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# Review on: Self micro Emulsifying drug delivery system

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**Abstract**
The self-micro emulsifying drug delivery system (SMEDDS) is a highly effective method for improving the solubility and bioavailability of poorly soluble drugs. The current study is exploring the potential of this medication delivery system based on the microstructural properties of the active ingredient and formulation. SMEDDS, an isotropic mixture of oil, surfactant, cosurfactant, and water, encapsulates drugs into a lipid base and forms a fine oil-in-water emulsion with gentle agitation. Emulsification requires minimal entropy change due to peristaltic action in the gut. Due to the microstructural characteristics of the active substance and the formulation as a whole, using this method, extensive research is currently being conducted to correlate the outcomes of in vitro experiments with reactions in vivo. Given that 40% of recently discovered medications have lipophilic properties, this suggests that research using this strategy will continue and that more commercial formulations will soon be made accessible. A better grasp of SMEDDS' current function in medicine and drug administration is made possible by this review, which provides an overview of the technology with sequential demystification.

**Keywords:** Novel technique, lipophilic drug, bioavailability, self-emulsifying

## Introduction

The poor water solubility of the newest drugs is one of the major issues facing pharmaceutical method development nowadays. Over 40% of newly developed capsules have low water solubility. One Horrible bioavailability is caused by these tablets' poor solubility and, eventually, low dissolving charge in gastrointestinal fluids. The use of crystal polymorphism, surfactants, salt formation, pulverization, length reduction of debris, strong dispersion, microemulsion, liposomes, complex formation, nanoparticles, Nano and microspheres, pro-drugs, and permeation enhancers are some of the strategies for improving bioavailability. It has become popular recently to recommend lipid-based formulations to increase the oral bioavailability of drugs with poor water solubility [1]. SMEDDS is described as isotropic mixtures of natural or synthetic oils, liquid or stable surfactants, or one or more hydrophilic solvents and co-solvents/surfactants that, when slightly stirred and then diluted in aqueous media, such as GI fluids, can form satisfactory oil-in-water (o/w) microemulsions. These systems are made using a lipid provider that enhances the absorption of poorly water-soluble capsules in the gastrointestinal tract, keeps the drug in the dissolved kingdom by protecting it from enzymatic reaction, is thermodynamically stable, easy to manufacture, and suitable for oral drug transport. Oil has the ability to solubilize the lipophilic medication in this system, which enhances drug loading and bioavailability [2]. Hydrophobic drugs dissolve readily in oil. Because solubility is limited in oils, and surfactant microemulsification is used to increase medicine solubility in oils. The main factors influencing the improvement of medication solubility are the drug's solubility in surfactant and the effectiveness and speed with which the selected oil micro emulsifies. Nonionic surfactants are typically preferred in components due to their lower CMC cost, lower toxicity, and improved emulsion stability across a broad range of pH and ionic strength. A key factor in lipid-based formulations is the co-surfactant concentration. Drug solubilization requires the choice of surfactant and co-surfactant. For oral medication delivery, organic solvents like ethanol, propylene glycol, and polyethylene glycol are suitable.

Formulation strategies can enhance the bioavailability of class II drugs by increasing the dissolution rate or maintaining the drug in solution in the intestinal lumen. However, class IV drugs' bioavailability is compromised by poor membrane permeability. Maintaining a solubilized class II drug in the gut achieves an absorption profile similar to class I drugs [3].

**Table 1:** SMEDDS Applications Related to BCS Classification

| BCS CLASS | Aqueous Solubility | Membrane Permeability | Overcoming obstacles with SMEDDS |
|---|---|---|---|
| I | High | High | Degradation by enzymes and efflux from the gut wall |
| II | Low | High | Solubilization and bioavailability |
| III | High | Low | Bioavailability, intestinal wall efflux, and enzymatic degradation |
| IV | Low | Low | Solubilization, Bioavailability of gut wall efflux and enzymatic degradation |

- **Mechanism of self emulsification**

Reiss explains that the self-micro emulsification process is related to free energy, which is a direct function of the energy needed to create a new surface between the oil and water phases. It can be described by the equation.DG=S N p r 2s Where DG is the free energy related to the process, N is the number of droplets of radius r and s represents the interfacial energy. Emulsifying agents stabilize the emulsion by separating the two phases and forming a monolayer of droplets, reducing interfacial energy and providing a barrier to avoid coalescence. Emulsification requires minimal input energy through destabilization and contraction of the local interfacial region [4].

