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# SELF EMULSIFYING DRUG DELIVERY SYSTEMS: AN APPROACH TO MODIFY DRUG PERFORMANCE

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***Abstract***

Self-emulsifying drug delivery systems (SEDDS) are methods that have been proven to work by increasing the solubility and bioavailability of insoluble substances. There are two types: self-emulsifying drug delivery system (SEDDS) and self-microemulsifying drug delivery system (SMEDDS). SEDDS and its isotropic mixtures contain oils, surfactants and sometimes solvents. The ability of these formulations and methods to produce thin oily liquids (o/w) after mixing and dissolution in the aqueous phase in the digestive tract makes it a promising approach for lipophilic drugs with limited absorption. An important feature of this system for lipophilic drugs is the ability to form oil-in-water (o/w) emulsions or microemulsions after dispersion in the aqueous phase through the digestive tract, indicating limited absorption of the dispersion. SEDDS may be a promising strategy to increase the rate and extent of oral absorption. Insulin, beta-lactamase, cyclosporine, ritonavir, valproic acid, bexarotene, clofazimine, dronabinol, ibuprofen, and calcitriol can be formulated using SEDDS using various combinations of surfactants and cosurfactants. This article provides an overview of SEDDS, including advantages, mechanisms of SEDDS, and different formulation approaches. SEDDS design methodology and SEDDS evaluation.

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## Introduction:-

Emulsions act as drug carriers for drugs and can increase the oral bioavailability of drugs due to their low absorption profile [1]. One of the main strategies to improve the stability of oral APIs is to use lipid-based drug delivery systems. According to the literature, the terminology of lipid-based technology is highly controversial. Initial droplet size is not the main determinant of self-microemulsification drug delivery systems (SMEDDS) and self-nanoemulsification drug delivery systems (SNEDDS). If the emulsion droplet size is in the nanoscale range, SNEDDS should be used. Self-emulsifying drug delivery systems (SEDDS) are oil and surfactant-based formulations that can be rapidly emulsified in water for sustained release [2]. Chemical Composition and Physical

Properties of SEDDS Physical properties are the determinants of performance and resistance. Therefore, this variable must be created during initialization [3].
Self-emulsion drug delivery systems are defined as natural or synthetic oils, solid or liquid surfactants, or isotropic mixtures of one or more hydrophilic solutes and co-solvents/surfactants. After gentle agitation in aqueous media such as digestive fluids, these systems can form oil-in-water emulsions (o/w) or microemulsions [5]. Microemulsions are believed to be formed spontaneously through the interaction of small free molecules with specific molecules Energy Medicine [6]. Microemulsion droplets dispersed in the digestive tract provide a large surface area that facilitates rapid release of drugs in solution and/or micelle mixtures, as well as drug diffusion through immobile water layers. In addition to increased drug release by SEDDS, another factor contributing to increased bioavailability is lymphatic transport as part of overall drug absorption. The lipid content of SEDDS can be associated with increased drug delivery by stimulating the formation of lipoproteins and intestinal lymph fluid [7,8,9].

**Need:**
Self-emulsifying drug delivery system (SEDDS) is a proven method for poorly soluble substances to be used by increasing solubility and bioavailability. SEDDS and isotropic mixtures consist of oil, surfactant, and sometimes solvent [10]. The ability of these formulations and methods to form microemulsions or thin oil emulsions (o/w) after mixing and dissolution with an aqueous phase medium throughout the GI tract may be a limiting method for distributing lipophilic agents absorption (Figure 1)[4,10].

