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Self micro emulsifying drug delivery system

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Abstract
In terms of formulation design and bioavailability of new pharmaceutical products, about 40% of drugs have low solubility in water, which presents a difficulty in the development of the ideal oral solid dosage form. Many methods have been employed to get around these issues, including changing the solubility or keeping the medicine dissolved during the stomach transit time. Lipid solutions, emulsions, and emulsion pre-concentrates, which can be created as physically stable formulations ideal for encapsulating such weakly soluble medicines, have received a lot of interest. Recently, a lot of attention has been paid to oral dosage forms that use a self-micro-emulsifying drug delivery system in order to increase the solubility and absorption of drugs that are not highly water soluble. SMEDDS are physically stable, easy to manufacture, and can be filled in soft gelatin capsules. A combination of a drug, an oil, a surfactant, and/or other additives make up SMEDDS. Micro-emulsions with droplet sizes between 10 and 100 nm are produced when these substances are gently mixed in aqueous solutions. Rapid self-micro emulsification in the stomach and subsequent dispersion of emulsion droplets into the gastrointestinal tract to reach the sites of absorption are the mechanisms by which SMEDDS have been shown to boost drug absorption. SMEDDS's unique components stimulate the intestinal lymphatic transport of pharmaceuticals, and the resultant small droplet size from SMEDDS offers a high interfacial surface area for drug release and absorption. SMEDDS has also improved the oral absorption of various drugs. The goal of this review is to give a brief overview of SMEDDS formulation, potential methods for enhancing bioavailability, and assessments of those methods.

Keywords: SMEDDS (Self-micro emulsifying drug delivery system), bioavailability, low solubility, lymphatic transport, interfacial surface area

Introduction
Around 40% of newly discovered medication candidates have low water solubility, which results in poor bioavailability. Enhancing the water solubility of insoluble and sparingly soluble drugs is very important, since most newly developed drugs are highly lipophilic in nature and its investigations are primarily carried out utilizing natural solvents like benzene, toluene, acetone, water, methyl acetate. The majority of these organic solvents are hazardous, expensive, and volatile [1].

Poorly water-soluble pharmaceuticals have had their aqueous solubility improved using a variety of methods like solid dispersion, liposomes, polymer micelles, nano emulsions, cyclodextrin inclusion, and self-emulsifying drug delivery system (SEDDS). Recently, lipid solutions, emulsions and pre-emulsion concentrates have received a lot of consideration because they are arranged as physically steady formulations appropriate for epitome of such ineffectively dissolvable drugs. Emulsion frameworks are related with their claim set of complications counting stability and fabricating issues related to their commercial production. Self-emulsification frameworks are one definition procedure that can be an appropriate to such problems. These methods may provide an enhancement within the rates and degree of assimilation and lead to more repeatable blood-time profiles for lipophilic medicate compounds that display dissolution rate-limited absorption.

The two types of self-emulsifying systems are
1) Self-emulsifying drug delivery system (SEDDS).
2) Self-micro emulsifying drug delivery system(SMEDDS)

Self-emulsifying drug delivery system(SEDDS) is a resistant combination of drug, lubricate, surfactant and co-surfactant, which may also be called microemulsion preconcentrate if they lead to the formation of microemulsion upon dilution with water, whereas a self-micro emulsifying drug delivery system (SMEDDS) is a form of SEDDS that can form tiny oil-in-

water droplets with a diameter of 50nm when the GI tract is slightly stirred without going through the dissolution process. SMEDDS has the potential to deliver drugs that are less water soluble because SMEDDS microemulsions provide 100% drug trapping and protection from GI breakdown [2, 3].

SEDDS typically create emulsions with droplet sizes ranging from 100-300 nm, whereas SMEDDS form obvious microemulsions with a bead estimate of below 50nm also, SMEDDhave an oil concentration of less than 20% compared to SEDDS's 40–80%. Compared with emulsions which are delicate and ultra-stable dispersions, SMEDDS are physically stable that are simple to fabricate. Thus, for lipophilic compounds that display disintegration rate-limiting retention, these frameworks may offer an advancement in the absorption rate [4].

SMEDDS can be transformed into solid-SMEDDS by employing techniques such as met granulation, spray-drying, adsorption etc. Moreover, the creation of solid dosage forms like tablets, capsules, dry emulsions, pellets etc has improved prospects with solid-SMEDDS. Solid-SMEDDS integrates the benefits of two together SMEDDS and solid dosage forms. Moreover, solid-SMEDDS have greater stability when compared to SMEDDS. For the purpose of creating a dosage form that is more bioavailable, SMEDDS and solid-SMEDDS have been created by dilution method and absorption technique, respectively [5].