**Advantages** [5]

- A novel method to increase the water solubility and bioavailability of lipophilic drugs.
- The plasma profile of liquid or solid dose forms fluctuates due to significant variations in absorption.
- A tiny particulate oil-in-water emulsion is created when the SMEDDS lipid matrix and water interact. Drugs are delivered to the gastrointestinal mucosa by emulsion droplets, which raises AUC and C max.
- Provides peptides that are susceptible to enzymatic hydrolysis in the gastrointestinal tract, enabling extended drug release upon polymer incorporation.

**Disadvantages** [6]

- Challenges of In-vitro Appraisal.
- Inadequate predictive models.
- A high concentration of surfactant irritates.
- Lipophilic drugs are precipitated by volatile co-solvents found in gelatin capsules.
- A suitable animal model for in-vivo research and inadequate IVIVC correlation.

**Composition of Smedds**

According to reports, the properties of the oil surfactant combination are specific to the self-emulsification procedure. The method is dependent upon:

- Oils.
- The amount and proportion of oil and surfactant and cosurfactant.
- The temperature at self-emulsification takes place [7].

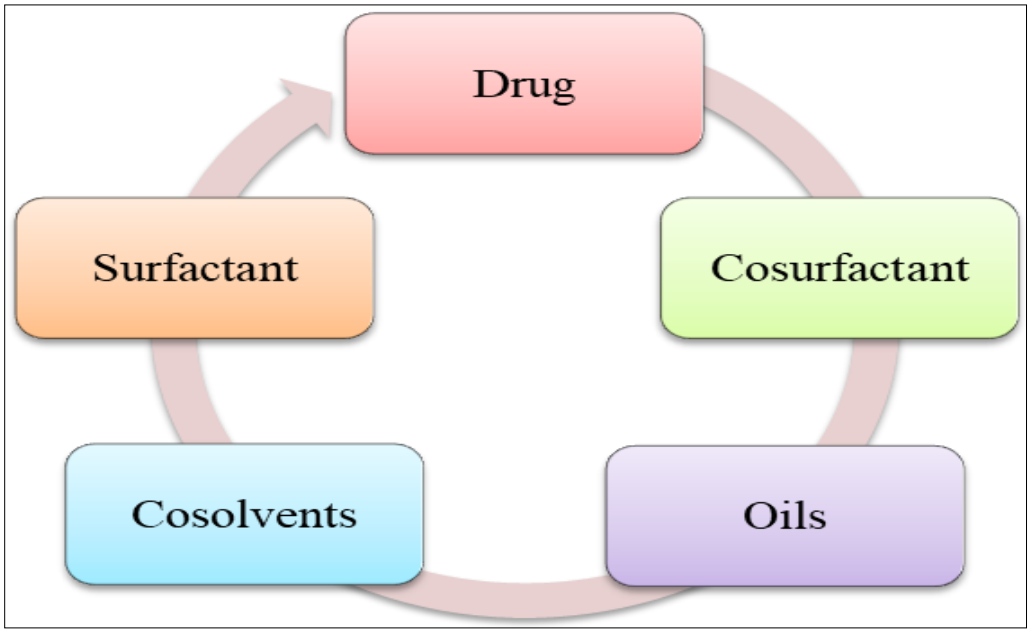


**Fig 1:** Composition of SMEDDS

- **Oils**

Oils like soybean oil, medium-chain triglycerides, and long-chain triglycerides like Gelucire are used in SMEDDS detailing due to their biocompatibility and the use of olive oil, corn oil, soybean oil, and creature fats.

- **Surfactants & Cosurfactant**

SMEDDS requires a surfactant for self-emulsification, enhancing dissolution rate by solubilizing hydrophobic drugs. Surfactants with active ingredients are popular due to their inhibitory effect on active precipitation. They improve permeability by opening tight junctions. Natural surfactants are less toxic but limited in self-emulsification [8].

- **Cosolvents**

Organic solvents like ethanol, PG, and PEG can dissolve hydrophilic surfactants or medications in lipid bases and serve as co-surfactants in self-emulsifying drug delivery systems. Alcohol-free self-emulsifying microemulsions may show advantages over traditional self-emulsifying systems in dose structures, but their lipophilic medication disintegration capacity may be limited [9].