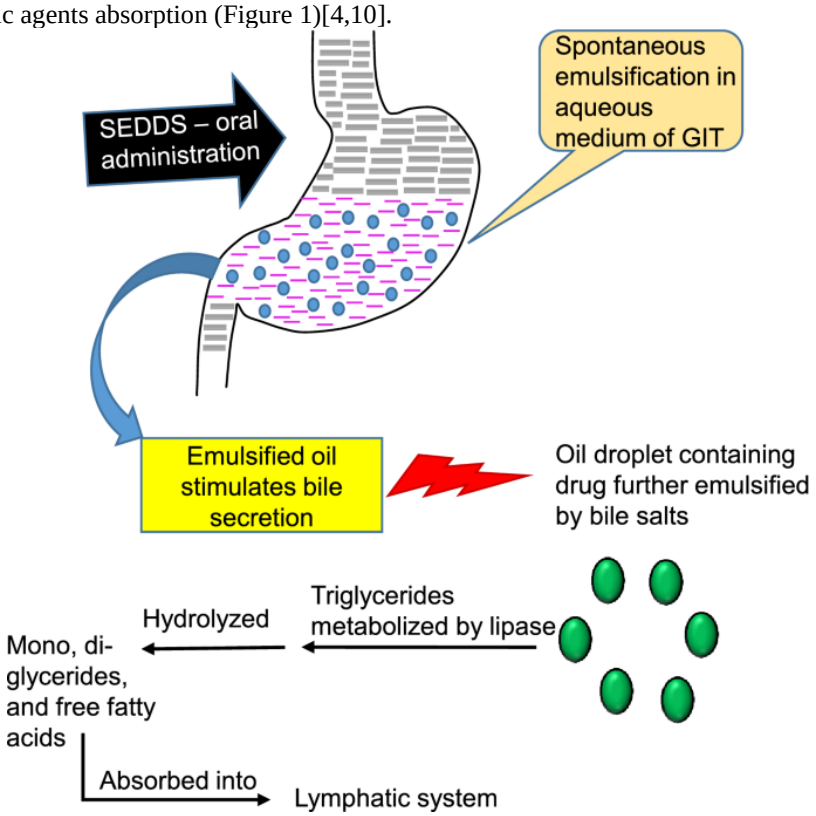


**Figure 1:-** Advantages of SEDDS system [11].

**Reasons for the development of self-emulsifying drug delivery system:**
Self-emulsifying drug delivery systems (SEDDS) have the unique ability to increase the oral bioavailability of water-soluble drugs. For most of the oral cavity, this system diffuses rapidly into the digestive fluid, resulting in micro-emulsions or nano-emulsions containing soluble drugs [12]. Among these technologies, self-emulsifying drug delivery systems (SEDDS) are lipid-based formulations that can improve the solubility, bioavailability, and absorption of many insoluble drugs. This formulation is an isotropic mixture of oil and a nonionic emulsifier that forms a dilute water or microemulsion when exposed to an aqueous environment in a soft mixture [13, 14]. This system helps to dissolve the drug, helps to form a soluble phase, increases the absorption of the drug through the intestinal fluid system and inhibits the secretion of P-glycoprotein. These spontaneous emulsions with small droplet

size and large surface area dissolve the drug and release the drug independently of intestinal physiology or fasting conditions [13, 15].

Self-microemulsifying drug delivery systems or self-emulsifying formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or one or more hydrophilic solvents and cosolvents / co-surfactants. These systems can form oil-in-water (o/w) emulsion after gentle mixing and subsequent dissolution with an aqueous medium such as digestion fluid. Self-emulsified formulations are easily distributed in the digestive tract, and the digestive movements of the stomach and intestines provide the stimulation (peristalsis) necessary for self-emulsification [16]. Compared to emulsions, which are sensitive and unstable dispersions, self-emulsifying drug delivery systems (SEDDS) are physically stable and easy to manufacture. Therefore, for lipophilic drug compounds that exhibit dissolution rate-limiting absorption, this system can provide an increased absorption rate and extent, leading to an enhanced blood profile [16, 17].

**Advantages of SEDDS**[18-20]:

1. Drug targeting for site selection in GIT.
2. After dissolution, hydrophobic drugs are rapidly absorbed by the lymphatic system (Figure 1).
3. A peptide prone to enzymatic hydrolysis in the GIT can be delivered in this formulation,
4. Lipid absorption process does not affect SEDDS.
5. SEDDS formulation reduces drug dosage by increasing drug solubility and bioavailability.
6. Delivery profile control.
7. Rapid onset of action.