SMEDDS in particular have gained more attention recently, mainly because they are physically stable, simple to make, and can be put inside soft gelatine capsules, where they will produce a drug-containing microemulsion with a sizable surface area when they are dispersed throughout the gastrointestinal tract. By partitioning the drugs into the liquid portion of stomach fluids, the emulsion will further facilitate the incorporation of the drug due a faster digestion by gastrointestinal enzymes and after transfer to various micelles or possible direct incorporation from the emulsion particle [6].

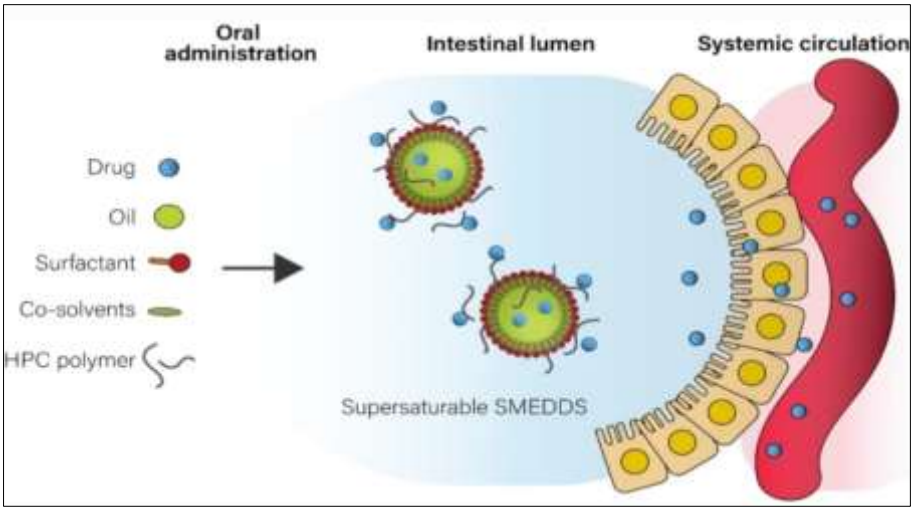

Fig 1: Graphical Abstract of SMEDDS

This article provides an overview of SMEDDS as a crucial technology for creating lipophilic medications and boosting their oral bioavailability.

Advantages of SMEDDS

1. **Storage:** SMEDDS share emulsions benefit of encouraging the dissolvability of hydrophobic drugs. Microemulsions gradually cream over time, whereas SMEDDS can be kept with ease since they are thermodynamically stable.
2. **Stability:** Since SMEDDS does not contain water, they have better physical and/or chemical stability during long-term storage than micro/nano emulsions do.
3. **Compliance:** Majority of SMEDDS formulations come in capsule or tablet forms, which take up small volume, simple to manage and hence enhanced patient compliance.
4. **Palatability:** The lipid formulation's concerns with palatability can be resolved by simply filling capsules with SMEDDS formulation.
5. **Effect of food:** Food has no impact on how well a medicine from the SMEDDS formulation is absorbed. The lipophilic content of fatty foods facilitates the drug's absorption from these systems.
6. **Quick onset of action:** SMEDDS has the potential to promote the drug's rapid oral absorbs cause a rapid onset.
7. **Ease of manufacture and scale-up:** SMEDDS can be produced at a large scale with ease because it only needs basic and affordable production facilities, like a basic mixer with an agitator and volumetric liquid filling machinery [7].

Limitations of SMEDDS

1. **Drug precipitation on dilution:** Diluted SMEDDS aid in drug precipitation in the gastrointestinal juices. The constant need for lipophilic formulations is that they deliver the medicine in its solubilized form to the gastrointestinal tract (GIT). The advantages provided by the lipid-based formulation technique are negated when the drug precipitates out of the system.
2. The influence of the hydrophilic solvents will result in a higher precipitation property of the formulation under dilution impact. For the purpose of reducing drug precipitation *in vivo*, polymers must also be added.
3. **Encapsulation in soft gelatine capsules:** Most commercially available SMEDDS formulations are available in the soft gelatine capsule form. However, there are certain drawbacks to the gelatine capsule. A few concerns related to animal gelatine include the cost of assembly, transmissible spongiform encephalopathy

(TSE), and buyers' inclination/religion. In order to guarantee the precipitation of the lipophilic drugs, volatile co-solvents self-micro emulsifying drug delivery systems are well known to migrate into the hard or soft gelatine capsule shells. These problems create a demand in the market for a soft gelatine capsule replacement.