- **Active agent**

Lipid-based definitions are preferred for deficient medication ingestion due to solvency. SMEDDS can be used at low doses for maximum bioavailability, especially for drugs with high octanol: water partition coefficient. Compounds with low bioavailability due to pre-systemic metabolism can be made as SMEDDS [10]. Some excipients used in different preparations are shown in Table 2.

**Table 2:** Excipients Used in Different SMEDDS Formulations

| S. no | Drug | Oil | Surfactant | Cosurfactant | Cosolvent | Use |
|---|---|---|---|---|---|---|
| 1. | Atorvastatin | Labrafil, estol, isopropyl, myristate | Cremophor RH40, Cremophor EL | PG, PEG 400, Transcutol | - | Cardiovascular |
| 2. | Acyclovir | Crodamol GTCC | Labrasol | Plurol oleque CC 497 | Macrogol 400 | Anti-viral |
| 3. | Danazol | Capmul MCM | Tween 80 | Transcutol HP | - | Endometerosi s |
| 4. | Simvastatin | Capryol 90 | Cremophor EL | Carbitol | - | HMG CoA Inhibitors (statin) |

**Formulation Design Of SMEDDS**

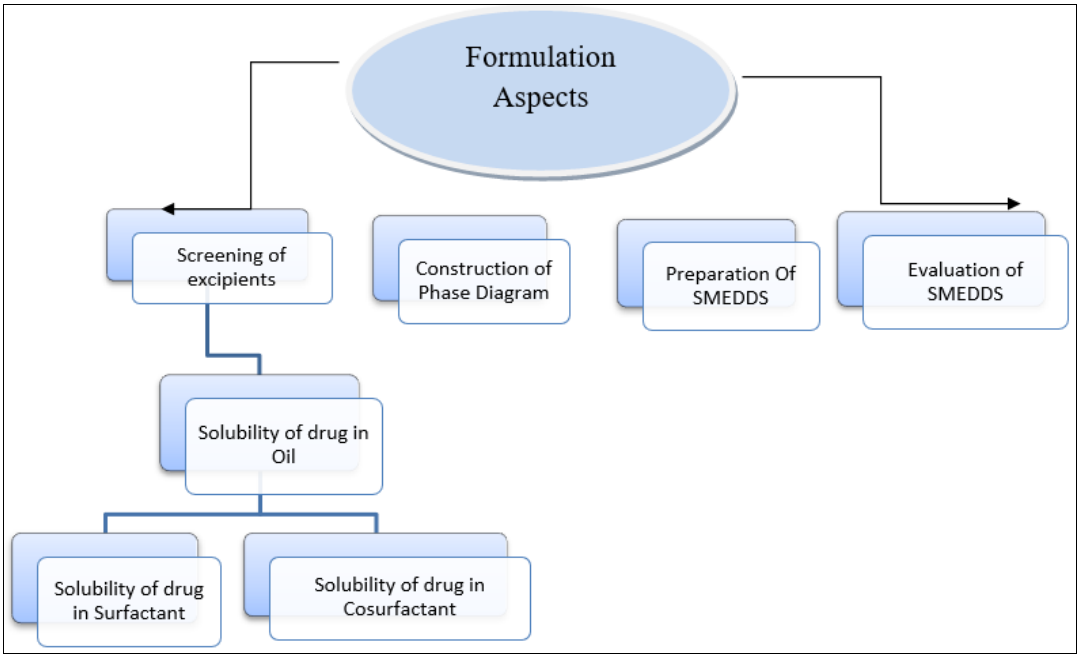


**Fig 2:** Formulation Design Of SMEDDS

- **Selection of Active Pharmaceutical Ingredient**

When choosing an active pharmaceutical component for SMEDDS, it is crucial to understand that the chosen active pharmaceutical ingredient can also significantly impact the various characteristics of SMEDDS, such as phase behavior and micro-emulsion particle size. The functioning of SMEDDS is significantly impacted by many physicochemical properties of the API, such as pKa, log P, atomic structure and weight, presence of the ionizable group, and quantity. Typically, medications with modest therapeutic doses are submitted to SMEDDS [11].

- **Selection of Oil**

The shaking flask method was used to examine the saturation solubility of API in a few oils in order to choose the best oil with a high capacity to solubilize the API. In the container that contained 0.5 g of each solvent, more API was added. To ensure that the API and vehicles were properly mixed, the mixture was vortexed for 10 minutes using a cyclomixer after sealing. After allowing the combination to reach equilibrium at room temperature for 72 hours, it was centrifuged for 15 minutes at the proper rpm. After the supernatant was separated, it was diluted with the mobile phase and passed through a membrane filter (0.45µm). High-performance liquid chromatography (HPLC) technology was used to evaluate the drug content.

