SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM

Abstract

In recent year many drugs are generated which have many challenges during the administration of the drug. The major challenges are the low aqueous solubility in the gastrointestinal track (GIT track) as well as they have poor bioavailability when they are administrated as oral route. These problems can be overcome by developing the self-micro drug delivery system (SMEDDS). Through which we can improve the aqueous solubility of drug and the bioavailability of drug. SMEDDS are the effective method in case of oral administration of drug. They form the physically stable emulsion in git track. The examples of some drug are griseofulvin, cyclosporine, ibuprofen, ritonavir etc.

Keywords: SMEDDS, Formulation Methods, Evaluation Parameters, Challenges in Drug Delivery System, Future Prospects.

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I. INTRODUCTION

Oral administration is one of the most used ways, but it has disadvantages for drugs with low solubility. [1] Solubility is essential to achieve therapeutic medication concentrations in vivo. [2] Most innovative drugs are lipid-soluble, which limits their bioavailability and makes drug administration difficult. [1] The small intestine absorbs poorly soluble drugs. Atorvastatin, simvastatin, seocalcitol, and carvedilol are lipophilic drugs. These drugs are poorly water-soluble and bioavailable. SMEDDS, self-micro emulsifying drug delivery systems, can solve this problem. This improves the drug's water solubility and bioavailability. The GIT absorbs more medicine [3].

The research defines smedds as "the isotropic mixture of natural or synthetic oil or the liquid surfactant or hydrophilic solvent and combination of surfactant to form unique ability to form oil-in-water emulsion by mild agitation followed by dilution in aqueous media such as the gastrointestinal tract." A Pharmaceutical Research article on smedds' composition provided this definition. Smedds, a mixture of oil, surfactant, and co-surfactant, forms an oil-in-water microemulsion when diluted with aqueous and gently agitated [1]. Smedds help lipid-soluble medicines absorb and dissolve in water for oral use. Smedds are edible [4].

SMEDDS can be encapsulated in hard or soft gelatine capsules [5]. Standard emulsion preparation beads are 100–500 nm in diameter. Self-micro emulsifying drug delivery devices require beads below 50 nm. SMEDDs may self-emulsify at body temperature and be sterilised by filtration, making them excellent for oral drug administration systems and improving solubility [6,7].

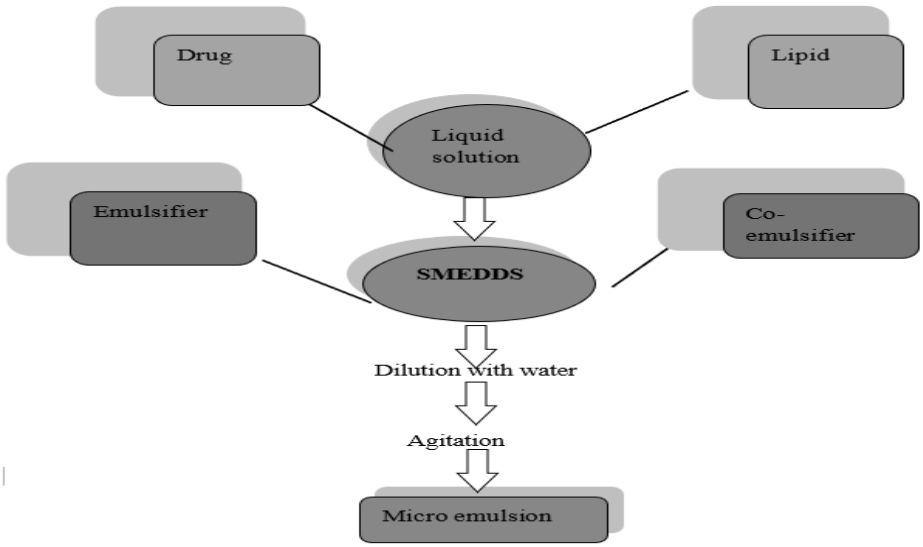

Figure 1: Formulation of SMEDDS [8]

1. **History:** Cambridge University professors T.P. Hoar and J.H. Shulman introduced team micro emulsion in 1943. Smedds are called translucent emulsion, inflated micelle, micellar solution, and solubilized oil. When the oil/water contact surface tension is very low, micro-emulsions develop [2]. The interface layer is as flexible as possible. Co-surfactants allow flexibility at the oil/water interface, which results in a thermodynamically stable structure, and precise material proportioning can satisfy both

criteria. It forms steadily with only agitation. Particles are tiny compared to the wavelength visible to the naked eye [9]. To speed up lipophilic drug dissolution, lipid-based formulation approaches have gained popularity. Two SDLBF types exist [10].

- An autologous emulsifier (SEDDS).
- A self-micro emulsifying drug delivery system (SMEDDS)