**Disadvantages of SEDDS** [20,21]**:**

1. Leakage of formula contents from soft gelatin capsules.
2. Quality control tests for SEDDS are rigorous and thorough.
3. Liquid formulation may cause rupture when administered into GI fluid.
4. High surfactant concentration in the formulation causes GI irritation.
5. Liquid SEDDS is less stable due to microbial degradation.
6. Effects of liquid or semi-solid SEDDS preparations on long-term storage of soft gelatin capsules.

**Classifications of SEDDS:**

There are two types: self-emulsifying drug delivery system (SEDDS) and self-microemulsifying drug delivery system (SMEDDS). Both SEDDS and SMEDDS have drug delivery capabilities. SEDDS formulations can be simple two-component systems: a lipophilic phase and a drug, or a lipophilic phase, a surfactant and a drug. SMEDDS formulations require the use of co-surfactants to form microemulsions [22]. SEDDS formulations were characterized by an in vitro lipid droplet size of 200 nm to 5 mm and a cloudy dispersed appearance. SMEDDS has small lipid droplet size (<200) and transparent optical dispersion. Both systems involve the formation of large surface dispersions that provide favorable conditions for the absorption of poorly soluble drugs. The choice of the preferred formulation type of SEDDS or SMEDDS often depends on the intrinsic properties of the drug compound and its solubility and dispersion characteristics during in vitro studies with multiple receptors[22,23].

**Table 1:-** Types of Self-emulsifying drug delivery system (SEDDS) [22,23].

| | |
|---|---|
| **Self-emulsifying drug delivery system (SEDDS)** | • Globule size: 200nm to 5µm.<br>• Appearance of dispersion is turbid.<br>• Required HLB value <12. |
| **Self-microemulsifying drug delivery system (SMEDDS)** | • Globule size: 0 - 100nm.<br>• Appearance of dispersion is optically clear to translucent.<br>• Required HLB value >12. |
| **Self-nanoemulsifying drug delivery system (SNEDDS)** | • Globule size: <100nm.<br>• Appearance of dispersion is optically clear.<br>• Required HLB value >12. |

**Different Methods Of Preparation Of Sedds:**

**High energy approach:**

Energetic methods require high mechanical energy to combine surfactants, oils, and solvents to form nanoemulsions. Many energetic methods are used to form nanoemulsions. Large-sized dots are divided into nano-sized dots using

strong breaking force caused by large mechanical energy, so the produced nanoemulsion has high kinetic energy. In general, SNEDDS requires less energy and relies on self-emulsification phenomena [4,24].

**High pressure homogenizer:**
High pressure is needed to prepare nano formulations. A thin emulsion is formed at high shear stress. There are two theories that can explain the droplet size and they include turbulence and cavitation. This method allows the production of nanoemulsions with droplet sizes smaller than 100 nm. Various factors are involved in the production of droplet nanoemulsions using high pressure homogenizers, including homogenizer type, sample composition, and homogenizer operating conditions such as time, intensity, and temperature. High pressure homogenization is used to produce nanoemulsions for food, medicine and biotechnology [4,25].

**Sonication method:**
A useful method for forming SNEDDS is ultrasound. In terms of cleanliness and productivity, ultrasonic methods are superior to other high-energy methods. In ultrasonic emulsions, the cavitation forces created by ultrasonic waves break the macroemulsion into nanoemulsion. This process reduces the size of the emulsion droplets and as a result, nano-sized emulsions are produced. Ultrasonic technology works to reduce droplet size [4,26].

**Micro-fluidization:**
Microcooler is an essential device for the micro cooling method. The product is fed into the reaction chamber by a positive displacement pump. Micro channels are small point channels that exist in this system. The produced products are transported through the microchannels to the barrier zone, where a nanoemulsion of very fine droplets is produced. Then, when the mixture of the aqueous phase and the oil phase is mixed with a homogenizer, an emulsion is naturally produced. Subsequent processing leads to the formation of transparent, homogeneous and stable nanoemulsions [4,27].