- **Screening of surfactant for emulsifying ability**

The different surfactants are screened for their emulsification capability. A 1:1 ratio of surfactants can be applied to the specific oil. It homogenizes the mixture. To create a transparent emulsion, a predetermined amount of isotropic admixture is diluted with double-purified water. Using double-purified water as the blank, the resultant emulsions may be examined externally for their relative polluting influence and their transmittance can be measured in a UV-visible spectrophotometer [12].

- **Screening of Co-Surfactant**

Following oil screening, the ability of several co-surfactants to emulsify with the screened oil was examined in order to identify a suitable co-surfactant with good solubilizing potential. 0.2 g of co-surfactant and 0.3 g of oil phase were weighed and vortexed for two minutes followed by warming at 40-45°C for 30 seconds to create an isotropic mixture. In a volumetric flask, 50 mg of the isotropic mixture was taken and diluted with double-distilled water that had been filtered using a membrane filter (0.45µm). In order to produce a transparent emulsion, the quantity of flask incursions was visually examined. After the transmittance was observed, the resultant emulsion was left to stand for two hours. The co-surfactant was chosen because it produces a transparent emulsion with higher transmittance and fewer inversions.

- **A drug's solubility in oils, surfactants, and co-surfactants**

How well a drug dissolves in oils, surfactants, and co-surfactants the ability of the oils, surfactants, and co-surfactants to dissolve a large amount of pure medication was evaluated. A further amount of the medication is taken in glass vials with clear screw caps that include oil, surfactant, and co-surfactant. The mixture is then blended on a cyclomixer (vortex mixture). After shaking, the mixture is centrifuged. At the necessary wavelength, an aliquant portion of the supernatant is extracted and subjected to additional analysis using a UV visible spectrophotometer [13].

**Phase diagram preparation**

Phase diagrams can be used to illustrate microemulsions, which are made using the spontaneous emulsification method (also known as the phase titration method). A helpful method for examining the intricate sequence of interactions that can happen when several components are combined is to construct a phase diagram. Depending on the

chemical makeup and concentration of each component, microemulsions and a variety of association structures (such as emulsion, micelles, lamellar, hexagonal, cubic, and different gels and oily dispersion) can occur. Delineating the phase boundaries and comprehending their phase equilibrium are crucial components of the research. A pseudo-ternary phase diagram is frequently created to identify the various zones, including the microemulsion zone, where each corner of the diagram represents 100% of the specific component because quaternary phase diagrams (four component systems) are laborious and challenging to read. Pseudo-ternary phase diagrams are used when four or more components are being studied; in these diagrams, a corner usually represents a binary mixing of two components, such as oil/drug, water/drug, or surfactant/co-surfactant [14].

One can visually determine how many distinct phases are present in a given mixture. The picture below (Fig.3) shows a very schematic (pseudo) ternary phase diagram that depicts these characteristics.

A phase diagram is created using the titration method. Oil and surfactant mixtures are made in various ratios (e.g., 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10) and put into various bottles. The vials are filled with a tiny amount of water in 5% (w/w) increments. After adding water, the liquid in vials is centrifuged for two to three minutes and then gently shaken for 48 hours at 25°C. Both microscopic and ocular inspection are used to assess the resultant mixture. the area of transparent, isotropic solution is the microemulsion in the phase diagram. The area of hazy dispersion is known as a coarse emulsion [15].