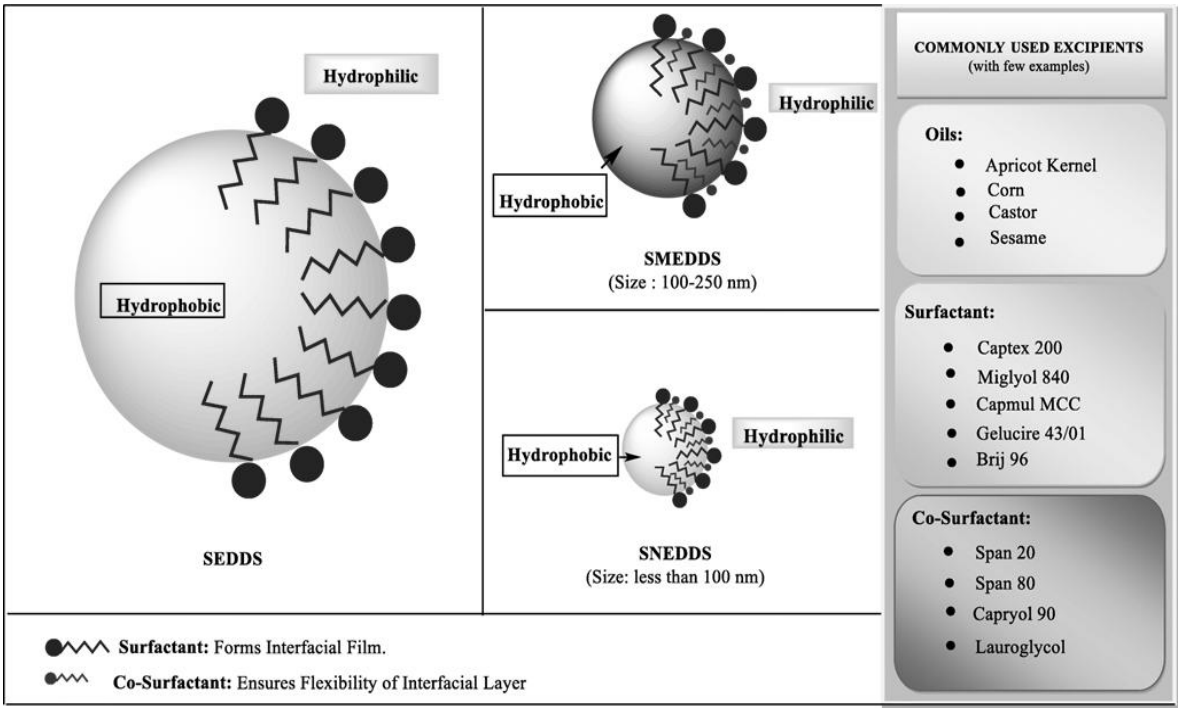

Figure 2: Structure of SMEDDS:[11]

Need of the (SMEDDS) Self-Micro Emulsifying Drug Delivery System: Oral administration for weakly water-soluble compounds involves pre-dissolving the medicine in a solvent and filling capsules. This approach avoids the rate-limiting stage of particle dissolution in the GIT's aqueous environment by pre-dissolving the chemical. Partitioning kinetics will want the medicine to end up in lipid droplets, hence dissolving it in a lipid carrier may minimise precipitation during dilution in the GIT. A water-soluble polymer can boost the therapeutic compound's resource solubility in poorly soluble capsules. The drug may crystallise in the polymer matrix if it chooses a more thermodynamically stable state [12].

PVP and PEG 6000 have been used to make solid solutions with poorly soluble drugs. The medicine may crystallise in the polymer matrix if it chooses a more thermodynamically stable state. Thus, differential scanning calorimetry and X-ray crystallography must be utilised to assess physical stability of such compositions. Smedds exploit the gastrointestinal tract to improve the drug's bioavailability, solubility, and digestion when taken orally [13].

Advantages: A novel method for improving water immersion that could lead to higher bioavailability of lipophilic medicines. In oil-in-water (Oil/Water) droplet emulsion system, Smedds readily interact with water to produce fine particles. [14].

- **Oral Bioavailability Development:** Rate-dependent dissolution limits bioavailability of several poorly soluble drugs. SMEDDS' ability to deliver drugs to the gastrointestinal tract in solubilized and micro emulsified forms (sphere sizes between 1-100 nm) [14] increases specific surface area, which improves drug delivery across the intestine's aqueous boundary layer and absorption membrane, improving bioavailability [10].

- **Ease of Manufacturing and Scaling:** SMEDDS has a distinct advantage over other drug delivery technologies including microemulsion, liposomes, nanoparticles, and others that require improved processing. Absorption is called bioavailability. SMEDDS requires simple, low-cost manufacturing equipment including streamlined rotary mixers and volumetric liquid filling equipment for large-scale production [10].

- **Food Impacts on Inter- and Intra-Subject Variability Reduction:**

- **Ease of Manufacturing and Scaling:** SMEDDS outperforms microemulsion, liposomes, nanoparticles, and other drug delivery methods that require enhanced processing. Bioavailability is absorption. For large-scale production, SMEDDS needs inexpensive rotary mixers and volumetric liquid filling equipment [10].

- **Distribution of GIT-Hydrolysable Peptides:** SMEDDS are unique in their ability to transport macromolecules such peptides, hormones, enzyme substrates, and inhibitors and protect against enzymatic hydrolysis. Polysorbate 20 protects prodrugs against intestinal cholinesterase. [10]

- **Lipid Digesting Process has No Effect:** SMEDDS' efficacy is unaffected by lipolysis, bile salt emulsification, or mixed micelle formation, unlike other lipid-based drug carriers. Micro-emulsified SMEDDS can swiftly permeate the mucin and water unstirred layer without digestion [10].

- **Increased Capacity for Drug Loading:** SMEDDS offer a larger drug loading capacity than conventional lipid solutions because amphiphilic surfactants, co-surfactants, and co-solvents solubilize weakly water-soluble medications with intermediary partition coefficients better than natural lipids [10].

Disadvantages

- This in vitro model needs more development and validation before its strength can be appraised.
- Alternative prototype lipid-based preparations must be generated and tested in vivo in a suitable animal study because future progress will depend on in vitro-in vivo correlations.
- Medication chemical instability and high surfactant concentrations (30-60%) irritate the GIT.
- Why Volatile cosolvents in typical self-micro emulsifying formulations enter soft or hard gelatine capsule shells, precipitating lipophilic medications.
- The hydrophilic solvent dilutes the medication, increasing its precipitation ability [15,16].

Advantages of Over The Other Conventional Emulsion

- SMEDDS promote hydrophobic drug solubility like emulsions, but they don't layer. SMEDDS micro emulsions are optically transparent and thermodynamically stable. Droplet size distinguishes micro and regular emulsions. Ordinary emulsion droplets are 0.2 to 10 μm, while SMEDDS micro emulsion droplets are 2 to 100 nm.

- SMEDDS distributes emulsions only orally, however packed hard gelatine, soft gelatine capsules, and tablets are available [17].

2. Factor Affecting the Smedds

- **Nature and Dose of Drug:** SMEDDS has the most trouble delivering drugs with low water and lipid solubility (log P values of around). The drug's oil phase solubility affects SMEDDS's solubilization ability. As previously stated, if a surfactant or co-surfactant plays a bigger part in drug solubilization, precipitation may occur due to SMEDDS dilution reducing their ability. Equilibrium solubility can predict gastric precipitation. The gut's solubilizing and colloidal stabilising environment may impede crystallisation [18].

  High dose drugs are not suitable for SMEDDS unless they are very soluble in at least one element, preferably lipophilic [1].

- **Polarity of Lipophilic Phase:** Lipid phase polarity affects microemulsion medication release. The droplet's polarity depends on the HLB, fatty acid chain length and unsaturation, hydrophilic portion molecular weight, and emulsifier concentration. A medicine's polarity reflects its affinity for oil and water and the forces it generates. Strong polarity releases the drug fast into the aqueous phase. Sang-Cheol Chi found that oil phase polarity affects SMEDDS release. High-polarity oil phase formulations released the most [1].

