely dispersed droplets, which absorb more surfactant and surfactant with co-surfactant until their bulk state is diminished sufficiently to reestablish positive interfacial tension [11,15]. This is known as spontaneous emulsification, and it is what inevitably leads to emulsions.

Polymers

In SEDDS, around 5-40% w/w Polymer matrix (inert) is found, which is not ionizable at biological pH and may be used to produce matrix. They inhibit precipitation when added to SEDDS formulation [20,21].

Antioxidant agents

Lipophilic antioxidants help to keep SEDDS formulations oil part stable [19].

Diagrammatic representation of SEDDS and commonly used excipients in SEDDS formulation is presented in Figure 5.

Dosage Forms of SEDDS

The dosage forms of SEDDS are summarized in Figure 6.

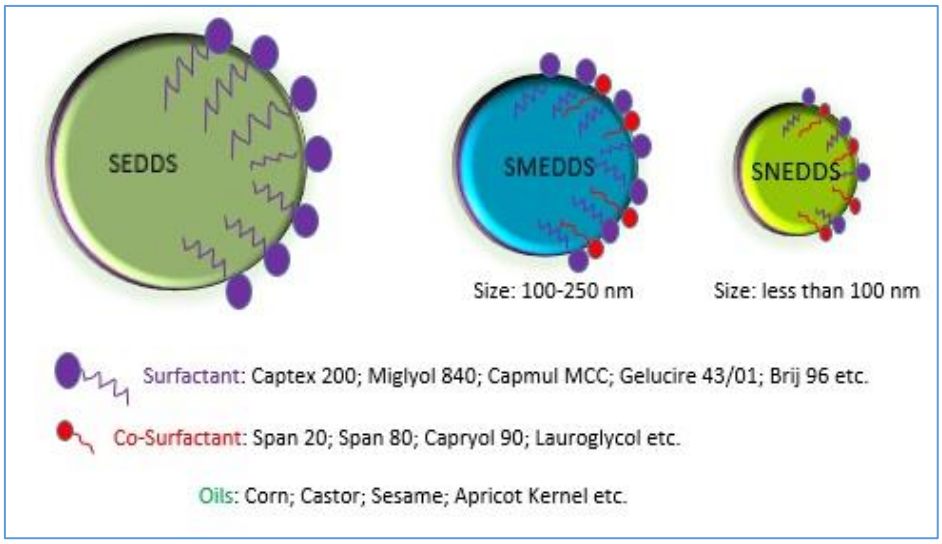

Figure 5. SEDDS, SMEDDS, and SNEDDS are depicted in a diagram

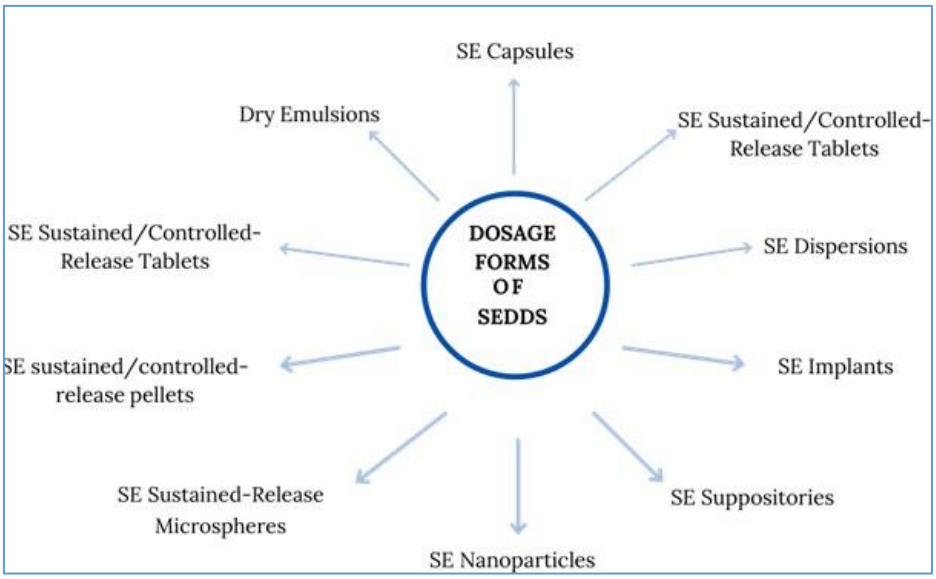

Figure 6. Diagram of SEDDS dosage forms

Dry Emulsions

Dry emulsions are powders that emulsify spontaneously when introduced to an aqueous medium or when introduced to an aqueous medium. They can be utilized in the production of capsules and tablets. Dry emulsion preparations are commonly produced via spray drying, freeze-drying and rotary evaporation in the aqueous phase from (O/W) emulsions including a solid carrier (maltodextrin lactose, and so on). This technique eliminates some of the issues associated with traditional emulsions during storage (phase separation, microbe contamination, etc) [21,22].

