Self-Microemulsifying Drug Delivery System

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***Abstract*—In many conditions, the oral route is the most practical approach to provide medication, and it is still the first method being researched when novel dosage forms are being developed. Low and inconsistent bioavailability, which is primarily caused by poor water solubility, is the fundamental issue with oral medication formulations. Poor water solubility affects around 40% of prospective pharmaceutical medicines. Lipid-based formulations are gaining popularity for the therapeutic administration of lipophilic active moieties (Class II medicines in the biopharmaceutical classification system). The poor solubility, dissolving rate, and bioavailability of insoluble pharmaceuticals can now be addressed by a variety of technologies. Self-microemulsifying drug delivery systems (SMEDDS) are a promising method. Due to their capacity to improve the solubility and bioavailability of poorly soluble medications, SMEDDS have become more well-known. Formulations to enhance the oral absorption of extremely lipophilic medicinal molecules can be designed using SMEDDS, which are isotropic combinations of oils, surfactants, solvents, and co-solvents/surfactants. The majority of conventional SMEDDS are made in liquid form, which has certain drawbacks. SMEDDS can create fine, reasonably stable oil-in-water emulsions can be taken orally in soft or hard gelatin capsules. Solid-SMEDDS, which have grown in popularity, are made by solidifying liquid or semisolid self-micron emulsifying materials into powders. This page provides a thorough review of SMEDDS; nonetheless, the concept, design, and assessment of SMEDDS have received more attention than its use.**

***Index Terms*—Self-microemulsifying drug delivery system, Surfactant, Oil, Co-surfactant, Bioavailability, Lipophilic, Biopharmaceutical classification system Class II drugs.**

I. INTRODUCTION

The term "self-microemulsifying drug delivery system" (SMEDDS) refers to isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents, and cosolvents/surfactants that have the special capacity to form fine oil-in-water (o/w) microemulsions upon mild agitation and dilution in aqueous media, such as gastrointestinal (GI) fluids. The digestive motility of the stomach and intestine provides the agitation required for self-emulsification, and SMEDDS disseminate easily in the GI tract (GIT). Self-emulsifying drug delivery systems (SEDDS), also known as self-emulsifying oil formulation, and SMEDDS differ primarily in that SMEDDS form transparent microemulsions with a droplet size of less than 50 nm, whereas SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm. Additionally, SMEDDS's oil concentration is less than 20%, whereas SEDDS's is between 40 and 80%. SMEDDS are physically stable formulations that are simple to produce, even though a variety of techniques can be used to improve the solubilization of poorly water-soluble drugs and further increase their bioavailability [1]. Therefore, these methods may increase the rate and extent of absorption and produce more consistent blood-time profiles for lipophilic medicinal molecules that show dissolution rate-limited absorption (Table 1).

The simplest and most practical method of noninvasive administration is oral. The global medication delivery market has always been dominated by oral drug administration systems since they are the most economical. For therapeutic compounds with limited aqueous solubility, this oral route could be problematic. When a medication is

taken orally, solubilization and penetration are the first stages of absorption. A significant obstacle to contemporary medication delivery systems is the poor water solubility of about 40% of novel chemical entities. Solubilization in the GIT is frequently a rate-limiting stage for these medications' absorption. According to the Biopharmaceutical Classification System (BCS), these medications have high permeability and poor water solubility, making them Class II medicines. Various formulation techniques have emerged, including solid dispersion, micronization, and complexation with cyclodextrins. Although these strategies have been effective in a few specific instances, they have numerous significant drawbacks [2].