**Mechanism of SEDDS:**
The mechanism related to "negative free energy for nano-emulsion formation at transient negative surface tension or very low surface tension" has been widely reported in the literature as a general explanation for self-emulsion or self-nanoemulsion. This mechanism provides a thermodynamic perspective on the phenomenon. The formation of nano-emulsions is caused by a decrease in surface tension due to the presence of surfactants in the oil-water interface, which causes a decrease in free energy. In addition, changes in the entropy of the system contribute to the free energy range associated with nano-emulsion formation [28]. This relationship can be described as follows:

$$\Delta G = \gamma \Delta A - T\Delta S$$

Where,

$\Delta G$ is the free energy of formation,
$\gamma$ is the interfacial tension,
$\Delta A$ is the change in interfacial area upon nano-emulsification,
$\Delta S$ is the change in system entropy
T is the temperature.

In a balanced thermodynamic system characterized by an immiscible fluid, the enthalpy required to increase the surface area ($\gamma\Delta A$) is very large and dominantly positive. The positive enthalpy contribution does not correspond to the small entropy dispersion ($T\Delta S$). As a result, Gibbs free energy ($\Delta G = \gamma\Delta A - T\Delta S$) shows a real positive value ($\Delta G > 0$) and the emergence of emulsion requires the input of external energy in the form of mechanical or thermal energy, this is necessary [29].

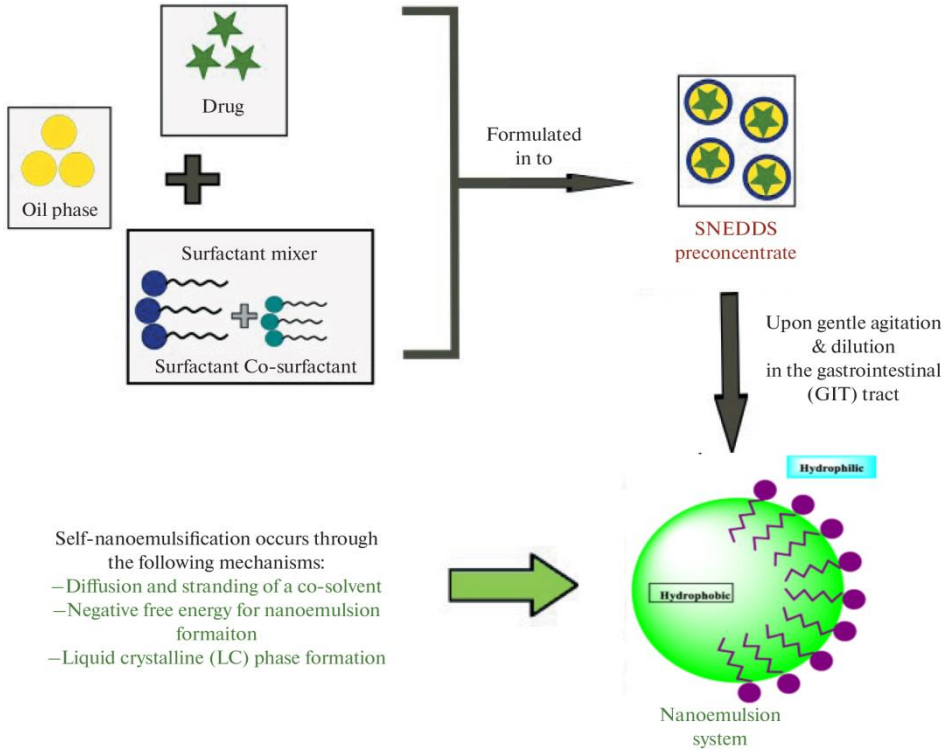


**Figure 2:-** Mechanism of Self-emulsifying drug delivery systems (SEDDS) [30].

**Dosage Form Of SEDDS:**

**Self-emulsifying Powder formulation**:

Lipids and surfactants are widely used in the production of self-emulsion tablets. To reduce the amount of solid additives needed to convert SEDDS into a solid dosage form, SEDDS produced by Patil et al. In the study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent in oil-based systems, which has the dual advantage of reducing the amount of solids required and delaying drug release [31]. SE formulated a powder formulation to improve the solubility and absorption of the water-insoluble drug griseofulvin alidatel. In this case, Capmul GMO-50, poloxamer and mivasate are used as surfactants and cosurfactants. Excretion and bioavailability of griseofulvin are significantly increased [32,33].