4. **Storage and handling:** SMEDDS in liquid form have handling, storage, and stability issues. As a result, developing strong SMEDDS appears to be a rational option to handle these issues.
5. **Limited targeting to lymphatic:** Depending on the medicine, a different amount of the drug may enter the lymphatics. Hence, a deeper understanding of a drug's lipophilicity and triglyceride solubility in connection to lymphatic transport is needed, as well as the requirement for a more accurate predictive model.
6. **Lack of good *in vitro* models:** The lack of reliable predictive in-vitro models for the evaluation of the formulation is another challenge in the development of self-micro emulsifying drug delivery systems and other lipid-based arrangements.
7. **Oxidation and polymorphism of lipids used to produc e SEDDS/SMEDDS**: Unsaturated fatty acids and their derivatives are found in lipid excipients, which are subject to lipid oxidation. This necessitates adding a lipid-soluble antioxidant to the formulation of the capsules. To reduce polymorphic variations of the excipient matrix caused by polymorphism related to thermos-softening lipid excipients, specific process management is required in their application [8].

Biopharmaceutical classification system

There are a variety of formulation techniques that might be used to increase the bioavailability of class II medications, including delivering the drug in solution and keeping it there while it dissolves in the intestinal lumen. Figure 2 below illustrates this. Class IV medications' bioavailability can be increased by paying close attention to the formulation. Class IV medications may have better bioavailability through formulation, but their weak membrane permeability is likely to make them less effective. A class II medication's absorption profile may resemble that of a class I drug if it is kept in a solubilized condition in the gut lumen. Ineffective membrane permeability limits the absorption of class IV and class III medications, which formulation methods can't do much to help with [10].

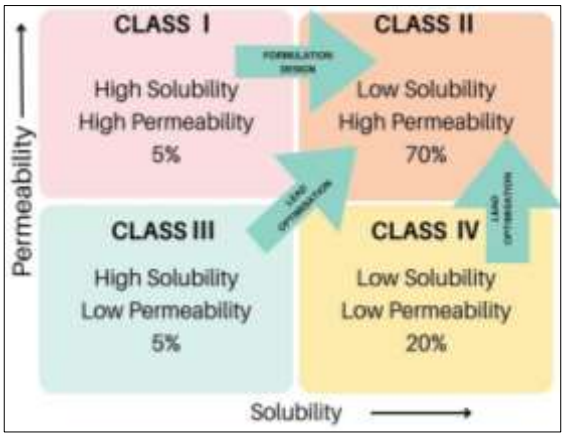

Fig 2: An Example Illustration of the Biopharmaceutical Classification System.

Table 1: List of examples of drugs from the I, II, III, and IV classes

Class I (Amphiphilic)	Class II (Lipophilic)	Class III (Hydrophilic)	Class IV
Diltiazem Labetalol Captopril Amiloride L-Dopa Glucose	Naproxen Diclofenac Phenytoin Dapsone Folic acid Verapamil	Famotidine Cimetidine Atenolol Ethambutol Biperiden Captopril Metformin-Hydrochloride	Cyclosporine Acetazolamide Furosemide Albendazole Terfenadine

Table 2: SMEDDS as a Solution to Various Issues with Several Drug Classes

BCS Class	Problems
Class I	Enzymatic degradation, gut wall efflux
Class II	Solubilization and bioavailability
Class III	Enzymatic degradation, gut wall efflux and bioavailability
Class IV	Solubilization, Enzymatic degradation, gut wall efflux and bioavailability

Mechanism of self-emulsification

Self-emulsification's mechanism is still not fully understood. However, self-emulsification is assumed to occur when the entropy change favours the distribution over the energy required to expand the distribution area. The energy required to produce a new interface between the oil and water phases directly affects the free energy of a standard emulsion formulation. The effective free energy (ΔG) during emulsification is given as:

$$\Delta G=\Sigma\ Ni\Pi r^{-2}\sigma$$

Where,
ΔG = free energy produced by the process
N = number of droplets
r = Radius of the Droplets
σ = interfacial energy

The two phases of the emulsion have a tendency to separate over time, decreasing the system's free energy and interfacial area. By producing a monolayer surrounding the emulsion droplets, the traditional emulsifying agent stabilises the emulsion that results from aqueous dilution, lowering the interfacial energy, and creating a barrier to coalescence [4].

Drug Selection for SMEDDS

For Biopharmaceutical Classification System BCS Class II and IV, lipid-based formulations are helpful. For lipidic system design, drug lipophilicity (logP) is helpful. Drugs with a high logP (higher than 4) are preferred. Low melting point and low drug dosage are ideal for SMEDDS formulation [10].