A lipid-based drug delivery system would be ideal for a medicine that is poorly soluble in water because it is hydrophobic, or highly lipophilic. SMEDDS are typically manufactured in a liquid dosage form that can be taken in soft gelatin capsules. These capsules have certain drawbacks, mostly related to the manufacturing process and incompatibilities with the soft gelatin shells. Recent descriptions of solid-SMEDDS have demonstrated more commercial potential and patient acceptability while overcoming the drawbacks of liquid SMEDDS. Conventional liquid SMEDDS can be converted to solid using a variety of processes, including adsorptions to solid carriers, spray drying, spray chilling, melt extrusion, nanoparticle technology, and supercritical fluid-based procedures. According to certain research, using SMEDDS may improve the GI adsorption of poorly water-soluble medications as well as their rectal and vaginal adsorption. When long chain triglycerides were used instead of medium chain triglycerides in the SMEDDS formulations, Khoo et al. (1998) showed improved drug absorption [3]. SMEDDS have many benefits, including enhanced bioavailability, thermodynamic stability, spontaneous production, and preparation practicality. SMEDDS's primary benefits are increased solubility and bioavailability [4].

PRINCIPLE

This system's fundamental feature is its capacity to create fine oil-in-water microemulsions when gently stirred, followed by an aqueous phase [5]. Through better solubility and diffusion, easier intestinal lymphatic drug transport, defense against enzymatic hydrolysis, and P-glycoprotein-induced efflux inhibition, SMEDDS can improve medication absorption. For BCS II medications like silymarin, oridonin, and curcumin, this approach has been demonstrated to be successful. The bioavailability of BCS IV substances with SMEDDS is limited, despite the fact that SMEDDS has been shown to increase the water solubility of numerous medications [6].

Table 1: LFCS showing typical compositions and properties of lipid-based drug delivery system

Formulation type	Composition	Characteristics
Type 1	Oils without surfactants	Non-dispersing, poor solvent capacity except for highly lipophilic drugs, requires digestion to release drug
Type II	Oils and water-insoluble surfactants	SEDDS, turbid o/w dispersion (particle size 0.25-2 μm), unlikely to lose solvent capacity on dispersion, possible loss of solvent capacity on digestion
Type III	Oils, water-soluble surfactants and co-solvent	SEDDS/SMEDDS, slightly bluish to clear dispersion, possible loss of solvent capacity on dispersion, less easily digested, possible loss of solvents solvent capacity on digestion
Type IV	Water-soluble surfactants and co-solvent (oil free)	Forms a clear micellar solution on dispersion, likely loss of solvent capacity on dispersion unlikely to be digested

SEDDS: Self-emulsifying drug delivery systems, SMEDDS: Self-microemulsifying drug delivery systems, LFCS: Lipid formulation classification system

Stability, manufacturing processes, the interaction between the filling and the capsule shell, and storage temperature were some of the delivery system's drawbacks. The active ingredient and/or excipients may precipitate when the product is stored at lower temperatures [7].

History of micronemulsions

Hoar and Shulman, chemistry professors at Cambridge University, coined the word "microemulsion" in 1943. Microemulsions are formed when:

1. At the oil/water interface, the interfacial tension is reduced to an extremely low level.
2. High levels of fluidity and flexibility are maintained at the interfacial layer.

These two requirements are typically satisfied by using a "co-surfactant," which gives the oil/water interface flexibility, and by carefully selecting the components and their amounts. In contrast to traditional emulsions, these conditions result in a thermodynamically optimized structure that is stable and does not require a significant energy input (via agitation) to develop. Microemulsions are translucent and their structure cannot be seen with an optical microscope because the particle size is substantially smaller than the visible light wavelength [8].

II. NEED OF SMEDDS

When administering poorly water-soluble compounds orally, the formulation is filled into capsules after the substance has been pre-dissolved in an appropriate solvent. This method's primary advantage is that it circumvents the first rate-limiting stage of particle dissolution in the GIT's aqueous environment by pre-dissolving the chemical. Precipitation on dilution in the GIT is less likely if the medication can dissolve in a lipid vehicle because partitioning kinetics will favor the drug staying in the lipid droplets. Formulating in a solid solution with a water-soluble polymer to increase the therapeutic compound's solubility is another tactic for poorly soluble medications. Figure 1 illustrates the biopharmaceutical classification system class of medications. The drug may prefer a more thermodynamically stable state in this kind of formulation, which could lead to the molecule crystallizing in the polymer matrix [9].