- **Drug Solubility in Oil Phase:** The drug's oily phase solubility determines SMEDDS's solubility. Dilution of SMEDDS lowers the solvent capacity of the surfactant or co-surfactant, which increases the likelihood of precipitation [19].

- **Equilibrium Solubility Measurement:** Predicts gastrointestinal precipitation. However, gut solubility may impede crystallisation. Poutons found that such a formulation can take 5 days to attain equilibrium and stay hyper saturated for 24 hours after the event emulsification event.

- **Charge of Emulsion Droplets:** Physiological investigations have established that absorptive cells, like all cells in the body, have a negative apical potential in proportion to the lumen's mucosal solution54. Gershanik and Benita55 showed that positively charged emulsion droplets formed by adding oleylamine (OA) to appropriate SEDDS interact electrostatically with the CACO-2 monolayer and the everted rat gut mucosa. This formulation enhanced oral progesterone bioavailability in young rats. Benzoic acid increased the self-emulsifying effectiveness of SEOFs and SMEOFs in 0.1N HCl by creating a positively charged emulsion [20].

Principle: SMEDDS generate oil-in-water emulsions by agitating and diluting aqueous phase. This phase improves medication absorption and disintegration. This improved solubility protects the medication against enzymatic hydrolysis and p-glycoprotein efflux. SMEDDS increase BCS class II medication aqueous solubility, however class IV drug bioavailability is limited [(9)].

II. COMPOSITION OF SMEDDS

SMEDDs solution disperses quickly and consistently after dilution. Hydrophobic SMEDDs medicine re-solubilizes and stays solubilized till absorbed. Globule size and droplet polarity determine how well the formulation releases drugs.
The component of the smedds:

- Drug
- Oil
- Surfactant
- Co- Surfactant
- Polymer
- Consistency Builder
- Other Component

1. Selection Criteria of Drug:

- Smedds can use low-therapeutic-dose drugs [(21)].
- Drugs that are administered orally at high doses are not suited for smedds
- The drug must remain chemically and physically stable, and should have considerable solubilization property for manufacture of SMEDDS
- The order of drug release must stay constant throughout the preparation process.
- The SMEDDS can assist in solving the problems listed below for all of the BCS Class categories shown in the table below. [(21)] Smedds are used in a variety of BCS Class drugs.

Table 1: Role of SMEDDS in Various BSC Class of Drug. [(8)]

Drug Class	Role of SMEDDS	Example
Class 1	Prevents Enzymatic breakdown of drugs in stomach and promotes intestinal wall efflux.	Diazepam, Captopril, Diltiazem
Class 2	Enhances solubilization and bioavailability of drugs	Dapsone, Ibuprofen,Carbamazepine
Class 3	Enzymatic breakdown, gut wall efflux, and bioavailability are all classified as Class 3.	Atropine sulphate, Biperiden
Class 4	Least use of this drug Solubilization, enzymatic activity, gastrointestinal wall efflux, and bioavailability	Albendazole, Acetazolamide

2. Selection of Excipient: These facts are supported by the fact that efficient self-emulsifying systems require precise pharmacological excipient combinations. After identifying a list of candidate excipients, a binary drug-excipient screening for solubility, compatibility, and stability should be done to select the optimum lipid system(s) for the drug.

The components are chosen with goals in mind, such as:
Maximum medication loading.

- To minimise stomach self-emulsification duration and droplet size for optimal absorption;
- To minimise emulsion droplet size fluctuation due to pH and electrolyte content of the aqueous medium.
- To prevent pharmaceutical breakdown and metabolism [22,23].

SMEDDS are made up of the Following Components:

1. **Oil:** The oil is an essential excipient in SMEDDS because it can dissolve the therapeutic level of the lipophilic drug, facilitate self-emulsification, and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing GI tract absorption.

   The selected drug candidate's best solubilization and nano emulsion preparation require oil. Triglycerides are extremely lipophilic oily substances, and medicine solvent potential is often a function of dosage in ester groups. Medium chain triglycerides (MCT) have the highest solvent capacity and oxidation resistance.

   Novel semi-synthetic MCT can improve water solubility of poorly soluble drugs, as can vegetable oils, digestible or non-digestible oils and fats like olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil and hydrogenated oil.

   40–80% concentration is used. Modified and hydrolysed vegetable oils are preferred because they have a larger solubility potential, better self-emulsification with so many surfactants, and are safe for oral consumption [15].

Table 2: List of Oil/Lipid used in Formulation of SMEDDS. [8]

Class	Example	Characteristics	
Triglycerides	LCT	Corn oil, soybean oil, olive oil, peanut oil, sesame oil, sunflower oil,	1420 carbon in chain of fatty acid GRAS status administration, digestion, absorption, poor self-dispensing capabilities of LCT, and typically reduced loading capacity for medicines with intermediate log P value systems After dispersion and digesting of the composition, they have such a higher solubilizing potential.

	MCT	Fractionated coconut oil, palm seed oil, triglycerides of caprylic/capric acid	fatty acid chains have 612 carbon atoms. MCTs have a high solubilizing potential for less lipophilic medicines as well as a high self-dispensing capability. The oxidation resistance of semisynthetic MTC containing hydrogenated double bond.
Mixed mono-, di-, and triglyceride		Imwitor988, Imwitor 308 Maisine 35-1 Capryol, Myrj	Because of their amphiphilic character, they have surface active properties and are efficient in replacing conventionally used oil due to their improved self-dispensing abilities and enhanced solubilizing capacity for weakly water-soluble medicines.

2. **Surfactant:** Surfactants improve hydrophobic drug solubility in oil, disperse produced emulsion in GIT secretions, increase bioavailability by increasing permeability, prevent drug precipitation in the GI lumen, and prolong the drug moiety in dissolved form for effective absorption. Some surfactants are edible.

They form a more stable micro-emulsion at the oil-water contact and in the interior phase. Combining ionic and non-ionic improves micro-emulsion degree/area. Anionic-non-ionic surfactant mixtures cause synergy in essential micelle concentration.

Excess surfactant irritates the gut. 30-60% surfactant creates stability. Surfactant concentration lowers droplet size. Surfactant concentration can increase mean droplet size [(15)]. They are divided into four categories.

- **Anionic Surfactant:** Carboxyl (RCOO-), sulphonate (RSO3-), or sulphates are examples of hydrophilic groups with a negatively charged (RO- SO3-). Potassium laurate and sodium lauryl sulphate are two examples. Those are the most popular.