SMEDDS-compatible drug characteristics

1. The dose should not be too high.
2. The drug must be soluble in oil.
3. A drug with a high melting point is not ideal for SMEDDS.
4. It should have a high log P value [11].

Biopharmaceutical aspects of SMEDDS

Mechanism by which SMEDDS increases drug absorption

- **Alterations (reduction) in gastric transit:** Lipids enhance bioavailability by extending the time available for disintegration and slowing transport to the absorption site.
- **Increase in effective luminal drug solubility:** The development of intestinal mixed micelles is caused by the presence of lipids in the gastrointestinal tract (GIT) which discharge bile salts and biliary lipids such as phospholipids and cholesterol. This improves GIT's ability to dissolve substances. The potential for solubilization is further increased by the addition of lipids from the formulation.
- **Stimulation of intestinal lymphatic transport:** Lipids may increase the amount of lymphatic transport for highly lipophilic medicines and boost bioavailability either directly or indirectly by lowering first-pass metabolism.
- **Reduced metabolism and efflux activity of drug:** Some surfactants and lipids exhibit decreased efflux transporter activity in the gut wall, thereby increasing drug absorption.
- **Affecting intestinal permeability:** Lipids may alter the gut wall's ability to act as a physical barrier, increasing the permeability of the drug [12, 10].

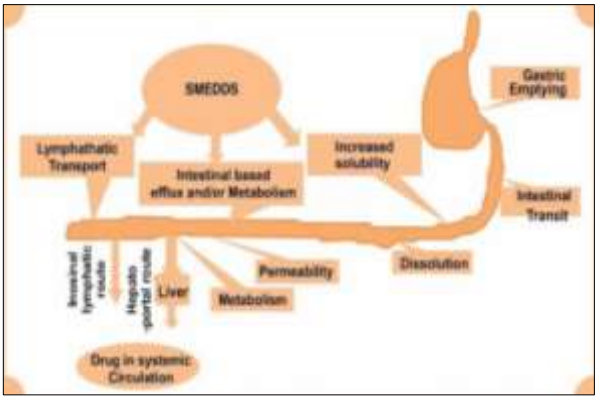

Fig 3: Mechanism of action of SMEDDS on oral administration of drug

Composition of SMEDDS

Many research has demonstrated that the self-micro emulsification process is dependent on the kind of oil/surfactant ratio, oil/surfactant pair, surfactant concentration, cosurfactant concentration and nature, surfactant and cosurfactant ratio, and temperature. The kind of dosage form determines the use of additional excipients in the SMEDDS. The SMEDDS formulation is unique to that medicine alone.

Components used in SMEDDS

- Oils
- Surfactant
- Co-surfactant
- Co-solvent
- Consistency Builder
- Enzyme Inhibitor
- Polymer
- Other Components [13, 11].

1) Oils

The oil is a crucial element since it facilitates the creation of self-micro emulsion. Drugs that are soluble in oils, such as those that are lipophilic, can travel more quickly through the intestinal lymphatic system and improve drug absorption. In order to reduce the amount of the formulation for the administration of an effective dose, the drug's solubility in the oil is the primary factor for choosing it. The lipid component of SMEDDS formulation, which generally consists of non-polar lipids, forms the core of the emulsion particle. The oil phase in the formulation of SMEDDS has been made up of long chain triglycerides (LCTs) and medium chain triglycerides (MCTs) oils with varying saturation levels. Unmodified edible oils are the most biocompatible lipid carriers, but their ability to dissolve large doses of lipophilic drugs and less effective self-emulsification restricts their use in SMEDDS formulations. In contrast, Vegetable oils that have been hydrogenated are excellent for lipid-based delivery systems because of their many benefits. Because of their complete digestion and absorption without posing any safety risks, they are typically consumed with meals. Long-chain triglycerides, often referred to as glycerolises esters (LCT), are the end products of glycerolises those results in vegetable oils. Each fatty acid is present in varying amounts in oils derived from various vegetable sources [14].

2) Surfactants

As the name suggests, an amphiphilic molecule (surfactant) is made up of polar (hydrophilic) and nonpolar (lipophilic) groups. The selection of an appropriate amphiphile is the key to attaining extremely low interfacial tension at the oil-water contact. The effectiveness and speed with which the chosen oil can b microemulsion, the drug's solubilizing capacity, safety (based on the administration route),the type of emulsion to be created, the surfactant's cloud point, and its capacity to inhibit p-gp are the main factors that influence the choice of surfactant (if the active ingredient is p-gp substrate). The drug-containing oil phase in SMEDDS is emulsified into nano-sized particles. The effective surface volume multiplies as the size of the drug-containing oil phase shrinks to nanoscale levels, necessitating a high concentration of surfactant is needed to stabilize it. A surfactant concentration that is too high, however, can cause the interfacial film to be ruptured, which causes the film to be ejected or bulge into the aqueous phase and thereby increasing the droplet size of the emulsion. Moreover, the oil's molecular volume influences the surfactant concentration. Large molecular volume oils, such as LCT generally require more surfactant than short-chain mono/diglycerides [15].