Self-emulsifying Capsules

For providing suitable single-unit dose preparations, lipophilic active pharmaceutical ingredients could be dissolved in SEDDS and encapsulated in soft or hard gelatin capsules [21,23]. When traditional liquid SE preparations are administered in capsule form, microemulsion droplets develop and scatter throughout the GIT to reach absorption areas. However, if the micro emulsion's phase separation is

permanent, no enhancement in medication absorption may be predicted; Sodium dodecyl sulphate was included in the SE composition to address this issue [21,24].

Self-emulsifying Sustained/controlled-release Tablets

SE tablets are frequently produced because they're more stable than other dosing types. A polymeric method can be used to provide sustained action [25]. SE tablets are made up of compressed or molded liquid SEDDS that have been solidified. These preparations have a number of benefits, including the ability to liquefy at body temperature under agitation owing to the peristalsis of the GIT, which decreases the liquidation period, which causes quicker emulsification and higher drug plasma concentration (shown in Figure 7). A gelled SEDDS has been created to minimize the quantity of solidifying agents needed for the conversion of SEDDS into solid dosage forms [21-25].

The SE osmotic pump tablets are the most recent innovation of SE tablets research. This approach offers several advantages, including steady plasma concentrations, a controlled release rate, and increased drug absorption [26,27].

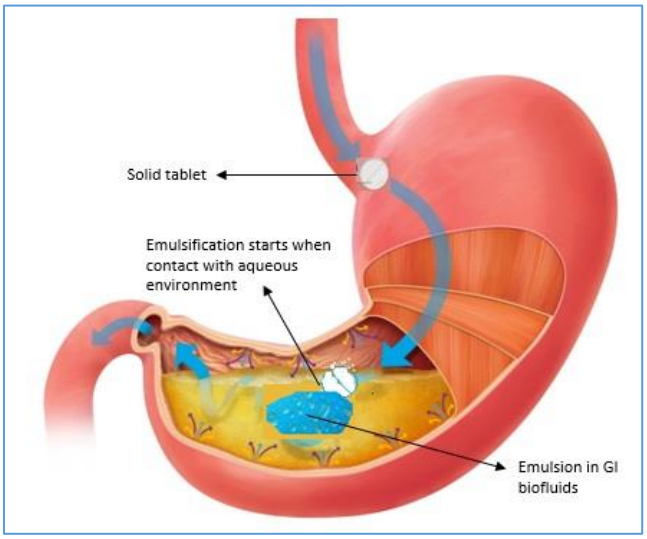

Figure 7. Mechanism of action of solid self-emulsifying tablet

Self-emulsifying Controlled/sustained Release Pellets

Even though the use of SEDDS is mainly designed to increase the absorption of lipophilic medications, it would also be desired to offer sustained release action in the case of pharmaceuticals with a short biological half-life and frequent dosing. As a result, researchers had the idea of combining SEDDS with control release agents in terms of designing matrix-type controlled release solid SEDDS. Solid SEDDS matrix-type spherical pellets have been designed [28].

Self-emulsifying Beads

It was theorized that by utilizing capillary forces, SEDDS might be designed to convert a liquid SE formulation into a solid form with little solidifying aids while avoiding the leakage and leaching issues that face conventional liquid SE formulations [16].

Self-emulsifying Sustained-release Microspheres

ZTO (a conventional drug used in China) has a wide range of pharmacological effects, such as tumor suppressive, antimicrobial, and antithrombotic properties. In one of the preparations of solid SE sustained release microspheres, ZTO was used as the oil phase. When compared to standard liquid SEDDS, following oral delivery of these microspheres, the concentration of plasma was attained with a 135.6% enhancement in the bioavailability [21,25].