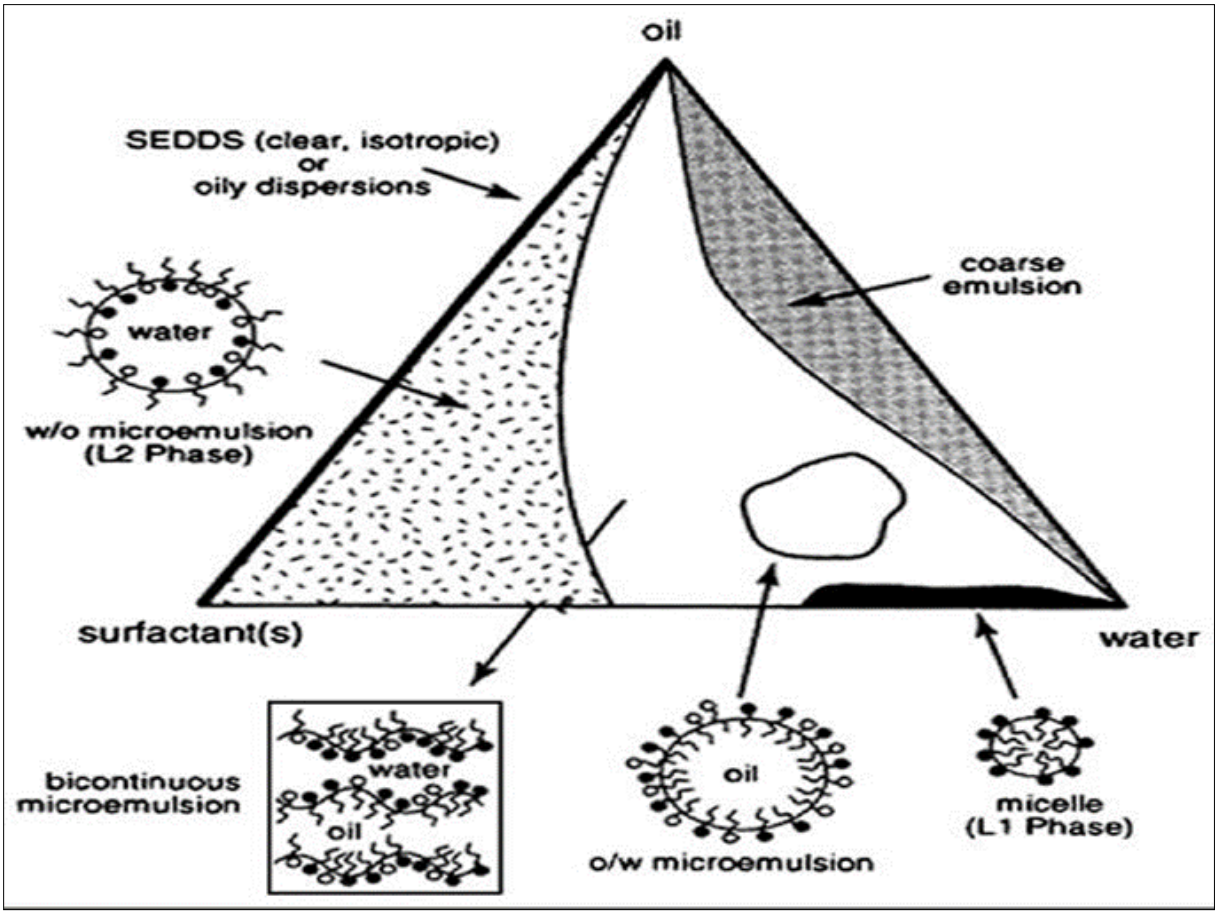


**Fig 3:** A schematic pseudo-ternary phase diagram of an oil/surfactant/water system illustrating the microemulsion, emulsion, and micellar phases.

- **Preparation of SMEDDS**

Different ratios of oil, surfactant, co-surfactant, and drug were used to create a number of SMEDDS. After precisely weighing the surfactant and co-surfactant and vertexing them for 5 minutes, the formulation was created by creating the optimal ratio of the Smix. The Smix was then baked for 1 hour at 50°C. In order to create an isotropic mixture, oils in various amounts were then added to the Smix, vortexed for 5 to 10 minutes, and baked for 1 hour at 50 °C. After that, the medication was added to these isotropic formulations and vortexed until a transparent solution formed [16].

**• Methods of Solidification for Converting Liquid To Solid SMEDDS**

When compared to conventional emulsion formulation, which is thermodynamically unstable, SMEDDS are spontaneous, kinetically stable, and need little energy input throughout the emulsion formation process. To increase patient compliance, stability, and reproducibility, liquid SMEDDS formulations can also be solidified.