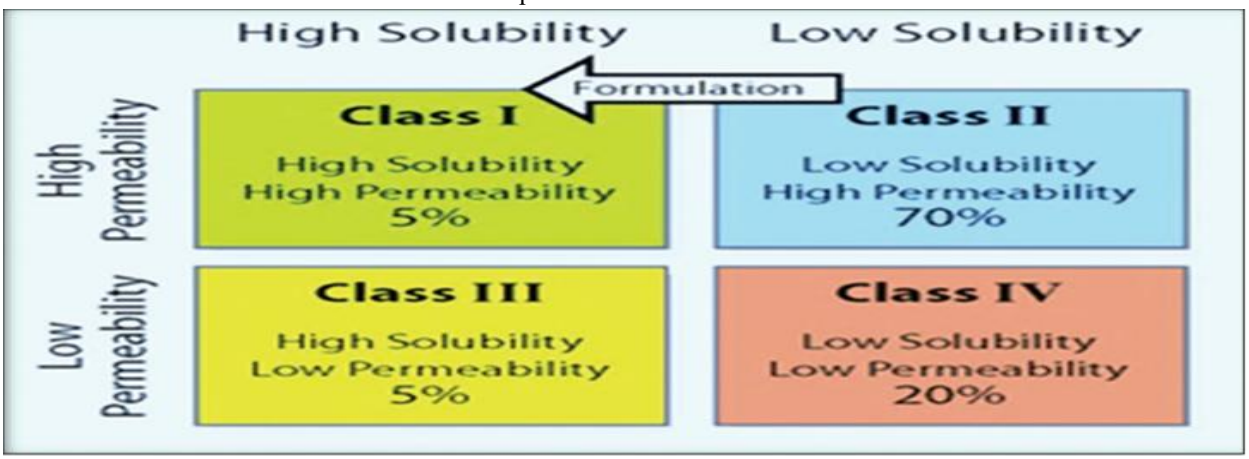

Fig. 1: Classification of biopharmaceutical classification system class of drugs

Advantages of SMEDDS

- enhancement in oral bioavailability through improved medication transport and solubility.
- Compared to other lipid dosage forms, it is easier to produce and scale up.
- decrease in dietary effects and variability both within and across subjects.
- the capacity to distribute peptides that are vulnerable to GIT enzymatic hydrolysis.
- Unlike other lipid-based drug delivery methods, there is no impact of the lipid digestion process.
- A sustained release of medication is provided when polymer is added to the formulation of SMEDDS [10].

Disadvantages of SMEDDS

- inadequate predictive in vitro models for formulation evaluation.

- Before its strength can be assessed, this in vitro model needs to be further developed and validated.
- Since in vitro-in vivo correlations will be the basis for future development, various prototype lipid-based formulations must be created and evaluated in vivo using an appropriate animal model.
- Another is the GIT-irritating chemical instability of medications and formulations with high surfactant concentrations (about 30–60%).
- Furthermore, it is known that the lipophilic medications precipitate when volatile cosolvents in traditional self-microemulsifying formulations migrate into the shells of soft or hard gelatin capsules.
- Because of the hydrophilic solvent's dilution effect, the medication may have a greater tendency to precipitate when diluted [11].

MECHANISM OF SMEDDS

The surfactant molecules that surround the internal phase droplet in a film stabilize the emulsion. Thermodynamic spontaneous emulsification occurs in the case of SMEDDS because the free energy of formation is extremely low, positive, or even negative. It has been proposed that water penetrates the liquid crystalline (LC) phase that forms at the oil/surfactant-water interface during self-emulsification with the help of mild agitation.

The contact is disrupted and droplets form when water enters to a certain degree (Fig. 2). The great stability of the resultant microemulsion against coalesce is thought to be caused by this LC phase [12].

Formulation components of SMEDDS

- The active component of pharmaceuticals
- Oil
- Surfactant
- Co-surfactant
- Co-solvents
- Other components.