- **Cationic Surfactant:** Cationic surfactants have a positive charge on the hydrophilic group. Quaternary ammonium halide is an example.

- **Ampholytic Surfactants:** Zwitterionic surfactants (also known as ampholytic surfactants) have both a negative and positive charge. Sulfobetaines, for example.

- **Non-Ionic Surfactant:** Non-ionic surfactants, which have no charge on the hydrophilic group but get their water solubility from highly polar groups like hydroxyl or polyoxymethylene (OCH2CH2O). Sorbitan ester (Spans) and Polysorbate (Tween) are two examples [(24)].

3. **Co-Surfactant:** A co-surfactant is an oral organic solvent like ethanol, propylene glycol, or polyethylene glycol (PEG) that dissolves large amounts of water-loving or lipid-soluble pharmaceutical surfactants faster. These solvents are microemulsion co-

surfactants. However, liquor and other co-surfactants disperse into the elegantly folded gelatine or hard gelatine case shells [8]. A liquid mixture with high surfactant and co-surfactant concentrations forms smedds.

Evaporating alcohol and other volatile liquids from soft or firm gelatine capsule shells makes the proper medicament [13].

4. **Consistency Builder:** Polymers are made up of five percent to fortieth of the total weight of a substance that cannot be ionised or broken down by the body's physiological processes. In order to modify the emulsion's consistency, a certain component is introduced into the system. This substance must be entirely inert and it must not have any kind of reaction with the remainder of the emulsion or the smedds. There are several other examples, such as stearic corrosive, cetyl liquor, tragacanth, and beeswax [8].

5. **Other Components:** Flavour, antioxidant, and pH adjuster are utilised. When oxidised, lipid compounds, especially unsaturated ones, form peroxide. Free radicals like ROO, RO, and OH can damage and poison medicines. Lipid peroxides can also be produced through auto-oxidation. Lipid hydrolysis is fast due to solution pH or processing energy, including ultrasonic radiation. Lipophilic antioxidants as -tocopherol, propyl gallate, and BHT may be needed to preserve the oily residue of smedds [8].

Table 3: Excipient used in the Formation of Smedds. [25]

Oils	**Co-solvents**	**Surfactant/ Co-surfactant**	**Consistency Builder**	**Polymers**
Cotton seed oil Corn oil Soyabean oil Castor oil	Ethanol Glycerine Polyethylene glycol Polypropylene Glycol	Span 20 Span 80 Tween 20 Tween 80	Tragacanth Cetyl alcohol, Stearic acid, Bees wax	Hydroxy propyl Methyl cellulose, Ethyl cellulose
Consistency Builder: To change the consistency of the emulsion, ingredients such as tragacanth, cetyl alcohol, stearic acid, or beeswax can be added.				

III. METHOD OF PREPARATION

Newly reported approaches can be employed to generate self-micro emulsifying drug delivery systems (SMEDDS). The methodology involves the addition of varying amounts of oil, surfactant, and co-surfactant into a vial, followed by a gentle mixing of the constituents. The acquisition of a clear and unambiguous solution, known as Self-Micro emulsifying Drug Delivery Systems (SMEDDS), can be achieved upon complete dissolution. In certain instances, a drug may be dissolved within one of the excipients, with the remaining excipients afterwards being introduced into the drug solution. Subsequently, it is imperative to ensure that the solution is thoroughly blended and subjected to rigorous examination for the presence of turbidity. Following a 48-hour period of equilibration at room temperature, it may be

necessary to apply heat to facilitate the production of a clear solution. The selection of appropriate capsule size [26] for storage of the formulation is contingent upon the ultimate volume.

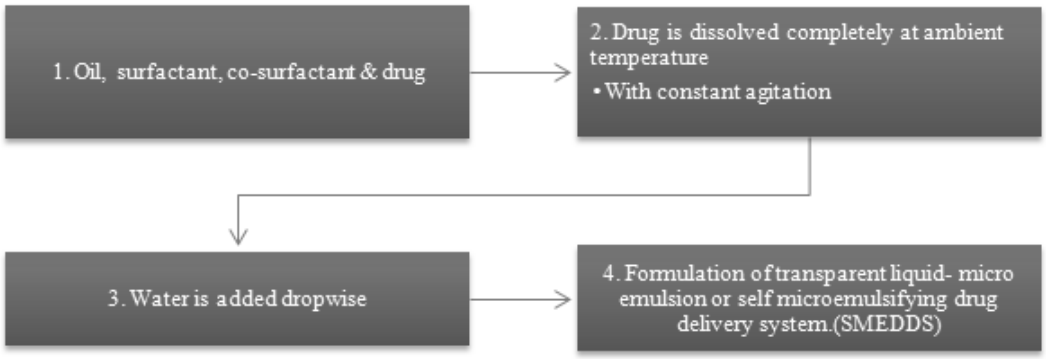

Figure 3: Step of Formulation of SMEDDS. [27]

Some of the methods are enlisted below for preparation of SMEDDS:

1. **Phase Titration Method:** The phase titration method, also known as the spontaneous emulsification technique, is employed for the production of microemulsions. These microemulsions can be effectively characterised and represented through the use of phase diagrams. The utilisation of a phase diagram as a means to investigate the intricate array of interactions that may arise during the blending of different components is a commendable approach. Microemulsions are formed by the composition and concentration of different components, resulting in a variety of association structures such as emulsion, micelles, lamellar, hexagonal, cubic, and varied gel and greasy dispersion.

   The study necessitates a comprehension of the equilibrium circumstances pertaining to the system under investigation, as well as the demarcation of phase boundaries within that system. The utilisation of a pseudo ternary phase diagram is preferred over a quaternary phase diagram due to the complexities and time-consuming nature of building the latter. The pseudo ternary phase diagram allows for the identification of several zones, such as the microemulsion zone, where each corner of the diagram represents 100% of a specific component. This alternative approach facilitates a more accessible and comprehensible representation of the system.

   The classification of the region can be determined based on its composition, namely whether it is characterised as water-in-oil (w/o) or oil-in-water (o/w) microemulsion. Thorough scrutiny is necessary to ascertain the exclusion of metastable systems [28].

2. **Phase Inversion Method:** Phase inversion in microemulsions occurs when an excess of the dispersion medium is introduced or when the temperature is elevated. Phase inversion is a critical process that induces notable physical transformations, such as modifications in particle size, which can have an impact on the release of medication both in vivo and in vitro. These methodologies operate by modifying the inherent curvature of the surfactant.