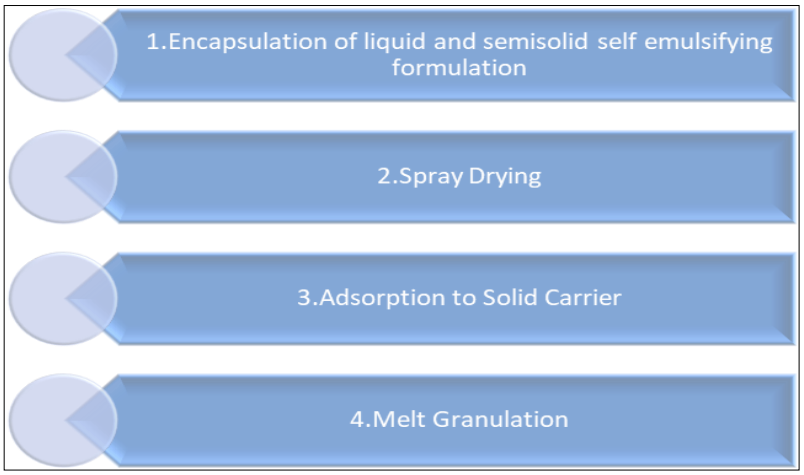


**Fig 4:** Methods of Solidification for Converting Liquid to Solid SMEDDS

**1. Encapsulation of liquid and semisolid Self-emulsifying formulation**

Capsule filling of a liquid and semisolid formulation is one of the most common and simplest techniques with suitability for both low-dose potent drug and high-dose drug loading (up to 50%) for conversion to solid SMEDDS.For liquid formulation, direct filling and sealing of the capsule are possible whereas, for a semisolid formulation, they are heated to a minimum of 20°C above the melting temperature which will be followed by active component incorporation with continuous agitation into the capsule and sealing it [17].

**2. Spray drying**

The key ingredients - oil phase, aqueous phase, surfactants, co-surfactants, and drug are combined to create a liquid or semisolid formulation of SMEDDS that is ready for spray drying. The volatile phase (such as the water in the system) is then vaporized to generate dry particles that can be processed into tablet or capsule formulations when this formulation is added to a spray of droplets in a drying chamber with regulated temperature and airflow conditions [18].

The overall design of the temperature and airflow parameters is chosen based on the powder specification and the drying properties of the medication product.

**3. Adsorption to a solid carrier**

Depending on the drug's properties, a variety of adsorbents, such as magnesium trisilicates, silica, magnesium hydroxide, talcum, and aerosol 200, are employed to absorb liquid or semisolid SMEDDS and create free-flowing powders or granules. The procedure is straightforward and entails adding liquid SMEDDS to carriers by combining them with blenders. The resulting powder can either be put straight into a capsule or, by combining the appropriate excipients, can be used to manufacture tablets. Using an appropriate adsorbent result in high-level absorption (up to 70% w/w) and good content homogeneity. Recently, a variety of nanoparticle absorbents have been employed, including silicon dioxide, carbon nanotubes, charcoal, and bamboo charcoal [19].

**4. Melt granulation**

The process of adding binders to a formulation that comparatively melts at a low temperature and forms granules is known as "melt granulation."

Since this method only requires one step of granulation and skips the drying phase, it is more comparable to spray drying. A defined impeller speed, binder particle size and viscosity, and overall mixing duration are applied to the mixture. Gelucire 1 is a widely used binder made from polyethene glycol (PEG) esters of fatty acids and mixes of mono-, di-, and tri-glycerides [20]

**Evaluation Parameters**

By identifying the assessment parameter, the effectiveness of self-micro-emulsification may be approximated.

- **Visual evaluation**

Self-emulsion is assessed via a visual evaluation. The impermeable, milky white phenomenon that arises when SMEDDS is diluted with water represents the development of the macroemulsion, while the fine, isotropic, transparent solution represents the formation of the microemulsion. When there isn't any specific medication precipitation, the planning might be regarded as consistent. 'Precipitation is common if the preparation contains water-soluble co-solvents, although it can be prevented by raising the concentration of surfactant [21].

- **Measurement of droplet size and particle size**

Photon correlation spectroscopy or scanning electron microscopy (SEM) are used to determine the microemulsion's particle size. Sizes between 10 and 5000 nm can be measured using electron microscopy. The technology is compatible with excess water since the particle's nanometric size range is maintained even after being diluted 100 or 1000 times with distilled water [22].

- **Refractive index and transmission percentage**

These metrics demonstrate how clear the formulation is. The index of refraction of the Using a refractometer, SMEDDS is measured and contrasted with water. Using distilled water as a blank, the UV-visible spectrophotometer measures the system's transmittance percentage at a specific wavelength, provided that the system's refractive index is comparable to that of water. Formulation demonstrating that transmittance >99 percent is transparent [23].

- **Zeta potential measurement**

Using an appropriate Zeta sizer, the zeta potential of a micro emulsion can be ascertained in triplicate samples [24].