Surfactants are mainly

a) Non-ionic
b) Anionic
c) Cationic or zwitterionic Surfactants.

Surfactants with higher hydrophilic-lipophilic balance (HLB) values are more hydrophilic and have better solubility in aqueous media, whereas those with lower lipophilic values are more hydrophobic and have greater solubility in oils. In order to create an o/w microemulsion, it is preferable to use a surfactant with a high HLB (8–18), whereas a w/o microemulsion is created using a surfactant with a low HLB (3-6) [12].

In order to create stable SMEDDS, the surfactant concentration typically falls between 30% and 60% w/w. It is crucial to accurately calculate the surfactant concentration since high levels of surfactants may irritate the GI tract. SMEDDS are formed by lipid mixtures with increased surfactant and co-surfactant/oil ratios [16].

3) Co-surfactant and Co-solvents

When a co-surfactant is introduced to a formulation, the concentration of the surfactant is reduced, which mostly aids in increasing the drug load capacity. The interfacial fluidity is increased by the addition of a co-surfactant, which lowers the likelihood of variability and local irritancy brought on by the surfactants. Moreover, it aids in the medium's dispersion process [17].

The co-function surfactantsare to drop interfacial tension to a very low, brief negative value alongside the surfactant. At this point, the interface would develop into finely dispersed droplets and then absorb additional surfactants and surfactant/co-surfactants until their bulk condition is low enough to make interfacial tension positive once more. The microemulsion is created by a process called "spontaneous emulsification." For many non-ionic surfactants, however, the use of co-surfactant in self-emulsifying systems is not required. Both the creation of SEDDS and the solubilization of the medication in the SEDDS depend on the choice of surfactant and cosurfactant [18].

Large quantities of hydrophilic surfactants orhydrophobic medication are dissolved in the lipid base using co-solvents. In microemulsion systems, these solvents can also behave as co-surfactants. Glycerol diethylene glycol monomethyl ether (transcutol), polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycolether (glycofurol), and polyethylene glycol 400 are a few examples of commonly used cosolvents. The molecular weight of these excipients governs their physical condition at normal temperature [12].

4) Consistency Builder

Beeswax and cetyl alcohol can be added to an emulsion to change its consistency.

5) Enzyme Inhibitors

Enzyme inhibitors can be added to SMEDDS, such as amino acids and modified amino acids, if the active pharmaceutical ingredient is susceptible to enzymatic degradation.

6) Polymers

The polymer matrix, such as hydroxypropyl methyl cellulose and ethyl cellulose, becomes a gelled polymer after ingestion when it comes into contact with GI fluid, allowing the release of the micro emulsified medicinal agent through diffusion in a continuous and sustained way [11].

7) Other components

Antioxidants, flavours, and pH adjusters are additional ingredients. With oxidation, certain unsaturated lipids produce peroxide. Free radicals such ROO', RO', and 'OH may toxicity and harm drugs. The lipid content of SMEDDS is hydrolyzed more quickly due to the pH of the solution. So, to stabilise the oil content of SMEDDS, lipophilic antioxidants such tocopherol, ascorbyl palmitate, propyl gallate, and BHT can be added [19].

Table 3: Examples of oils, surfactant, co-surfactant and co-solvents used in SMEDDS

Oils	Surfactant	Co-surfactant/Co-solvent
Cotton Seed oil	Polysorbate 20 [Tween 20]	Span 20
Soybean oil	Polysorbate 80 [Tween 80]	Span 80
Corn oil	D-alpha Tocopheryl glycol 1000 succinate	Capryol 90
Sunflower oil	Polyoxy-35-castor oil [Cremophor RH40]	Lauro glycol
Castor oil	Polyoxy-40-hydrogenated castor oil	Transcutol
Sesame oil	Labrasol	Capmul

Formulation of SMEDDS

The following steps are involved in the formation of SMEDDS.

1. Selection of active pharmaceutical ingredient (API) for self-micro-emulsifying drug delivery system (SMEDDS).
2. Surfactant testing for emulsifying potential.
3. Choosing the right excipients for self-micro emulsifying drug delivery system.
4. The solubility of a drug in oils, surfactant, and co-surfactant.
5. Creating a pseudo-ternary phase diagram.