The objective can be achieved through the use of non-ionic surfactants, wherein the temperature of the system is raised. This temperature increase induces a transition from an oil-in-water (o/w) microemulsion at low temperatures to a water-in-oil (w/o) microemulsion at high temperatures, known as a transitional phase inversion. During the cooling process, the system undergoes a phase characterised by a lack of spontaneous curvature and reduced surface tension, facilitating the formation of finely dispersed oil droplets. The approach is commonly referred to as the phase inversion temperature (PIT) technique. Instead of considering temperature, alternative factors such as salt content or pH value might be assessed. Modifying the volume percentage of water can also induce a transition within the spontaneous radius of curvature.

Water droplets are formed in a continuous oil phase through the gradual addition of water to the oil. The surfactant's spontaneous curvature undergoes a transition from initially providing stabilisation to a water-in-oil (w/o) microemulsion, to promoting the formation of an oil-in-water (o/w) microemulsion at the inverted locus, when the water volume percentage is increased. In the vicinity of the oil/water interface, surfactants with shorter chain lengths form pliable monolayers, leading to the formation of a microemulsion with a discontinuous structure precisely at the site of inversion [(28)].

- **Mechanism of Self-Emulsification**: Several formulation methods have been reported; however, none can explain all micro emulsion properties. According to "Reiss," self-micro emulsification occurs when the entropy shift that favours dispersion is greater than the energy needed to increase surface area [(29)]. The free energy of a typical emulsion in dispersion determines the energy needed to construct a new oil-water surface. The equation describes it.

$$\Delta G = \sum N_i \pi r_i^2 \sigma$$

Where the G = free energy associated with process

N= number of droplets
r = radius
σ= interfacial tension

The emulsion produced by aqueous dilution is stabilised by conventional emulsifying agents, which form a monolayer around the droplet to reduce interfacial energy and prevent coalescence. Emulsification is energy-efficient. Emulsification requires surface-sharing-resistant interfacial structures. Self-micro emulsification systems require very low, positive, or negative free energy for the emulsion. (Emulsification occurs automatically)[30].

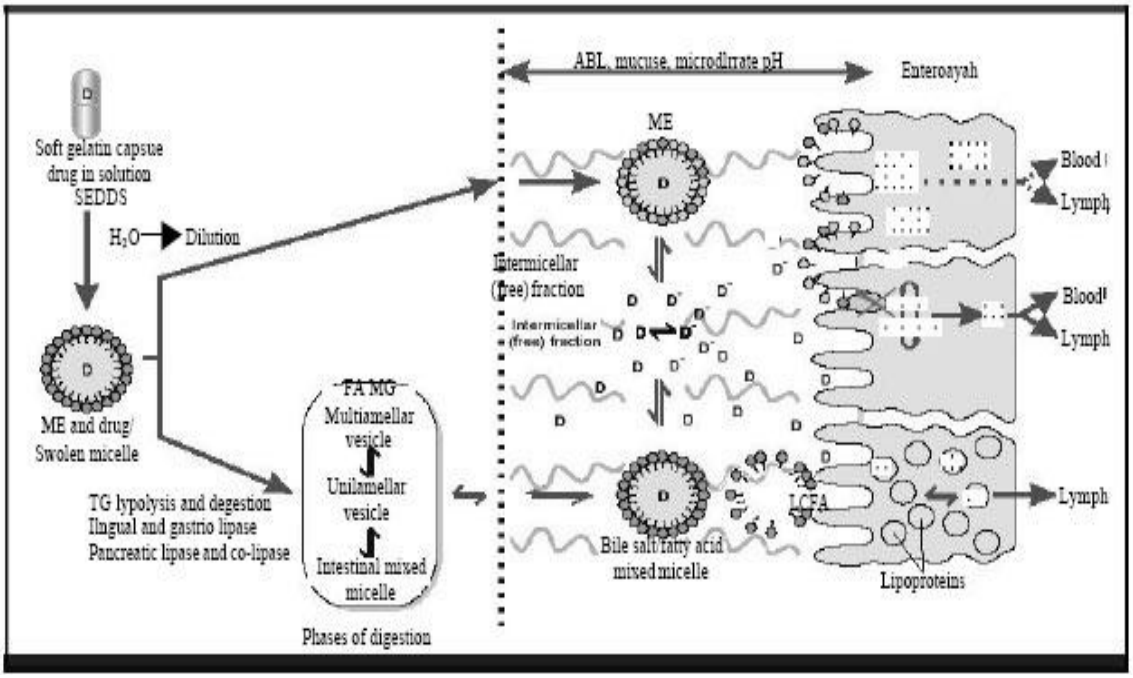

Figure 4: Mechanism of Self-Emulsifying Drug Delivery System [11]

- **Ternary Phase Diagram:** A phase diagram can determine the quantity, type, weight percent, and composition of each phase at a certain temperature and system composition. To simplify drawing and interpretation, the diagram is three-dimensional yet drawn in two dimensions. Ternary-phase diagrams are used to characterise microemulsion areas. A microemulsion requires an oil phase, aqueous phase, and surfactant [2]. Dilute the ternary phase diagram.

  Ternary combinations with different surfactants, co-surfactants, and oils are needed. Surfactant concentrations are 30–75% (w/w), oil concentrations are 25–75%, and co-surfactant concentrations are 0–30%. Each mixture has 100% surfactant, co-surfactant, and oil conc. For nano emulsion manufacture, excipient ratios are tested by diluting combinations with enough double distilled water. The ternary phase diagram for the system that produces nano emulsion with a desired globule size will determine the nano emulsion production zone [15].