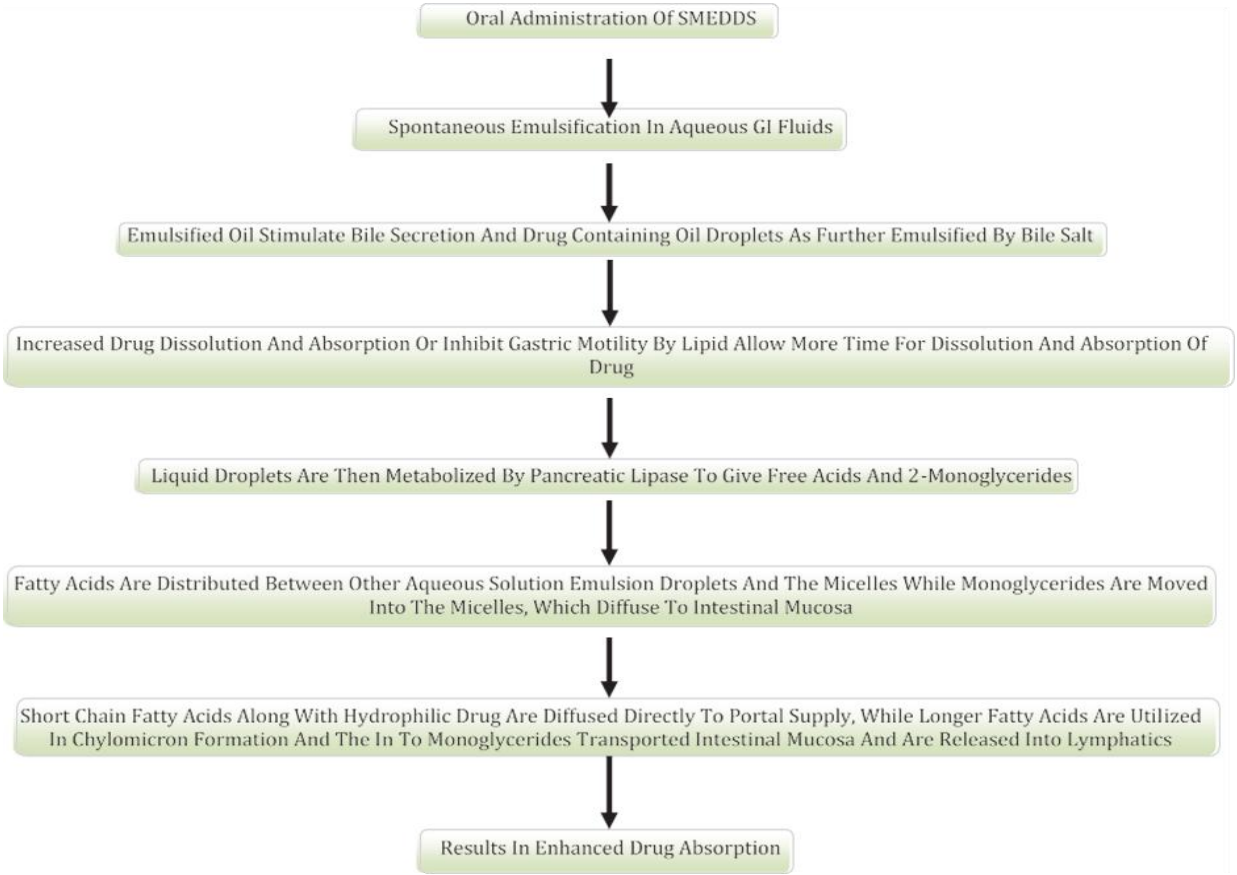

Fig. 2: Mechanisms proposed for bioavailability enhancement of drug

Active pharmaceutical ingredient: The drug must be soluble in the oil phase because this affects SMEDDS's capacity to keep the API solubilized. Cinnarizine and other lipophilic medications with log p>5 are ideal candidates for SMEDDS [13].

Oil: Because it solubilizes the lipophilic medication in the necessary amount, oil is the most crucial excipient in the SMEDDS formulation. In order to decrease the volume of the formulation for the administration of an effective dose, the primary criterion for choosing the oil is that the medication should be highly soluble in it [14].

