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Self Emulsifying Drug Delivery System

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Abstract:- Self-emulsifying drug delivery systems (SEEDS) are mixtures of perfect isotropic oils and surfactants, with or without cosolvents, that emulsify when gently agitated, similar to the conditions found in the gastrointestinal tract. These systems cause the gastro-intestinal tract (GIT) to mildly agitate while forming fine emulsions (or micro-emulsions). The oral absorption of drugs from SEEDS is greatly influenced by a number of factors, including surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size, and charge. This formulation improves bioavailability by increasing drug solubility and reducing gastric irritation.Gelatin capsules in either soft or firm form may be used orally. More than 40% of novel chemical entities, however, have low aqueous solubility, which leads to ineffective oral medication administration. Self-emulsifying drug delivery systems (SEEDS), which increase the oral bioavailability of poorly water soluble medicines, have received a lot of interest latel.

Keywords:- *Self emulsifying drug delivery system (SEDDS) ,Self-Emulsifying formulation, Mechanism, evaluation, Bioavailability enhancement.*

I. INTRODUCTION

For the treatment of many chronic diseases, the oral route has become a major route of drug delivery. However, in recent years, the formulation of poorly soluble compounds has presented interesting challenges for pharmaceutical formulation scientists because up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble orlipophilic compounds, resulting in poor oral bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality.[1,2]

Prior to now, these problems were dealt with by changing the compound's physicochemical characteristics, such as salt production and particle size reduction, which may be one strategy to increase the drug's rate of dissolution but has its own drawbacks. Other formulation techniques, including the use of cyclodextrins, nanoparticles, solid dispersions, and permeation, have been employed to get around these restrictions.

In truth, these methods have worked in a few instances. Recent years have seen a lot of interest in lipids. Lipid-based formulations are used to increase the oral bioavailability of drugs with poor water solubility. The incorporation of the therapeutic ingredient into inert lipid carriers such as oils, surfactant dispersions, self-emulsifying formulations, emulsions, and liposomes is really the most extensively employed technique(SEDDS) .[3,4]

II. SELF EMULSIFYING DRUG DELIVERY SYSTEM [SEDDS]

There has been a great deal of interest in self-emulsifying drug delivery systems (SEEDS), which improve the oral bioavailability of lipophilic drugs. SEEDS, or self-emulsifying oil formulations, are supposedly isotropic mixtures of hydrophilic solvents and co-solvents, solid or liquid surfactants, natural or synthetic oils, and solid or liquid surfactants. When softly agitated and subsequently diluted in aqueous media, such as GI fluids, these systems can create fine oil-in-water (o/w) emulsions or micro emulsions [5,6,7].Fine oil droplets would spread the drug's distribution throughout the GI tract and pass quickly from the stomach, reducing the discomfort that is typically experienced when bulk drug compounds are in prolonged contact with the gut wall. SEEDS have an additional benefit over straightforward oily solutions in that they offer a significant interfacial region for partitioning.

A. Statement of novelty

This review of Self Emulsifying Drug Delivery Systems (SEDDS) is written because these drug delivery systems, Delivery systems have unrivalled potential in improving the bioavailability of poorly soluble drugs classification of biopharmaceuticals An extensive and up-to-date literature description reports on various types of self-emulsifying formulations, techniques used characterization, optimization, and use strategies are thoroughly discussed to direct the formulation scientists in the creation of a self-emulsifying that is stable, safe, and effective formulation. The figures are self-created and demonstrate the concept, mechanism, and significance of SEDDS.

III. SEDDS BENEFITS

- Rapid Start of Action.
- Drug dosage reduction.
- Scale-up and Manufacturing Simplicity.
- enhanced oral bioavailability.
- Variability between and within subjects as well as the effects of food.
- a high rate of drug loading in relation to both liquid and solid dose forms.
- safeguarding highly sensitive pharmacological compounds
- Possibility of delivering peptides in the GIT that are susceptible to enzymatic hydrolysis.
- no impact on the digestion of lipids.
- Drug(s) protection from the gut environment
- Delivery profile management.