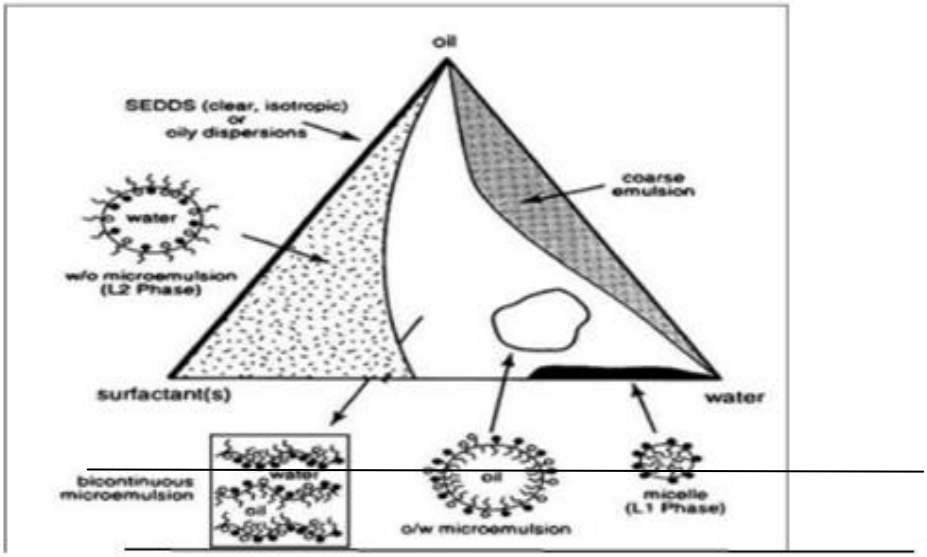

Figure 5: Ternary Phase Diagram [31]

- **Pseudo Phase Diagram:** At room temperature, titration of homogeneous liquid mixes of oil, surfactant, and co-surfactant with water produces a pseudo-ternary phase diagram. Oil phase and Smixes (surfactant: co-surfactant ratio) are vortexed in screw-cap glass tubes at 9:1 to 1:9. To reach equilibrium, slowly titrate each combination with distilled water aliquots and stir at room temperature. Visual evaluation ensures transparency. After equilibrium, the mixture is titrated with distilled water until no turbidity remains. Micro-emulsions are transparent and isotropic. The findings determine the oil, surfactant, and cosurfactant percentages, which are associated on the phase diagram and used to make smedds [15].

Some of the formulations of SMEDDS include:

- Tween 80 PEG 400 used as the Smix, while Capmol MUM C8 used as the oil phase.
- In other formulation 20 PEG 400 is used as the Smix and Capryol is used as the oil phase. [32]

IV. CHARACTERIZATION OF SMEDDS

- **Particle Size: (**1) Proton correlation spectroscopy (PCS) or scanning electron microscopy (SEM) may be able to identify particle or molecule size, which can be determined within a range of 10 to 5000 nm.

The measurement of zeta potential is an important aspect of our study [33,1]. Zeta potential, often referred to as electrokinetic potential, is a technique employed to quantify the electrostatic potential present at the electrical double layer. This method is utilised to determine the charge characteristics of a given sample. The Zetasizer HAS 300 instrument is employed for the purpose of measuring the zeta potential of micro emulsions. The specimen is positioned within a disposable zeta cell, which afterwards documents the outcomes. Prior to introducing the material into the cell, it undergoes a

methanol wash and subsequent rinse with the sample, even preceding the commencement of the experiment.

- The zeta potential is employed to quantify the charge present on the globules. The stability of a sample is directly influenced by the magnitude of the zeta potential, as it is responsible for the repulsive forces between individual globules during their random movement in the media.

Stability Studies: There are two types of studies;

1. **Temperature Studies [34]:** The Smedds are diluted using filtered water and subjected to various temperatures (2-8°C, room temperature, and high temperature) to assess the thermal stability of the sample. The subsequent observation of the process is conducted to detect any indications of phase separation, flocculation, or precipitation. This step is essential in order to propose suitable storage conditions for the resulting product, as it directly impacts the stability of the product.

2. **Centrifugation Studies[12]:** The diluted improved self-micro emulsifying drug delivery system (SMEDDS) is mixed with either filtered water or distilled water in order to evaluate its metastable nature. At this stage, the microemulsion is subjected to centrifugation for a duration of 15 minutes at a temperature of 0°C and a rotational speed of 1000 revolutions per minute (RPM) in order to enhance the uniformity of the emulsion at a smaller scale.

3. **Visual Assessment[3]:** In order to evaluate the self-emulsification properties, the necessary formulation is introduced into a 100 ml volume of water contained within a glass Erlenmeyer flask, maintained at a temperature of 25 degrees Celsius. The contents are mixed by hand. If the formation of emulsion is reduced or absent, the propensity for the spontaneous generation of a transparent emulsion is considered to be favourable or unfavourable.

4. **Determination of Self-Emulsification Time[24]:** The USP 22 dissolution apparatus is employed for the assessment of the emulsification duration of self-micro emulsifying drug delivery systems (SMEDDS). A quantity of 300mg of the sample composition is introduced into 500ml of distilled water at a temperature of 30°C. The mixture is subjected to mild agitation using a standard stainless steel dissolution paddle revolving at a rate resulting in an emulsion time of 50 ppm.

5. **Differential Scanning Colorimetry(DSC) [3]:** Differential scanning colorimetry is method use for measurement of heat capacity of the molecule (the heat required to warm the sample).

   Differential scanning colorimetry for smedds can be evaluated using DSC 60. A liquid sample as well as a solid sample should have been placed in an aluminium pan, and the result should be recorded.

6. **Transmittance Test[35]:** Transmittance is measured using a UV spectrometer to verify the stability of the optimised for emulsion formation with regard to dilution (UV-1700 nm).

7. **In Vitro Study[35]:** The USP 24 methodology is employed to perform a quantitative in vitro release study using 900 mL of purified distilled water. In the release phase, the self-micro emulsifying drug delivery system (SMEDDS) is introduced into a dialysis bag in order to evaluate and compare its release profile with that of a conventional tablet. At predetermined time intervals, a volume of 10 mL of the sample solution is collected and subjected to filtration using a 0.45 membrane filter. The filtered solution is then properly diluted and analysed using spectrophotometry.

   Following the removal of the test sample, an equivalent volume of fresh dissolving media is reintroduced concurrently. The Beer-Lambert equation was employed to determine the percentage of medication dissolution at different time intervals.

8. **In Vivo Studies[12] [36-40]:** There are several models that are employed for the purpose of conducting in vivo studies. In order to conduct any animal-based in vivo experiments, researchers must obtain authorization from animal ethics committees and adhere to the rules established by these committees.

Various route of administration of self-micro emulsifying drug delivery system:

Smedds are predominantly administered via the oral route [19][41] [42], although the transdermal and parenteral routes are utilised to a lesser extent.

1. **Challenges to the Self-Micro Emulsifying Drug Delivery System**

- SMEDDSs are typically viscous fluids that are given in a capsule comprised of hard or soft gelatine. However, lipid-based products may leak into the capsules and may react with the capsule's components.

- The precipitation of the drug occurs in the gastrointestinal fluid upon dilution of SMEDDS. Maintaining the solubilized state of medicine inside the gastrointestinal tract is a common requirement for lipid formulations in the context of pharmaceutical applications. The precipitation of the drug from the system undermines the advantageous effects of the lipid-based formulation method.