Surfactant

Anionic surfactants are those in which the hydrophilic group is negatively charged. Examples include sodium lauryl sulfate and potassium laurate.

cationic surfactants, in which the hydrophilic group is positively charged. Quaternary ammonium halide is one example.

Zwitterionic surfactants, also known as ampholytic surfactants, have both a positive and a negative charge. Sulfobetaines, for instance.

Nonionic surfactants, in which highly polar groups provide the hydrophilic group its water solubility while the hydrophilic group carries no charge. Examples include polysorbates (Tweens) and sorbitan esters (Spans).

Co-surfactant: Co-surfactants are used to lower the concentration of surfactants since a high concentration of surfactant is needed to sufficiently reduce interfacial tension, which can be hazardous, in order to produce an optimal SMEDDS. Co-surfactants with an HLB value of 10–14, like ethanol, propylene glycol, and polyethylene glycol, are typically utilized.

Co-solvents: Large amounts of the medication or the hydrophilic surfactant can dissolve in the oil phase thanks to organic solvents. Examples include ethanol, butanol, propylene glycol, ethyl propionate, tributyl citrate, and amides like polyvinyl pyrollidine, caprolactum, and 2-pyrolidine [15].

Additional ingredients: Additional ingredients include polymers, pH adjusters, flavors, antioxidants, consistency builders, and enzyme inhibitors (Table 2).

Formulation design of SMEDDS

- Screening of Oil: The saturation solubility of API was examined in a few oils using the shake flask method in order to determine the proper oil with a good solubilizing capacity of API. A vial containing 0.5 g of each solvent was filled with an excess of API. To ensure that API was properly mixed with the vehicles, the mixture was vortexed using a cyclomixer for ten minutes after sealing. After being allowed to reach equilibrium for 72 hours at room temperature, the mixtures were centrifuged for 15 minutes at a sufficient speed. Supernatant aliquots were diluted with mobile phase after passing through a membrane filter (0.45 μm). High-performance liquid chromatography (HPLC) was used to directly quantify drug concentration.
- Surfactant screening: Following oil screening, the emulsifying capability of several surfactants with the screened oil was examined in order to identify a suitable surfactant with good solubilizing capacity. To create an isotropic mixture, 0.3 g of surfactant and 0.3 g of oil phase were weighed, vortexed for two minutes, and then heated to 40–45°C for thirty seconds. In a volumetric flask, 50 mg of the isotropic mixture was diluted with double-distilled water that had been filtered using a membrane filter (0.45 μm). To create a transparent emulsion, several volumetric flask inversions were visually observed. Transmittance was measured at 638 nm after the generated emulsions were allowed to stand for two hours. The surfactant that produces a transparent emulsion with higher transmittance and fewer inversions was chosen [16].
- Co-surfactant screening: Following oil screening, the emulsifying ability of several co-surfactants with the screened oil was examined in order to identify a suitable co-surfactant with good solubilizing capability. To create an isotropic mixture, 0.2 g of co-surfactant and 0.3 g of oil phase were weighed, vortexed for two minutes, and then warmed at 40–45°C for thirty seconds. In a volumetric flask, 50 mg of the isotropic mixture was diluted with double-distilled water that had been passed through a membrane filter with a pore size of 0.45 μm. A clean emulsion was formed by visually observing the number of volumetric flask inversions. Transmittance was measured at 638 nm after the generated emulsions were allowed to stand for two hours.The co-surfactant that produces a transparent emulsion with higher transmittance and fewer inversions was chosen.