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IV. CONTRAINS OF SEDDS

- Traditional dissolve techniques are ineffective because these formulations may require digestion before the medication is released.
- Before its strength can be assessed, this in vitro model needs to be improved and validated.
- The foundation for further research will be in vitro-in vivo correlations, hence several prototype lipid-based formulations must be created and tested in vivo using an appropriate animal model.
- The system's limitations include drug chemical instability and formulations with high surfactant concentrations (about 30–60%), which GIT
- Additionally, it is known for the volatile co-solvent in traditional self-emulsifying formulations to move into the shells of soft or hard gelatin capsules, precipitating the lipophilic medication.

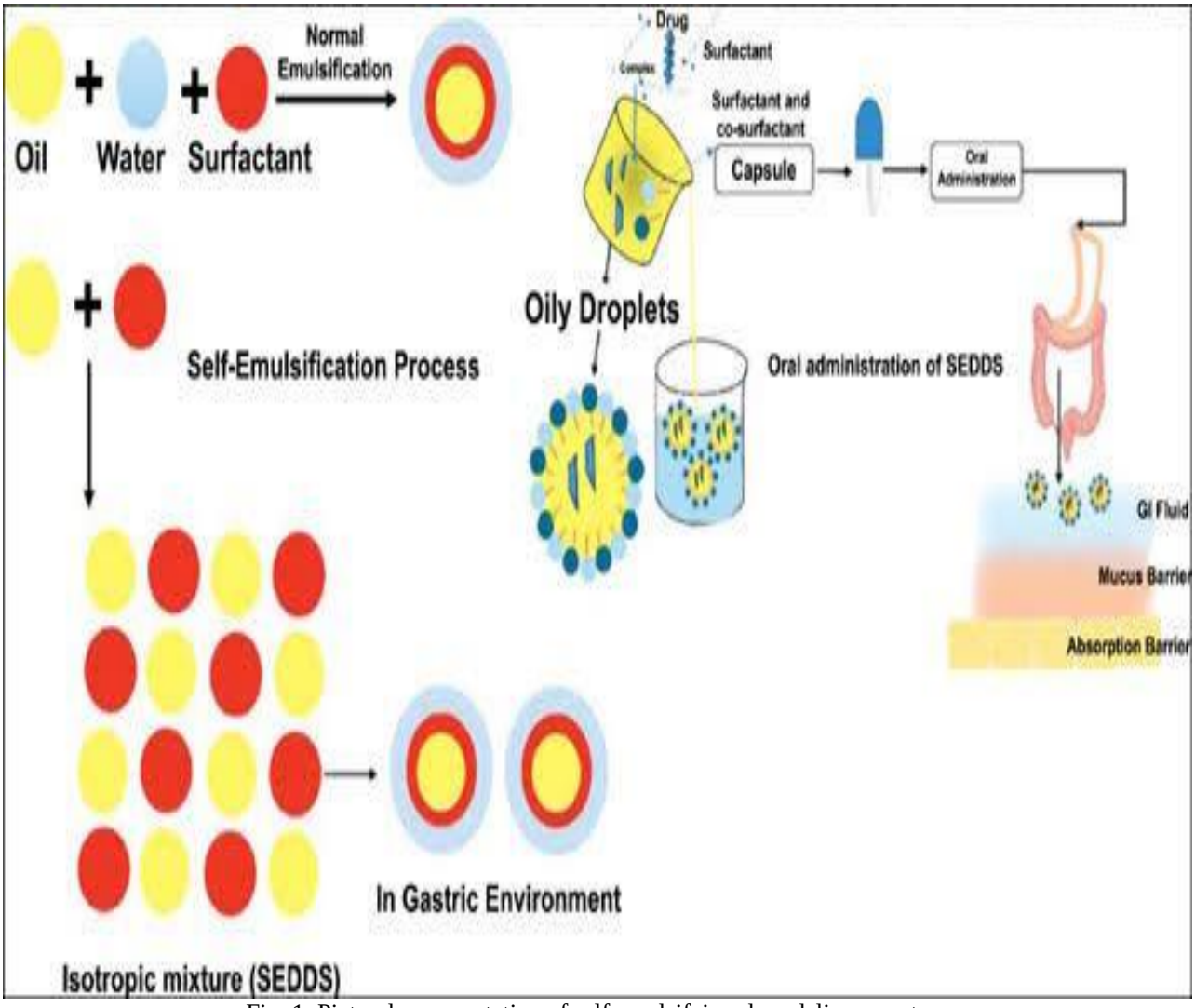

Fig. 1: Pictoral representation of self emulsifying drug delivery system

V. THE COMPOSITION OF SEDDS IS DETERMINED BY

- The nature of the oil-surfactant pair
- The surfactant concentration
- The temperature at which selfemulsification occurs.

A. Oils:

Oils can solubilize the lipophilic medication in a certain quantity. Because it promotes self-emulsification and raises the percentage of lipophilic drugs delivered by the intestinal lymphatic system, improving GI absorption, it is the most significant excipient. SEDDSs were created utilising medium- and long-chain triglyceride oils with various saturation levels. Vegetable oils that have been changed or hydrolyzed have greatly aided in the development and physiological success of SEDDS. Novel semi-synthetic medium chain triglyceride oils can be distinguished from traditional medium chain triglyceride oils by their surfactant qualities.

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Types of oils	Examples
Fixed oils (long chain triglycerides)	Castor oil, maize oil, peanut oil, palm, sesame oil, sunflower oil, cottonseed oil, arachis oil, hydrolysed corn oil, triolein, olive oil, soyabean oil.