- The drug is more likely to precipitate when diluted due to the dilution effect of the hydrophilic solvent. Consequently, the utilisation of polymers is imperative in mitigating medication precipitation inside the biological system.

- The majority of self-micro emulsifying drug delivery system (SMEDDS) formulations incorporate soft gelatine capsules. In contrast, gelatine capsules possess several drawbacks. Transmissible spongiform encephalopathy (TSE) and consumer preference/religion represent only a limited number of the concerns associated with animal gelatine. The migration of self-micro emulsifying formulation including volatile co solvents within the shells of gelatine capsules has been observed, resulting

in the precipitation of lipotropic medications. These issues have led to a demand in the market for a diverse range of soft gelatine capsules.

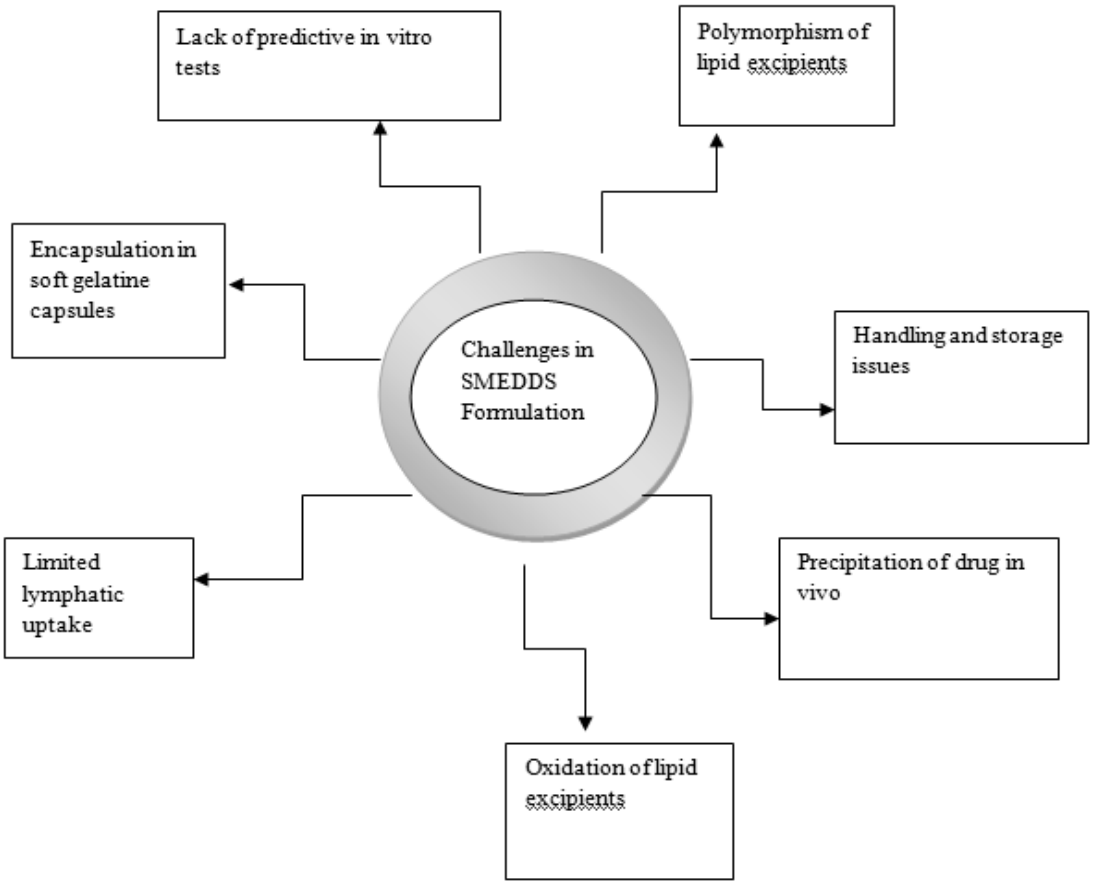

Figure 6: Challenges Occurs during the Formulation of SMEDDS [22]

- Limited targeting to lymphatics: There are two primary advantages associated with the targeting of lymphatics in comparison to the traditional method of portal blood absorption. Typically, lymphatic transport necessitates a high solubility of triglycerides and a high logarithm of the partition coefficient (log P). Nevertheless, the extent of drug transportation in to lymphatic system exhibit variability between different drugs. Therefore, it is imperative to have a comprehensive understanding of the lipophilicity and triglyceride solubility of a medicine in connection to its lymphatic trans.

- Lack of good in vitro models: One significant challenge encountered in the advancement of self-micro emulsifying drug delivery systems (SMEDDS) and other lipid-based formulations is the limited availability of dependable predictive in vitro models for assessment.

- Oxidation & polymorphism of a lipids utilised in SEDDS/SMEDDS formulation: Lipid excipients have the potential to induce lipid oxidation in unsaturated fatty acids and their derivatives. The use of a lipid-soluble antioxidant within the capsule is crucial in this context [43].

- Effect of food: The absorption of medication from the Self-Micro emulsifying Drug Delivery System (SMEDDS) formulation is not influenced by food. The consumption of food had a notable influence primarily on the absorption of itraconazole from the commercially available Sporanox capsule in human participants. In contrast, the impact was comparatively less pronounced for the self-emulsifying formulation of itraconazole [43].

Techniques for Transforming Liquid or Semisolid Self-Micro Emulsifying Drug Delivery System to Solid-Micro Emulsifying Drug-Delivery System: There are two potential dangers associated with the use of Liquid-SMEDDS formulations, namely the potential for medicine leakage from the capsule shells and the occurrence of drug precipitation. In order to tackle these challenges, a range of assertive methodologies have been employed to transform liquid self-micro emulsifying drug delivery systems (SMEDDS) into solid SMEDDS (S-SMEDDS). Consequently, the implementation of these tactics produced favourable outcomes, thereby showcasing the advantages associated with solid dose formulations in comparison to liquid dosage forms. The conversion of self-micro emulsifying drug delivery systems (SMEDDS) into solid oral dosage forms exhibits a synergistic impact, leading to enhanced solubility and bioavailability derived from SMEDDS. Additionally, this transformation offers advantages such as reduced processing expenses, improved stability and reproducibility, and enhanced patient adherence to solid dosage forms. [42]

- Spray drying
- Adsorption to solid carriers
- Melt granulation
- Melt extrusion /extrusion spheronization

Applications [43-44]

1. **Solubilization in SMEDDS:** Self-micro emulsifying drug delivery systems (SMEDDS) are commonly employed as efficient solubilizers for drugs exhibiting a wide spectrum of lipophilicity, owing to their substantial oil and surfactant constituents. Therefore, in the case of water-soluble drugs, the ability of a water-in-oil (w/o) microemulsion to enhance solubility is generally greater than that of an oil-in-water (o/w) microemulsion. Conversely, with oil-soluble pharmaceuticals, the converse holds true. Furthermore, the solubilization process is regulated by the composition of the self-micro emulsifying drug delivery system (SMEDDS).