Table 2: Example of surfactants, co-surfactant, and co-solvent used in commercial formulations	
Excipient name (commercial name)	Examples of commercial products in which it has been used
Surfactants/co-surfactants	
• Polysorbate 20 (Tween 20)	Targretin soft gelatin capsule
• Polysorbate 80 (Tween 80)	Gengraf hard gelatin capsule
• Sorbitan monooleate (Span 80)	Gengraf hard gelatin capsule
• Polyoxy-35-castor oil (Cremophor RH40)	Gengraf hard gelatin cap., Ritonavir soft gelatin capsule
• Polyoxy-40- hydrogenated castor oil (Cremophor RH40)	Nerol soft gelatin capsule, Ritonavir oral solution
• Polyoxyethylated glycerides (Labrafil M 2125 Cs)	Sandimmune soft gelatin capsules
• Polyoxyethlated oleic glycerides (Labrafil M1944 Cs)	Sandimmune oral solution
• D-alpha Tocopheryl polyethylene glycol 1000 succinate (TPGS)	Agenerage soft gelatin capsule, Agenarage oral solution
Co-solvents	
• Ethanol	Nerol soft gelatin capsule, Nerol oral solution, Gengraf hard gelatin Capsule, Sandimmune soft gelatin capsule, Sandimmune oral solution
• Glycerin	Nerol soft gelatin capsule, Sandimmune soft gelatin capsules
• Propylene glycol	Nerol soft gelatin capsule, Nerol oral solution, Lamprene soft gelatin capsule, Agenerage oral solution , Gengraf hard gelatin capsule
• Polyethylene glycol	Targretin soft gelatin capsule, Gengraf hard gelatin capsule, Agenerase soft capsule, Agenerase oral solution
Lipid ingredients	
• Corn oil mono, di, tri-glycerides	Nerol soft gelatin capsule, Nerol oral solution
• DL-alpha-Tocopherol	Nerol oral solution, Fortavase soft gelatin capsule
• Fractionated triglyceride of coconut oil (medium-chain triglyceride)	Rocaltrol soft gelatin capsule, Hectrol soft gelatin cap
• Fractionated triglyceride of palm seed oil (medium-chain triglyceride)	Rocatrol oral solution
• Mixture of mono- and di-glycerides of caprylic/capric acid	Avodat soft gelatin capsule
• Medium chain mono- and di-glycerides	Fortavase soft gelatin capsule
• Corn oil	Sandimmune soft gelatin capsule, Depakene capsule
• Olive oil	Sandimmune oral solution
• Oleic acid	Ritonavir soft gelatin capsule, Norvir soft gelatin capsule
• Sesame oil	Marinol soft gelatin capsule
• Hydrogenated soybean oil	Accutane soft gelatin capsule, Vesanoid soft gelatin capsule

• Hydrogenated vegetable oils	Accutane soft gelatin capsule, Vesanoid soft gelatin capsule
• Soybean oil	Accutane soft gelatin capsule
• Peanut oil	Prometrium soft gelatin capsule
• Beeswax	Vesanoid soft gelatin capsule

Construction of phase diagram

To determine the ratio of components that can produce the largest microemulsion existence area, phase diagrams were created. These figures were created at room temperature using the water titration method with oil, water, and surfactant/co-surfactant. To create an isotropic mixture, the process involved creating solutions with varying weight ratios of surfactant to co-surfactant, such as 1:1, 2:1, 3:1, etc. These solutions were then vortexed for five minutes and heated to 50°C for one hour (Fig. 3).

The following weight ratios of oil to Smix (a mixture of surfactant and co-surfactant) were then prepared using each of these solutions: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, and then vortexed for five minutes before being baked for one hour at 50°C. After that, each mixture was left at room temperature for a full day. Water was added to each combination at intervals of 10 to 15 minutes while being stirred on a magnetic stirrer, ranging from 5% to 95%. The combinations' appearance (turbid or clear) was noted following each addition. A clear isotropic solution would suggest the creation of a microemulsion, while turbidity of the samples would suggest the formation of a coarse emulsion. The ternary phase diagram was created using the percentage of oil, Smix, and water at which a clear mixture formed [17].