**Self-emulsifying capsule**

When a capsule containing a self-dissolving emulsion formulation is delivered, microemulsion droplets form in the digestive tract and disperse to the absorption zone. If the microemulsion phase separation is constant, no increase in drug absorption can be expected. To solve this problem, sodium dodecyl sulfate is added to the SE formulation [4,34].

**Self-emulsifying controlled release tablets:**

Self-Emulsified Control Release Tablets (SECRT) are the latest technological development for profiling-controlled drugs in the S-SEDDS system. This secret is AlphaRx Inc. (Markham, Canada) is a proprietary platform technology that forms particles with liquid SE formulations placed on top of rate-controlling polymers such as HPMC, HPC. This helps in the prolonged release of the drug from the polymer matrix. Systems containing drug formulations have important quality characteristics such as permeability and solubility of the intestinal wall, which contribute to the distribution of drugs in the digestive tract [34,35].

Coenzyme Q10 SE controlled hydrophilic matrix using Avicel-112 and Collidon V64 as a controlled release polymer significantly improved drug stability and control properties. Carvedilol SE tablet formulation containing Aeroperl, MCC and HPMC significantly increased drug uptake in HCT-116 cell line in vitro, probably through inhibition of P-gp efflux. SMEDDS solid tablets containing candesartan cilexetil have the ability to significantly

increase the speed and level of drug distribution and show oral bioavailability. Diclofenac SE tablets, made using natural ingredients such as goat fat and Tween 80, show a long-lasting drug profile[34,35,36].

**Self-emulsifying nanoparticles:**
Self-emulsifying nanoparticles are prepared using nanoparticle technology. One of them is a soluble injection, where a fat-soluble mass containing lipids, surfactants, and drugs is prepared. This lipid-soluble mass is injected dropwise into the insoluble system. It is filtered and dried to get nanoparticles. This method results in the production of 100 nm particles with drug loading efficiency of 70-75% [37].

**Self-emulsifying suppositories:**
Some researchers have shown that solid SEDDS can be used not only to improve gastrointestinal absorption, but also to improve rectal and vaginal absorption. Indomethacin suspension was prepared by self-emulsion technology [38].

**Solidification Of Self-Emulsified Formulations**
Insulin, beta-lactamase, cyclosporine, ritonavir, valproic acid, bexarotene, clofazimine, dronabinol, ibuprofen and calcitriol have been successfully synthesized using SEDDS and various surfactants and cosurfactants [39-44].

**Liquid and semi-solid self-emulsifying layers:**
This is a simple and common way to take a very strong dose of medicine. Microspray and bending processes are used to fill capsules with liquid self-emulsifying solutions. For the encapsulation of semi-solid and self-reactive formulations, the binders are heated to a melting point above 20°C. Add the melted mixture to fill the container. The capsule shell is then removed and filled with the dissolved drug mixture and cooled to room temperature. A bending or microspray process is used to seal the filled capsules [45].

**Spray drying:**
In this method, a solvent is used to mix and melt the liquid and solid components. The molten mixture is then atomized into a fine droplet spray. A drying chamber is then used to dry the microscopic droplets. The preparation of dry particles is carried out under controlled conditions and air flow. These particles can then be tableted. There are several formulations made that improve dissolution and stability, such as polyvinyl pyrrolidone (PVP) containing nifedipine (20-50%) and HIV-efavirenz solid dispersion containing Soluplus (Figure 3) [46,47].