2. **Sustain Release from SMEDDS:** The release of solubilized material in self-micro emulsifying drug delivery systems (SMEDDS) is influenced by a broad spectrum of behaviours, which can be attributed to the extensive variety of structures present within these systems. Consequently, in the context of an oil-in-water microemulsion, hydrophobic pharmaceutical compounds that exhibit solubility largely inside the oil droplets experience hindered diffusion, resulting in a gradual release profile determined by the substance's partitioning between the oil and water phases. In contrast, medications that are soluble in water dissolve readily and are released rapidly, as determined by the volume % of the dispersed phase.

3. **Increase the Bioavailability of Drug:** Due to the lipophilic nature of numerous drugs, they exhibit insolubility in aqueous solutions. The bioavailability of a lipophilic drug is expected to be somewhat low. The integration of drugs with oil to generate a complex within self-micro emulsifying drug delivery systems (SMEDDS) is deemed advantageous. The intestinal absorption of oil is facilitated, leading to enhanced solubility of medications. Consequently, enhance the bioavailability of the medicine.

Table 4: Recent Works on the Drug Loaded in the SMEDDS Which Improve the Bioavailability and Improve the Permeability. [45 -50]

Sr. No.	Name of Drug	Treatment	Surfactant	Co-surfactant	Oil	Drug dose	Log P Value
1	Simvastatin	Hyper cholesterolemia	cremophor	carbitol	Carpryol 90	6.98w/w	4.7
2	Carvedilol	Hypertension	40% kolliphor	40% PEG 400	Capmul/ Castor oil	12.5 mg	-
3	Exemestane	breast cancer	Cremophor ELP	Transcutol	Caproyl 90	25 mg	2.7
4	Lincomycin	antibiotic	Tween 80	-	PEG oil	-	-
5	Fenofibrate	Decreases the risk of heart attack	Tween 80	PEG 400	Labrafac CM 10	8.5%w/w	5.3
6	Olmesartan medoxomil (OLM)	Novel selective angiotensin II receptor blocker	Tween 20	carbitol	Castor oil	-	-

The following are the various dosage formulations of S-SMEDDS: [25]

- Dry emulsions
- Self-emulsifying capsules
- Self-emulsifying sustained/controlled-release tablets
- Self-emulsifying sustained/controlled-release pellets
- Self-emulsifying solid dispersions
- Self-emulsifying beads
- Self-emulsifying sustained-release microspheres
- Self-emulsifying nanoparticles
- Self-emulsifying suppositories

V. RECENT TRENDS

In recent years, there has been a development of a novel drug delivery technology known as self-micro emulsifying drug delivery system (SMEDDS), which utilises herbal components.

A diverse array of medicinal herbs and traditional pharmaceuticals are currently employed in the development of self-micro emulsifying drug delivery systems (SMEDDS). These substances primarily consist of extracts or volatile and fixed oils, including zedoary turmeric oil, quercetin silymarin, curcumin, vipoceptine, and berberine. Self-micro

emulsifying drug delivery systems (SMEDDS) primarily enhance the bioavailability of both crude herb and extract formulations [51].

The objective of this research is to develop a robust self-micro emulsifying delivery system (SMEDDS) for herbal extracts and evaluate its in vitro performance. The utilisation of self-micro emulsifying drug delivery systems (SMEDDS) has demonstrated its efficacy in providing a stable and secure means of administering herbal extracts. This is achieved through the encapsulation of liquids within a hard gelatine capsule. The determination of the solubility degree of herbal extract in different vehicles is conducted. The assessment is conducted via pseudo ternary phase diagrams.

The technique of micro emulsification, a dissolution method, is employed to evaluate the kinetics of herbal extract release. The clarity, precipitation, and particle size distribution of self-micro emulsifying drug delivery systems (SMEDDS) were assessed. A formulation and screening process was conducted based on solubility and phase diagram information. The experimental formulation consisted of an optimum combination of herbal extract (30%), surfactant (40%), and co-surfactant, which was utilised in the in vitro dissolution study (30% concentration).

When comparing the SMEDDS formulation to basic extract and standard marketed formulations with sluggish dissolving rates, it was observed that the SMEDDS formulation exhibited complete release within a duration of 10 minutes. The SMEDDS were subjected to storage conditions in accordance with the International Council for Harmonisation (ICH) guidelines for a duration of three months. The self-micro emulsifying drug delivery system (SMEDDS) successfully demonstrated excellent stability during the test. The enhancement of the dissolving profile of the herbal extract in self-micro emulsifying drug delivery systems (SMEDDS) was observed. The concept of Self-Micro emulsifying Drug Delivery Systems (SMEDDS) is indeed intriguing. One approach of enhancing solubility and hence, bioavailability [51].

VI. FUTURE PERSPECTIVE

Self-micro emulsifying drug delivery systems (SMEDDS) have demonstrated utility in enhancing the bioavailability of pharmaceuticals characterised by weak water solubility and low solubility in gastrointestinal (GIT) fluids. The understanding of the solubilization behaviour of Lipid Based Formulations (LBF) is enhanced through the application of a combination of in-vitro dispersion and digesting techniques, which allows for the investigation of the function of intestinal lipid processing. The present in-situ emulsion creation technology exhibits stability and can be effectively employed as an emulsion. In the context of linguistic analysis, the utilisation of prefixes can be employed as a means of formulating words. The future development of Self-Micro emulsifying Drug Delivery Systems (SMEDDS) is expected to effectively address and resolve many challenges associated with drug delivery. Due to their restricted water solubility, numerous drugs exhibit poor oral bioavailability, resulting in diminished effectiveness. Further investigation is required to gain a comprehensive understanding of pre-systemic metabolism or solubility within the context of the novel. Further investigation is necessary to advance the understanding and development of self-emulsifying osmotic pump tablet (SEOPT) formulations. This technological advancement is groundbreaking [10].

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