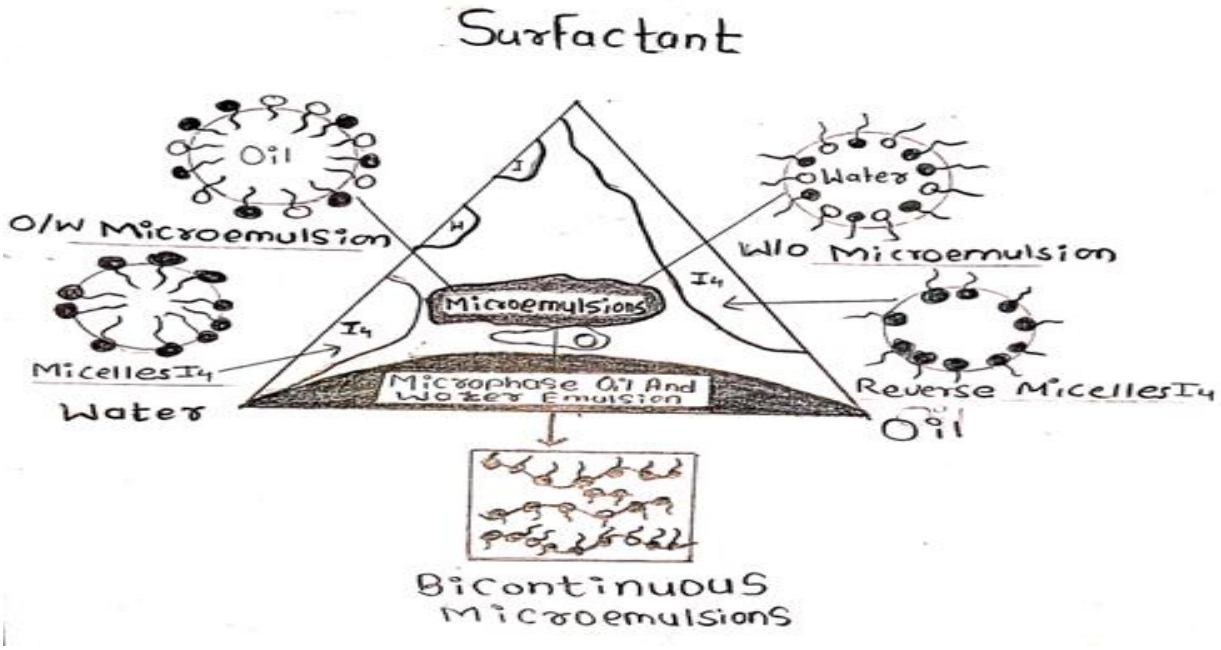

Fig. 3: Construction of phase diagram

Preparation of SMEDDS

The diagram ratio of surfactant to co-surfactant was tuned from the ternary phase. Different formulations with and without the medication were then created by adjusting the oil to Smix ratio. In order to prepare the formulations, the optimal ratio of Smix was first prepared. The surfactant and co-surfactant were then precisely weighed and vortexed for five to ten minutes. Smix was then baked for one hour at 50°C. To create an isotropic mixture, several ratios of oil were added to Smix, vortexed for five to ten minutes, and then baked at 50°C for one hour. At the end, the drug was

added to these isotropic formulations and vortexed using a vortex shaker until a clear solution was produced [18].