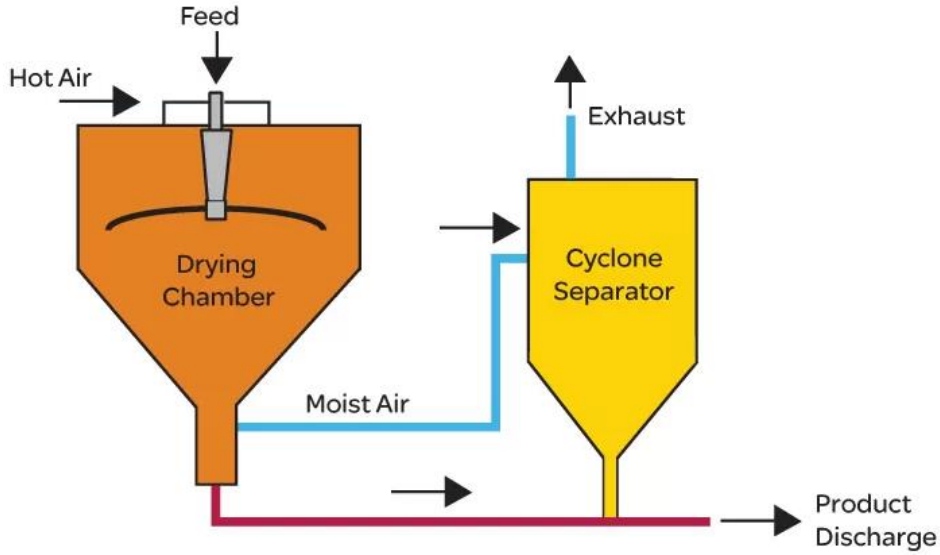


**Figure 3:-** Spray drying process.

**Adsorption on to solid carriers:**
Free-flowing powders have a high surface area and the ability to absorb oil. The adsorbent can absorb 70% of liquid SEDDS. By simply mixing the mixture, the liquid self-emulsifying compound is absorbed into this free-flowing powder [48].

**Melt granulation:**
In this process, glue is used to form powder grains. At a lower temperature, the binder melts or softens. It has significant advantages over conventional wet granulation because it is a one-step process that eliminates the mixing of liquid components and the subsequent drying step. Factors to be monitored during processing include mixing time, stirring speed, particle size, and binder viscosity [49].

**Spherization on extrusion/melt extrusion:**
Extrusion equipment was first introduced to self-emulsifying liquid formulations. Then mix the mixture with water. It uses force to extrude the mold while keeping the product temperature, pressure, and flow constant [50].

**Table 2:-** List of various excipients used in SEDDS formulation.

| | |
|---|---|
| Oil / Lipids | Cottonseed oil, Soybean oil, Palm oil, Castor oil, Hydrogenated specialty oil (hydrolyzed corn oil) etc.<br>Labrafac GG, Isopropyl myristate, Brij, Stepan GDL, Labrasol etc. |
| Surfactants | Potassium laurate, Sodium lauryl sulphate, Quaternary ammonium halide, Sulfobetaines, Sorbitan esters (Spans), Polysorbates (Tweens), Labrasol, Targat TQ. |
| Co-Surfactants | Hexanol, Pentanol, Octanol, Ethanol, PEG 400, PEG 300, ALkoline MCM, Transcutol P. |
| Co-solvents | Ethanol, PEG, Carbitol, Transcutol P, PG, Glycerin, Butanol, Menzyl alcohol, Glycerol. |

**Applications Of SEDDS:**
Lipids, surfactants, and solvents make up the SEDDS formulation. These systems can form o/w emulsions when separated by an aqueous phase with medium mixing. SEDDS delivers the drug in small droplets with uniform distribution and improves dissolution and permeability. Because the drug is loaded into the enteric phase and distributed through the lymphatic circulation, SEDDS protects the drug from enzymatic hydrolysis through the gastrointestinal tract and reduces systemic clearance in the gastrointestinal mucosa and first-pass metabolism in the liver reduced [51].

**Evaluation Parameters Of SEDDS:**
**Dissolution technique:**
In vitro dissolution studies were performed using a USP type II dissolution apparatus using 500 ml of simulated gastric fluid containing 0.5% w/v SLS (sodium lauryl sulfate) at a speed of 50 rpm/min to transfer the drug from the oil phase to the oil phase. Conducted for damage assessment, remove the sample at the same interval and replace the sample with fresh medium. The collected samples were analyzed by UV spectrophotometry or suitable methods [35,52].

**Thermodynamic stability studies:**
The physical stability of lipid-based formulations is also important for their performance and can affect drug entrapment in the receptor matrix. In addition, the low physical stability of the formulation can lead to phase separation of binders, which can affect not only the performance but also the appearance of the formulation. In addition, the incompatibility between the formulation and the gelatin capsule shell can cause swelling or deformation, dissolution, or incomplete drug release [53].