1. Choosing the active pharmaceutical ingredient (API) for the self-micro-emulsifying drug delivery system (SMEDDS)

The choice of active pharmaceutical component can also have a substantial impact on the various characteristics of SMEDDS, such as phase behaviour and microemulsion particle size, which is extremely important to know [20]. The performance of SMEDDS is significantly impacted by a variety of physicochemical properties of the API, such as pKa, log P, atomic structure and weight, presence of the ionizable group, and quantity. Low therapeutic dosage medications are accepted as standard drugs under SMEDDS. The ability to maintain active pharmaceutical ingredients that are soluble inside the G.I.T. is one of the main challenges in producing oral preparations.

Additionally, focus on how well drugs dissolve in the gut's primary absorption site. Drugs that are administered at extremely high doses shouldn't be used with SMEDDS unless they have excellent solubilization in at least one of the excipients, ideally in the lipophilic phase. The medication must be physically and chemically stable during manufacture, and its release rate must stay steady for the duration of the SMEDDSself-life [9].

2. Surfactant testing for emulsifying potential

The ability of the various surfactants to emulsify is tested. Surfactants can be mixed 1:1 with the specific oil. A homogenised admixture is produced. To create a transparent emulsion, a predetermined amount of isotropic admixture is diluted with twice-purified water [21, 22]. With the aid of

double-purified water used as the blank, the produced emulsions may be examined externally for their relative polluting impact, and their transmittance can be assessed in a UV-visible spectrophotometer [23, 24].

3. Choosing the right excipients for self-micro emulsifying drug delivery system

Excipients from the list of "GRAS" (generally regarded as safe) excipients published by the USFDA should be chosen. Effective preparation development requires careful evaluation of excipients' physical characteristics and their performance during preparation. The following elements require careful consideration in order to develop an efficient SMEDDS for the best treatment results;

- The physicochemical properties of the excipients and API;
- The collaboration in the development of drug excipients;
- The physiological factors that promote or inhibit bioavailability;
- The excipients' solubilization capacity, physical state, regulatory status, and miscibility at 25 °C;
- The excipients' regulatory properties; and
- The temperature at which self-emulsion takes place [21, 25].

4. The solubility of a drug in oils, surfactant, and co-surfactant

The capacity of drugs to dissolve in oils, surfactants, and co-surfactants was examined. The combined effects of oils, surfactants, and co-surfactants were examined for their capacities to dissolve a significant quantity of pure drug [26]. An extra dose of the medication is ingested in glass vials with transparent screw caps that include oil, surfactant, and cosurfactant. These are then blended on a cyclomixer (vortex mixture). After shaking, the mixture is centrifuged.

Withdrawing an aliquant portion of the supernatant for additional UV-Visible Spectrophotometer analysis at the required nm [27, 28].

5. Creating a pseudo-ternary phase diagram

To create diverse approaches, varying ratios of oil, surfactant, and cosurfactant are stirred. In a beaker containing 0.1 N HCl at 37 °C, a fixed amount of each system is introduced, and the components are stirred using a magnetic stirrer. The following grading approaches were used to visually assess the proposed dispersion's clarity;

A. Indicates the production of a transparent microemulsion with a blue tint.
B. Indicates a transparent micro emulsion development that appears blue.
C. Indicates a somewhat less transparent emulsion preparation.
D. Indicating the formation of a transparent white emulsion.
E. Denoting information that either had poor emulsification with many oil droplets on the surface or that the emulsion had not yet formed.

The findings are separated using a phase diagram. The smaller particle size makes Type A and B systems the most popular. The pyramid-like structure over there illustrates how a pseudo-ternary phase diagram is built. Figure 3 below shows an example of a pseudo-ternary phase diagram [8].