Self-emulsifying Nanoparticles

Nanoparticle methods are used in the manufacture of self-emulsifying nanoparticles. A solvent injection is one of these methods. In this technique, the main components are melted all together and then injected dropwise inside a stirred nonsolvent. The self-emulsifying nanoparticles are filtered and then dried. Nanoparticles (approx. 100 nm) are produced with a 74% drug loading efficiency by this method [17].

Self-emulsifying Suppositories

Solid SEDDS has been shown to improve gastrointestinal adsorption and also rectal adsorption in addition to vaginal adsorption. Glycyrrhizin, which hardly reaches therapeutic plasma concentrations whenever administered orally, may be reached at therapeutic quantities for chronic hepatic disorders via vaginal or rectal self-emulsifying suppositories [17,21].

Self-emulsifying Implants

Solid SEDDS have progressed thanks to self-emulsifying implants. Self-emulsifying implants are made from co-polymers with a hydrophilic area and about two cross linkable functional groups. These co-polymers function as sealants.

Carmustine is a short-acting drug employed to treat brain tumors. Compression molding was used to develop wafer-like implants from self-emulsifying carmustine, also known as Bis chloroethyl nitrosourea [3,25,27]. All types of SEDDS dosage forms are summarized in Table 2.

Table 2. Case studies on various types of dose formulations generated via solidifying SEDDS

Product Type	Formulation/ Strategy / Sample	Outcome
SE Beads	Self-microemulsifying system for nutraceuticals	Good stability in SGF as well as storage stability was achieved
SE Controlled release pellet	Solid self-microemulsifying pellets for curcumin	Bioavailability was found to be improved in comparison to drug suspension
SE Solid dispersion	Combined Self Nanoemulsifying and Solid Dispersion Systems	Enhanced dissolution was observed at an elevated pH
SE Implant	SEDDS of 1,3-bis(2-choloroethyl)-1-nittosourea-loaded PLGA wafer	First order release and good penetration depth was achieved by developing the SE wafer
SE Microsphere	Zedoary turmeric oil microspheres with SE ability	Bioavailability was found to be improved in comparison to conventional SE systems
SE Nanoparticle	Natural antiproliferative agent loaded self micro-emulsifying nanoparticle	Significant inhibition in the growth of carcinoma cells was observed with piperine loaded SE nanoparticles
SE Suppositories	Self-microemulsifying suppository formulation of β-artemether	Improved pharmacodynamics activity was observed compaired to PEG based suppositories

Bioavailability Enhancement Properties of SEDDS

When a drug is introduced into SEEDS, the solubility is increased since the dissolving stage is bypassed in the event of a Class-II drug (low solubility/high permeability). Parameters affecting the bioavailability of pharmaceuticals are listed in Figure 8.

Drug samples and the enhanced level of bioavailability by using SEDDs are given in Table 3. For example, Ketoprofen, a lipophilic nonsteroidal anti-inflammatory medication (NSAID), is a preferred agent for sustained release formulations, although it has a significant risk of gastritis in long-term treatment. Ketoprofen also demonstrates partial release from sustained release formulations due to its limited solubility. The lipid matrix of SEEDS rapidly interacts with water, resulting in a fine particle

oil-in-water (o/w) emulsion. The drug will be delivered to the gastrointestinal mucosa in a dissolved condition, making it readily available for absorption. As a result, several drugs exhibit a rise in AUC (bioavailability) and Cmax when delivered in SEEDS [16,29,30].