Long chain mono glycerides	Glycerylmonooleate (peceol, capmul, GMO), glycerylmonolinoleate (maisine-35)
Medium chain mono and di-glycerides	Mono and diglycerides of capric/caprylic, (capmul MCM and imwitor)
Medium chain triglycerides and related esters	Fractionated coconut oil, cabrafac CC, captex 300, triacetin ,caprylic/capric triglycerides.
Caprylic /capric/diglyceryl succinate	Miglyol 829
Proplene glycol (PG) fattyacids esters	PG disters of caprylic/capric acid (Labrafac PG) PG dicarprylate (Miglyol 840) PG monocaprylic ester (sefsol -218) PG monolaurate (capmul PG 12)
Fatty acids	Caprylic acid , oleic acid (Crossential 094)
Fatty acid esters	Isopropyl palmitate, ethyl oleate (crodamol EO)
vitamins	Vitamin E
Minerals	Liquid paraffin

Table 1: Examples of oils used in sedds :

B. Surfactant:

The formulation of SEDDSs uses non-ionic surfactants with high hydrophilic-lipophilic balance (HLB) values, such as Tween, Labrasol, Labrafac CM 10, Cremophore, etc. The average surfactant strength varies between 30 and 60% weight-for-weight of the formulation to produce a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which makes it easier for the formulation to spread quickly in aqueous conditions and/or to produce o/w droplets right away. Surfactants can dissolve or solubilize hydrophobic drug molecules at comparatively high concentrations because of their amphiphilic nature. As a result, the drug molecules may stay in the body for longer and may not precipitate within the GI lumen.

Surfactants	Drugs
Tween 80	Ketoprofen , carvedilol
TPGS	Tacrolimus
Labrafil M 1944 CS	probucol
Cremophor	Loratadine
Tween 85	Indomethacin

Table 2: Examples used in sedds

C. Cosolvents/Cosurfactants:

Co-surfactant/co-solvents like Spans, capyrol 90, Capmul, lauroglycol, diethylene glycol monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, and tetrahydrofurfuryl alcohol polyethylene glycol can help dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents can occasionally operate as cosurfactants in micro emulsion systems.