III. EVALUATION OF SMEDDS

- Zeta-potential and droplet size/distribution determination: Using a zetasizer that can measure size in the range of 10-5000 nm, photon correlation spectroscopy—which examines variations in light scattering caused by particle Brownian moments—is one method used to determine droplet size. For precise droplet size assessment, this method can only be used at comparatively low dilutions. since of the existence of certain groups, oil droplets have some charge on their surface. For example, traditional SMEDDS is negative since free fatty acids are present; however, adding cationic lipids at concentrations between 1% and 3% will result in cationic SMEDDS. The positive n-potential value of these systems is therefore between 35 and 45 mV. After the medicinal molecules are incorporated, this positive n-potential value is maintained [19].
- Brookfield viscometer and rotating viscometer for rheological analysis The microemulsion's rheological characteristics can be assessed using Rheomat 108. This analysis verifies whether the system is w/o or o/w. It ought to be carried out three times [20].
- Polarity: A number of factors, including the HLB, chain length, degree of unsaturation of the fatty acids, molecular weight of the hydrophilic region, and emulsifier content, control the polarity of oil droplets. The drug's affinity for water and/or oil as well as the kinds of forces that are created are influenced by polarity. The formulation with the highest polarity oil phase will yield the largest release [18].
- Dispersibility test: Using a conventional USP XXII dissolution apparatus 2, the effectiveness of self-emulsification of oral nano- or microemulsion is evaluated. 500 milliliters of water at 37±10°C were mixed with one milliliter of each formulation. A typical 50 rpm rotating stainless steel dissolving paddle is utilized to produce mild agitation. The following grading system is used to visually evaluate the formulations' in vitro performance:
- Grade A: Clear or bluish nanoemulsion that forms quickly (in less than a minute).
- Grade B: A bluish-white emulsion that forms quickly and is somewhat less transparent.
- Grade C: Within two minutes, a fine, milky emulsion formed.
- Grade D: A dull, grayish white emulsion that takes longer than two minutes to emulsify and has a slightly greasy appearance.
- Grade E: Formulation with big oil globules on the surface and either poor or minimum emulsification. When distributed in the GIT, Grade A and Grade B formulations will continue to be nano-emulsions. Formulations in Grade C, however, might be suggested for SEDDS formulations.
- Turbidimetric evaluation: Nephelo turbidimetric evaluation can be used to track emulsion growth. A turbidimeter is used to measure the increase in turbidity when a fixed amount of self-emulsifying system is added to a fixed amount of an appropriate medium (0.1 N hydrochloric acid) on a magnetic plate at room temperature while swirling continuously at 50 rpm. However, the rate of change of turbidity (rate of emulsification) cannot be tracked because the time needed for full emulsification is too short.
- Refractive index and percent transmittance: The refractive index and % transmittance demonstrate the formulation's transparency. By putting a drop of solution on a slide and comparing it to water, a refractometer may determine the refractive index (1.333). Using a UV spectrophotometer and distilled water as a blank, the system's % transmittance at a specific wavelength is determined. A formulation is considered transparent if its refractive index is comparable to that of water (1.333) and its transmittance percentage is greater than 99% [21].
- Electroconductivity test: This test is used to determine whether a system is electroconductive. An electro-conductometer is used to test the electroconductivity of the resulting system. The charge on an oil droplet in typical SMEDDSs is negative because of the existence of free fatty acids.

- Drug content: The drug is extracted from pre-weighed SMEDDS by dissolving it in an appropriate solvent. Using an appropriate analytical technique, the drug content in the solvent extract was compared to the drug's standard solvent solution [22].
- In vitro dissolution testing: The quantitative in vitro release test is carried out in US Pharmacopoeia XXIV dissolution apparatus 2 using 900 ml of buffer with pH (specified in the pharmacopoeia for the specific drug) as the dissolution medium. The temperature is set at 37°C, and the paddles are rotated at 100 rpm. The SMEDDS formulations are placed in firm gelatin capsules (size 00). A 5 ml sample of dissolving media must be removed for HPLC analysis during the drug release tests. Every time, 5 milliliters of new medium must be added to replace the withdrawn volume. To investigate how pH affects drug release, dissolution tests are also carried out in alternative media (buffer with a variable pH) [23].

IV. APPLICATIONS OF SMEDDS

- Improvement in solubility and bioavailability: The SMEDDS formulation reduces stomach irritation and improves bioavailability by making the medication more soluble.
- Extremely saturable SMEDDS Super saturable-SMEDDS were created to counteract the harmful effects of surfactants or the gastrointestinal adverse effects they might cause when used at extremely high concentrations, as is usually the case with SMEDDS.
- Protection from biodegradation: Drugs with low GIT solubility and degradation have limited oral bioavailability; SMEDDS is helpful for these drugs because it can both improve absorption and decrease degradation [24].

V. CONCLUSION

SMEDDS are a promising method for the formulation of therapeutic molecules with low aqueous solubility, according to the innovative drug delivery system. SMEDDSs, which have been demonstrated to significantly increase oral bioavailability and hence lower the drug's dose, can enable the oral delivery of hydrophobic medications that fall under BCS Class II. SMEDDSs will continue to facilitate new drug delivery applications and address issues related to the delivery of poorly soluble medications as this technology advances.

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