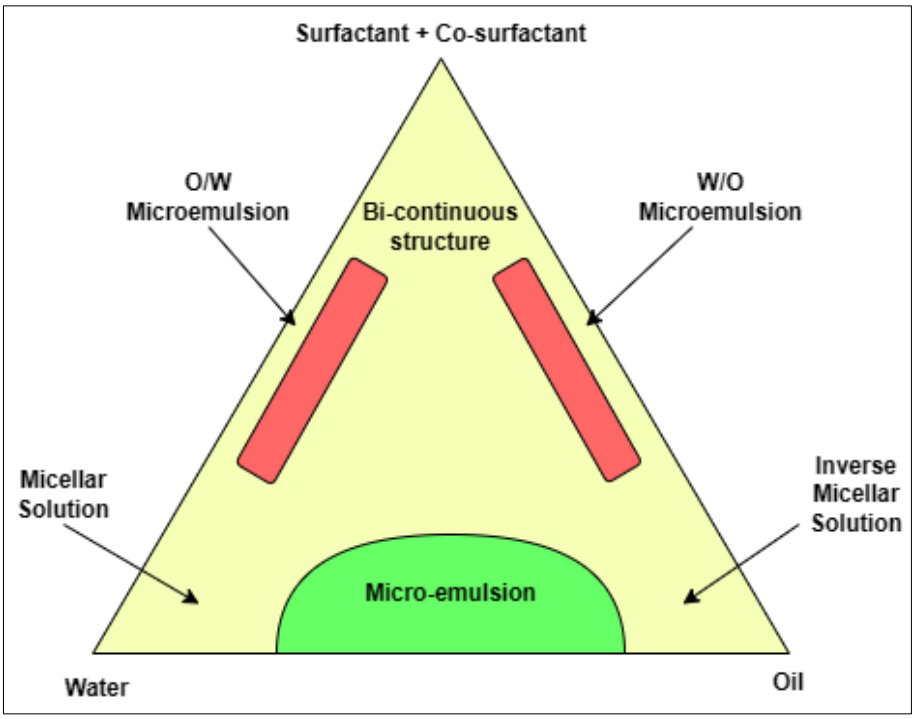

Fig 4: Pseudo-ternary phase diagram

Methods of preparation

A. Phase Titration Method

- The unrestricted emulsification method (stage titration approach) is used to create microemulsions, which may be seen with the use of stage graphs.
- To investigate the unexpected order of association that might occur when diverse elements are combined, the creation of a stage graph is a useful tool.
- Depending on the composition of the ingredients and the firmness of each part, microemulsions with various

organizational structures can be formed, including emulsion, micelle, layered, hexagonal, cubic, and other gels, as well as slick scattering. The investigation's foundational element includes understanding their stage balance and outlining the stage boundaries.

- A pseudo-ternary stage graph is created to find the several zones, including the microemulsion zone because the four-segment quaternary stage is monotonous and difficult to understand. This graph speaks to 100% of each individual portion on each side.
- By primarily focusing on whether the creation is oil-rich or water-rich, the location may be divided into w/o or o/w microemulsion. The metastable frames should be avoided by making careful perceptions [29].

B. Phase inversion method

- Phase inversion in the microemulsion happened as a result of introducing an excessive quantity of dispersion phase or in reaction to temperature.
- This approach results in significant physical alterations, such as a change in particle size, which may impact the drug's release both *in vitro* and *in vivo*. The procedures include modifying the surfactant's natural curvature. By causing a transition from an o/w microemulsion at a low temperature to a w/o microemulsion at a higher temperature, the system's temperature may be changed to achieve this for non-ionic surfactants (transition phase inversion).
- The formulation of finely distributed oil droplets is aided by the system crossing a point of zero spontaneous curvature and little surface tension after cooling. The Phase inversion temperature (PIT) technique is the name given to this procedure.
- Other factors, in addition to temperature, may be taken into account, such as pH level or salt content. Changes in the water volume fraction can also be used to determine a transition period in the spontaneous radius of curvature.
- Water droplets first develop on a continuous oil phase as a result of adding water to oil in stages. As the volume percent of water increases, the curvature of the surfactant changes from an initially stabilizing w/w emulsion to a w/w emulsion at the inversion locus. Bicontinuous microemulsions are inversion elements formed by short chain surfactants from flexible monolayers at the o/w interface [30].

Factors affecting SMEDDS

a) **Active Pharmaceutical Ingredient Dose:** Drugs with modest therapeutic doses are often selected for the formulation of SMEDDS. The lipid phase of SMEDDS, in particular, makes such drugs extremely soluble in all of their components. A drug that has a low Log P-value (about 2) and is poorly soluble in both oil and water is not a suitable candidate for SMEDDS**.**

b) **Drug solubility in the oil phase:** The ability of the SMEDDS system to maintain the drug in the solution state was impacted by the solubility of the drugs in the oil phase. The weakening of SMEDDS might result in the reduced dissolvable capacity of surfactant, which may lead to precipitation when the drug is already solvent with the help of surfactant and co-surfactant [31].

c) **The Polarity of the Lipophilic phase:** One of the variables influencing how drugs are released from microemulsions is the polarity of the lipid phase. The HLB, the length of the fatty acid chain and its degree of unsaturation as well as the molecular weight of the micronized drug, all influence the polarity of the droplet [32].