Cosolvents /cosurfactants used :
Span 20
Span 80
Capmul
Capryol
Transcutol
lauroglycol

Table 3: Examples of cosolvents /cosurfactants used in sedds

- Drug characteristics appropriate for SEDDS
  - The dosage shouldn't be so high.
  - Medicine must be oil soluble
  - High melting point medication is not ideal for sedds
  - A high Log P Value is desirable

VI. MECHANISM OF SEDDS

Numerous tactics are reported in the literature. The emergence of micro emulsions cannot be entirely explained by a single theory. According to Schulman et al., the surfactant and co-surfactant formed a complex layer at the oil-water interface, which was what led to the spontaneous formation of micro emulsion droplets. [8,9]

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The thermodynamic theory of microemulsion creation states that emulsification occurs when the free energy (G) is negative and the entropy shift that favours dispersion is greater than the energy required to increase the dispersion's surface area. The free energy in the micro emulsion creation can be understood as a direct function of the energy required to create a new interface between the two phases using the following equation:

$$\Delta G = \Sigma N_{л} r2\ \sigma$$

where G is the free energy of the operation (ignoring the free energy of the mixing).

are the interfacial energy, and N the number of droplets of radius r. Over time, the two phases of the emulsion have a tendency to separate, decreasing the interfacial area and, consequently, the free energy of the system. As a result, typical emulsifying chemicals stabilise the emulsion created by aqueous dilution by forming a mono layer around the emulsion droplets, lowering interfacial energy and acting as a barrier to prevent coalescence.

VII. FORMULATION

With a wide range of liquid or waxy excipients available, including oils, biological lipids, hydrophobic and hydrophilic surfactants, and water-soluble co-solvents, there are numerous combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures that disperse to produce fine colloidal emulsions. [10,11]

The following factors should be considered when developing a SEDDS:

- The drug's solubility in various oils, surfactants, and cosolvents.
- Choosing the oil, surfactant, and cosolvent based on the drug's solubility and preparing the phase diagram.
- SEDDS formulation is made by dissolving the drug in an oil, surfactant, and co-solvent mixture [18].

It is critical to include a drug in a SEDDS because the drug to some extent, it interferes with the self-emulsification process, resulting in a change in the optimal oil-surfactant ratio. As a result, designing an optimal SEDDS necessitates preformulation-solubility and phase-diagram studies. The polymer or gelling agent is added to the formulation of prolonged SEDDS.

VIII. FORMULATION TYPES

A. Lipid solutions with a single component:

The drug is dissolved in a single excipient, such as a plant oil, glyceride, or PEG, in this formulation, which is the simplest. Congeneric simplicity of this formulation strategy is an evident advantage. This formulation, with the exception of PEGs, relies on the gastrointestinal lipid handling routes to cause emulsification, which is required for straightforward drug release and absorption. In people whose lipid digestion has been preset by age or disease, drug absorption is less than optimum. Single-component PEG solutions usually offer a strong solubilizing capacity for drugs that are only marginally soluble in water. Because the degree of bioavailability enhancement is dose-dependent, PEG solution formulations are inefficient for high-dose drugs.

B. Self emulsifying formulations:

Formulations that self-emulsify are physically stable isotropic mixes of oil, surfactant, cosurfactant, and drug ingredient that are acceptable for oral administration in both soft and hard gelatin capsules. Aqueous dilution will cause the spontaneous development of lipid droplets with sizes ranging from about 100 nm (SEDDS) to less than 50 nm, depending on the excipients utilised and the relative composition of the formulation (SMEDDS). To encourage self-emulsification, the right amounts of oil, surfactant, and cosurfactant must be present. Smaller lipid droplets with a larger surface area are expected to assist digestion, resulting in more lipid and consistent medication release and absorption because droplet surface area is inversely related to droplet diameter. Self emulsifying for use improves drug absorption by keeping the drug solubilized until it can be absorbed from the GIT. In some cases, SMEDDS formulations have proven useful in reducing the enhancing effect that food can have on the absorption of poorly water-soluble drugs.

C. Self emulsifying solid dispersion formulations :

For maximum absorption, liquid self-emulsifying formulations rely on a micelle or solvent to completely solubilize the medication dose. However, the effectiveness of these formulations is constrained by their inability to solubilize the complete therapeutic dose in the amount of a single oral capsule. In these circumstances, solid dispersion formulations—which might not entirely dissolve the medication in the excipient matrix—can offer a workable substitute oral formulation. These formulations consist of a drug dispersion in an inert excipient matrix, with the drug existing in one or more of the following states: amorphous, solubilized, or finely divided crystalline.When compared to the PEG solid dispersions that were previously employed, these excipients have the potential to boost the absorption of medications that aren't very water soluble. Additionally, they can be simply poured into firm gelatin capsules while still liquid, skipping the grinding and mixing steps in the process.