**Solubility study:**
The solubility of drugs in various oils, surfactants, and cosurfactants was determined by the cholesterol method (table 2). Add 1 ml of selective vehicle (oil, surfactant, or solvent) to each vial. After sealing, the mixture was vortexed for 10 minutes using a cyclometer to promote proper mixing of the drug. The mixture was then stirred for 72 hours in an isothermal incubator maintained at 37 ± 1 °C for equilibration. The equalized samples were centrifuged at 5000 rpm for 15 minutes and then filtered through a membrane filter (0.22 μm). Drug concentration was then measured by high-performance liquid chromatography (HPLC) [54].

**Permeation / bioavailability studies:**
In-vitro or ex-vivo studies should be conducted to improve the oral bioavailability of the formulation. For this study, isolated and isolated organ systems have been developed [55]. This organ system has the advantage that scientists work with whole organs, where physiological cells are in contact and the cellular matrix is preserved [56]. There are many methods for such in vitro studies, the first of which is a single in-situ test where the efferent solution passes through the jejunum (part of the intestine), providing experimental conditions similar to those in-vivo. These

methods can also identify specific absorption mechanisms, such as passive absorption, active absorption, or carrier-mediated absorption. Permeability parameters were determined by calculating the amount of drug that was not absorbed from the intestine [57].

**First Pass metabolism by the lymphatic system:**
After oral administration, SEDDS forms a fine emulsion (micro/nano) in the digestive tract. The resulting emulsion is then absorbed through the lymphatic system. In SEDDS, the oral bioavailability of the drug is increased to prevent first pass hepatic effects. Therefore, SEDDS has become an important strategy to increase oral bioavailability of low water-soluble drugs [58].

By using the lymphatic route, it avoids first-pass hepatic metabolism, resulting in a significant increase in drug bioavailability. Since the lymphatic system is involved in the transport of fats and lipids, lipid-based drug formulations are mainly transported by the lymphatic system [59].

**Zeta potential measurement:**
The zeta potential indicates the stability of the emulsion after dissolution. If the zeta potential is high, the formulation is stable. Compared to surface charged particles, zwitterionic charged particles show better biocompatibility and longer blood retention time [60].

**Emulsification time:**
The time required to form an emulsion is determined by the oil/surfactant ratio and the oil phase. This is determined by a basket dissolver, which pours the formulation into a basket filled with water and then monitors the formation of a clear solution when mixed [61].

**Cloud point determination:**
The cloud point of a homogeneous solution is the temperature at which it loses its clarity. Above the cloud point, surfactants generally lose their ability to form micelles. This is determined by gradually increasing the temperature of the formulation and determining the turbidity spectrophotometrically. The cloud point of a surfactant is the temperature at which its conductivity decreases. The cloud point of the formulation should be above 37.5°C to maintain the emulsion itself [61].

**Viscosity measurements:**
The Brookfield viscometer, a rheometer consisting of a cone and a rotating plate, is used to evaluate the viscosity of liquid SMEDDS formulations containing microemulsions [62].

## Conclusion:-

SEDDS is a convenient formula for water insoluble drug molecules. SEDDS has been shown to significantly increase oral bioavailability and is used for oral administration of hydrophobic drugs. The effectiveness of SEDDS largely depends on its composition. Therefore, the formulation of the SEDDS equation must be carefully evaluated. As this technology advances in the future, SEDDS will continue to create new applications in drug delivery and address the challenges of delivering poorly soluble drugs. Several studies have confirmed that SEDDS significantly improves dissolution/dispersion, absorption, and bioavailability of poorly water-soluble drugs. As an upgrade to conventional liquid SEDDS or as an alternative, S-SEDDS is beneficial in reducing manufacturing costs, simplifying the manufacturing process, and improving patient stability and performance. Most importantly, S-SEDDS is very flexible to create different dosage forms to suit parents language and use. In addition, gastrointestinal irritation can be avoided and drug release can be controlled/sustained.

A key feature of this system is the ability of lipophilic drugs to form oil-in-water (o/w) emulsions or microemulsions after dissolution in the aqueous phase of the digestive tract; this shows the rate of dissolution limits absorption. SEDDS may be a promising strategy to increase the rate and extent of oral absorption.

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