Evaluation of SMEDDS

1. **Visual Assessment:** The Self-Micro Emulsifying property of SMEDDS and the consequent dispersion may be revealed in this way, which might be very useful information. The efficiency of self-emulsification can be estimated by analysing the emulsification rate and particle size distribution. In order to determine of a dispersion quickly and consistently approached equilibrium, pouton employed turbidity measurement to find an effective self-emulsifying system [33].
2. **Droplet size analysis:** The light-dispersion molecule size analyser was used in a dissemination approach to determine the microemulsion drop size. Moreover, relationship spectroscopy, which examines the variation in light dissipation due to Brownian motion, is used to estimate it. Transmission electron microscopy (TEM) and photon relationship spectroscopy (PCS) were also used to investigate the drop size of microemulsion [34].
3. **Droplet Polarity:** It is a significant emulsion property. The HBL value of the oil, the chain length and the level of fatty acid unsaturation, the molecular weight of the hydrophilic component, and the concentration of the emulsifier all influence how polar oil droplets behave. An adequate rate of drug release is made possible by the combination of tiny droplets and their proper polarity (lower PCo/w of the medication). The oil/water partition coefficient (PCo/w) of the lipophilic drugs also serves as a measure of the droplet polarity [35].
4. **Turbidity measurement:** This establishes if the dispersion finds equilibrium quickly and within a predictable period, which defines the effectiveness of Self-emulsification. Turbidity meters are used to take these measurements (The Hach turbidity meter and the orbeco-Helle turbidity meter) [20].
5. **Zeta potential measurement:** Zeta potential shows how stable an emulsion is after being properly diluted. If the formula has a greater zeta ability, it nevertheless stays powerful. As compared to particles with both surface charges, a zwitterion rate, however, has been found time have greater biocompatibility and a shorter blood residence period [36].
6. **Thermodynamic stability studies:** A 30-minute centrifugation at 1000 RCF was performed on the improved or detailed microemulsion to look for stage division, creaming, or breaking. Microemulsions inhibited heating and cooling cycles. At every temperature for at least 48 hours, six cycles between the colder temperatures of 4 °C and 45 °C were carried out at capacity. To test the thermodynamic stability of the microemulsion, the advanced detailing was exposed for three freeze-defrost cycles between – 21 °C and +25 °C with each temperature for at least 48 hours [35]
7. **Dispersibility Test:** The self-emulsifying effect of oral nano emulsions or microemulsions is evaluated using the general purpose USP Dissolve Apparatus II. In 500 ml of water at 37±0.5 °C are added one millilitre of each system. There is just slight agitation when a dissolving paddle rotates at 50 rmp.

Using the following grading system, the formulation's overall *in vitro* performance is visually evaluated

Grade A: Rapid formation of clear or blue nano emulsion (within 1 minute).

Grade B: Fast-drying, blue-white slightly opaque emulsion.

Grade C: A good milk emulsion is formed in 2 minutes.

Grade D: An off-white emulsion with a slightly oily appearance that slowly emulsifies (over 2 minutes).

Grade E: The formulation exhibits poor or low emulsification with large oil deposits on the surface [37].

Application of SMEDDS

1) Improvement in solubility and bioavailability

A drug's solubility is improved if it is included in SMEDDS because it avoids the dissolving stage in BCS classes II and IV. In SMEDDS, the water and lipid matrix interact quickly, resulting in the formation of tiny particles in the oil in water emulsion. The medicine will be delivered to the gastrointestinal mucosa in tiny droplets in a dissolved condition that is more easily absorbed and increases bioavailability.

2) Protection from biodegradation

Drugs with low solubility, GIT degradation, and limited oral bioavailability can benefit from the self-emulsifying drug delivery system's capacity to reduce degradation while increasing absorption. These types of medications are resistant to the physiological system deterioration that many pharmaceuticals experience, including hydrolytic degradation, enzymatic degradation, and degradation caused by an acidic stomach PH.

3) Supersaturable S-SMEDDS

S-SMEDDS was designed to reduce the negative effects of surfactants and to speed up the absorption of medications that are poorly water soluble since large concentrations of surfactant typically induce gastrointestinal discomfort. When a drug formulation is discharged from an adequate dosage form into an aqueous medium, the S-SMEDDS technique creates a prolonged supersaturated solution of the medication in order to boost the driving force for passing the biological barrier [38].

Conclusion

In conclusion, SMEDDS is a promising drug delivery system that offers several advantages over traditional drug delivery systems. Recent research has revealed that the formulation and characterisation of SMEDDS with care can significantly affect the effectiveness and performance of these systems. SMEDDS have been used effectively to administer a variety of medications, and their potential for application in additional routes of administration is now being researched. While there are still some challenges to be addressed, the future of SMEDDS looks bright, and they have the potential to revolutionize the field of drug delivery.

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