IX. EVALUATION OF SEDDS

Assessment of SEDDS is done by :

- **Thermodynamic stability:** To avoid choosing metastable formulations, selected formulations were put through a variety of thermodynamic stability experiments (Centrifugation, Heating Cooling Cycle, and Freeze Thaw Cycle).
- **Centrifugation:** Phase diagrams were used to choose formulations, which were then centrifuged at 3500 rpm for 30 min to check for phase separation, creaming, and cracking. Stable formulations were used for the heating and cooling cycles.
- **Viscosity :** The viscosity of several formulations was measured at 251.0°C1 using a Brookfield DV III ultra V6.0 RV cone and plate rheometer (Brookfield

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Engineering Laboratories, Inc., Middleboro, MA, spindle # CPE40).

- **Zeta potential analysis :** A zeta metre system (Malvern Instrument, Worcestershire, UK) was used to determine the formulation's zeta potential after diluting it.
- **Heating and cooling cycles (H/C cycles):**H/C cycle was used to study the effects of temperature fluctuation on nano emulsions. Six cycles between 4°C and 45°C in the refrigerator, with storage at each temperature lasting no less than 48 hours.
- **Differential scanning calorimetry :**Calorimetry that uses differential scanningof dry nitrogen was utilised as the effluent gas, and the samples (which weighed around 3.00 mg) were put in typical aluminium cups. The heat flow ranged from 0 to 250°C, and all samples were scanned at a temperature ramp speed of 5°C/min.
- **Freeze-thaw cycle:** Formulas that can withstand these temperatures underwent a freeze-thaw cycle.Three freeze-thaw cycleswere performed on the formulations between -21°C and +25°C, with storage at each temperature lasting at least 48 hours. Formulas that passed these thermodynamic stress tests were then subjected to dispersibility experiments to gauge how well they would self-emulsify.
- **Drug Release studies :**Utilizing the USP Dissolution Apparatus-II, the in vitro drug release of formulations was assessed (paddle method). The ibuprofen in USP monograph specifies a pH 7.4 phosphate buffer as the dissolving medium. Over 60 minutes, 5 ml of dissolving medium were taken out every 10 minutes. A UV Spectrophotometer (UV 1205 Shimadzu, Japan) operating at 221nm was used to measure the amount of medication that had been dissolved.
- **Anti-inflammatory activity evaluation:** The carrageenan-induced rat hind paw edoema method16 was used to assess the anti-inflammatory activity of prepared ibuprofen SEDDS.

The experimental protocol was created, and the Institutional Animal Ethics Committee (IAEC) approved it. Wistar strain male albino rats weighing 150-200 g were used in this study. The animals were kept in a light-controlled environment for 12 hours a day, with free access to food and water. Before the experiment, the animals were fasted overnight with free access to water.

- **Effect of pH and robustness :**Distilled water, 0.1M HCl, and simulated intestinal fluid were used to dilute the formulations 50, 100, 1000, and 3000 times (pH 6.8). After 24 hours of storage, the diluted emulsions were manually checked for any physical changes such as (droplet coalescence, precipitation, or phase separation).
- **Refractive index and percentage transmittance :**The system's refractive index was determined using Abbe's refractometer. The system's percent transmittance was measured at 221 nm using a UV spectrophotometer (Shimadzu, Japan) with distilled water as a blank.
- **Dispersibility tests :**A USP XXII dissolution apparatus II was used to evaluate dispersibility efficiency. Each formulation (0.5 mL) was added to 500 mL of distilled water kept at 370.5°C, with the paddle rotating at 50 rpm to ensure gentle agitation. The formulations' in vitro performance was visually assessed using the grading system shown below12.
  - Grade A: A clear or bluish nanoemulsion that forms quickly (within 1 minute).
  - Grade B: A bluish white emulsion that forms quickly and is slightly less clear.
  - Grade C: A fine milky emulsion that formed in less than 2 minutes.
  - Grade D: A dull, greyish white emulsion with a slightly oily appearance that emulsifies slowly (longer than 2 min).
  - Grade E: Formulation with poor or minimal emulsification and large oil globules on the surface.
- **Globule size analysis :** By employing a Zetasizer 3000 to analyse fluctuations in light scattering brought on by the motion of the particles, photon correlation spectroscopy was used to measure the mean globule size and polydispersity index (P.I.) of the resulting emulsions (Malvern Instruments Worcestershire, UK) Monitoring of light scattering was done at 25°C and a 90°angle.