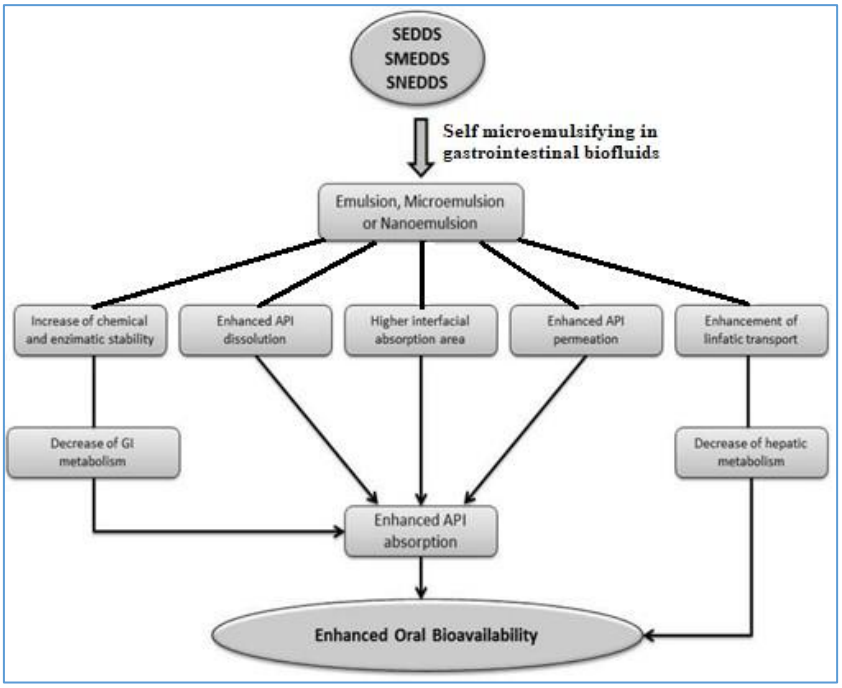

Figure 8. Parameters affecting the bioavailability of pharmaceuticals produced in SEDDS, SMEDDS, orSNEDDS

Table 3. Updated research on several claims of SEDDS enhancing bioavailability

Drug	Enhancement	With reference to	Species
Acyclovir	3.5 fold	Solution	Male albino rats
Anethole trihione	2.5 fold	Tablets	Rabbits
Atorvastatine	1.5 fold	Tablets	Beagle dogs
Bicalutamide	2 fold	Suspension	Rats
Carvedilol	4.13 fold	Tablets	Beagle dogs
Fenofibrate	1.075 fold	Tablets	Human
Gentamycin	5 fold	*iv* Saline	Beagle dogs
Insulin	1.15 fold	sc injection	Beagle dogs
Itraconazole	1.9-2.5 fold	Capsules	Human
Ketoconazole	2 fold	API	Rats
Ketoprofen	1.13 fold	API	Human
Mitotane	3.4 fold	Tablets	Rabbits
Nimedipine	2.6-6.6 fold	Tablets	Rabbits
Nitredipine	1.6 fold	Tablets	Beagle dogs
Slymarin	3.6 fold	Capsules	Rats
Oleanolic acid	2.4 fold	Tablets	Rats
Simvastatin	1.5 fold	Tablets	Beagle dogs
Tritionin	1.67 fold	Capsules	Beagle dogs

RESULT AND DISCUSSION

The quantity of novel therapeutically effective lipophilic molecules that are hydrophobic has steadily increased thanks to innovative drug development approaches. Transforming such compounds into oral delivery formulations having acceptable bioavailability is a huge issue for pharmaceutical experts. The use of SEDDS has been proven to be quite successful in enhancing the oral bioavailability of hydrophobic and lipophilic drug molecules among the strategies to increase oral bioavailability of these compounds.

The two major problems of a formulation intended for the oral route are the aqueous solubilization and the intestinal permeability of the molecule of interest. In the case of a BCS class II compound, characterized by low aqueous solubility and high intestinal permeability, dissolution in the digestive environment is the rate-limiting step for absorption.

The use of SEDDS during the step of pre-formulation makes it possible to solubilize the active principle BCS class II, thus authorizing their passage in sufficient quantity through the intestinal membrane. Furthermore, they make it possible to encapsulate molecules with different hydrophilic/lipophilic balances in the same system. They also allow the reduction of the volume of the vehicle, which minimizes the toxic side effects. In addition, these pharmaceutical forms make it possible to improve the bioavailability of the compound as well as to reduce its inter and intra- individual variability, and obtain a better dose/exposure linearity. This translates into better job security, especially since this molecule will have a narrow therapeutic window. They also limit the effect of food on the absorption of compounds.

The future of pharmaceutical research may not only pass through the discovery of new molecules but also better exploitation of those already known. Indeed, better absorption, a reduction in inter-individual variability, easier administration, and a reduction or even elimination of the side effects of these molecules would be of great benefit to patients.

AUTHOR CONTRIBUTIONS

Concept: N.B., O.M.S.; Design: N.B., O.M.S.; Control: O.M.S.; Sources: N.B., O.M.S.; Materials: N.B., O.M.S.; Data Collection and/or Processing: N.B.; Analysis and/or Interpretation: N.B.; Literature Review: N.B.; Manuscript Writing: N.B.; Critical Review: N.B., O.M.S.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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