X. APPLICATIONS

Lipids, surfactants, and cosolvents are the main ingredients in SEDDS formulation.When an aqueous phase is gently stirred while being dispersed by another phase, the system can create an oil-in-water emulsion. Small droplet size and proportionate drug distribution are features of SEDDSs, which also boost permeability and dissolution.

SEDDSs also guard against drug hydrolysis by digestive tract enzymes and lessen hepatic first-pass metabolism and pre-systemic clearance in the GI mucosa due to the ability to load medications in the inner phase and transport them via lymphatic bypass share.

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Brand name	Compound	Dosage form	Company	Used for
Neoral	Cyclosporine A/I	Soft gelatin, oral solution	Novartis	Immune Suppressant
Norvir	Ritonavir	Soft gelatin, oral solution	Abbott Lab	HIV antiviral
Fortovase	Saquinavir	Soft gelatin	Hoffmann-La Roche Inc	HIV antiviral
Agenerase	Amprenavir	Soft gelatin, oral solution	GlaxoSmithkline	HIV antiviral
Convulex	Valproic Acid	Hard gelatin	Pharmacia	Antiepileptic
Lipirex	Fenofibrate	Soft gelatin, oral solution	Sanofi-Aventis	Antihyperlipoproteine- mic
Sandimmune	Cyclosporine A/II	Soft gelatin	Novartis	Immuno suppressant Antineoplastic
Targretin	Bexarotene	Soft gelatin, Oral solution	Ligand	Calcium regulator
Rocaltrol	Calcitrol	Hard gelatin	Roche	Immuno suppressant
Gengraf	Cyclosporine A/III	Hard gelatin	Abbott Lab	Analgesic, Antipyretic
Solufen	Ibuprofen	Soft gelatin	Sanofi-Aventis	Anti-leprosy drug 2° hyperparathyroidism
Lamprene	Clofazimine	Soft gelatin	Novartis	Benign prostatic hyperplasia
Hectorol	Doxercalciferol	Soft gelatin	Genzyme corporation	Anticonvulsant Anti-emetic
Avodart	Dutasteride	Soft gelatin	Glaxosmithkline	Treatment of severe recalcitrant nodular acne
Depakene	Valproic acid	Capsule	Abbott Watson	Antineoplastic agent
Marinol	Dronabinol	Soft gelatin	Watson pharmaceuticals	Amenorrhea
Accutane	Isotretinoin	Soft gelatin	Hoffmann-La Roche Inc	
Vesanoid	Tretinoin	Soft gelatin	Par Pharmaceuticals	
Prometrium	Progestin	Soft gelatin	Schering- Plough	

Examples of marketed products formulated as self-emulsifying systems

XI. CONCLUSION

Self-micro emulsifying drug delivery devices therefore seem to offer a novel and commercially viable solution to the issue of limited oral bioavailability related to lipophilic medicines. We may claim that this is one of the methods for improving oral bioavailability of a medicine because there is an improvement in oral drug absorption of BCS II class pharmaceuticals. The toxicity of the surfactant being utilised should be considered because the SMEDDS formulation often uses a rather high concentration of surfactants. The toxicity and self-emulsifying capacity of the surfactant under consideration for use must be balanced. Two further critical elements that influence the effectiveness of GI absorption are the size and charge of the oil droplet in the resulting emulsion.

SEDDSs will continue to enable innovative drug delivery applications and address issues with the distribution of poorly soluble pharmaceuticals as this technology develops in the future.

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