- **Stability studies**

Samples were stored at two distinct temperatures (2–8°C in the refrigerator) and room temperature after SMEDDS was diluted with distilled water to ascertain their thermal stability and look for phase evidence. separation, flocculation, or precipitation of drugs. The enhanced SMEDDS details were weakened with refined water in order to measure metastable frameworks. To verify for changes in homogeneity, the microemulsion was centrifuged for 15 minutes at 37°C at 1000 rpm. The ability of a stable SMEDDS formulation to spontaneously emulsify should not be impacted by dilution. In the centrifugation test and the freeze-defrost cycle, all fluid definitions were judged to be stable. There was no obvious phase separation [25].

- **Centrifugation**

After passing through thaw cycles between 21 and 25°C, the formulations are stored at each temperature to ensure they don't 30 minutes at 3500 rpm is completed in less than 48 hours. For the freeze-thaw stress test, formulations that exhibit no phase separation are used [26].

- **In vitro release study**

The drug release properties of the SMEDD formulation were investigated in vitro, employing the dissemination cell, dialysis technique, and dissolving apparatus II. A modified diffusion cell was used to study the drug release in a 200 ml buffer solution with a pH of 6.8 and 1 gm. The SMEDD formulation was put in a boiling tube, with one side dipped in a buffer solution that was stored in a beaker underneath and the other side secured with a cellophane membrane [27]. Clamps held the upper side of the cylinder in place. The container was continuously mixed using an appealing stirrer, and after a number of times stretches, it was withdrawn and inspected using a UV Spectrophotometer to determine the percentage of drug breakup at different times Beer Lambert's equation was utilized for the calculation of intervals [28].

- **Bioavailability study**

The formulation is chosen for bioavailability research based on the stability of the microemulsion, particle size information, and self-emulsification characteristics. After the formulation is administered, the medication is quantified by in vivo research. The pharmacokinetic parameters of the drug's maximum plasma concentration (C max) and associated half-life (T max) after oral administration are computed. The following equation is used to determine the relative Bioavailability (BA) of SMEDDS form to the standard table. (AUC test/AUC reference) X (Dose reference/Dose test) = Relative BA (%) [29].

- **Flow Properties**

**1. Angle ofrepose**

The funnel method is used to calculate the angle of repose of S-SMEDDS. A specific volume of the sample is weighed before being put through a funnel. The tip of a funnel is positioned vertically so that it barely touches the pile of powder. The height of the pile and the diameter of the powder particles are measured after passing the S-SMEDDS.

The angle of repose is computed using the formula below: $\tan\theta$ = pile height divided by pile base radius [30]

**2. Density in bulk**

The tapped bulk density (TBD) and loose bulk density (LBD) are both calculated. Two grams of S-SMEDDS were added to a measuring cylinder that held 10 milliliters. At 2-second intervals, the cylinder is allowed to drop 2.5 cm onto a hard surface under its own weight to observe the initial volume. Until there is no more discernible change in volume, the tapping is continued. To determine LBD and TBD, the following formulas were applied:

LBD = Weight of powder/ initial volume (before tapping)
TBD = Weight of powder/volume after tapping [31]

**3. Index of Compressibility**

Carr's Compressibility Index is used to calculate the granules' compressibility.

Carr's compressibility index (%) is equal to $(TBD - LBD)/100$

**4. Hausner ratio**

The following formula can be used to compute the Hausner ratio:

Hausner ratio = $TBD/LBD$ [32]

- **Differential Scanning Calorimetry**

The differential scanning calorimeter is used to record the DSC thermograms for the drug and S-SMEDDS. In an aluminium pan (Al- Crucibles, 40 Al), 2–5 mg of each sample is heated from 30–300°C at a rate of 10°C per minute while being exposed to a stream of nitrogen flowing at a flow rate of 50 milliliters per minute [33].

- **Infrared spectroscopy using Fourier transform**

To record the result, a liquid sample needs to be put in the FTIR liquid sample container. Using this method, the researchers may determine whether the drug's functional groups and certain excipients have established new connections.

**Table 3:** List of Few Commercially Available SMEDDS Formulation

| S.N | GenericName | Brand Name | Company | Class | Formulation |
|---|---|---|---|---|---|
| 1. | Fenofibrate | Lipirex® | Genus | Antihyperlipidimic | Hard GelatinCapsules |
| 2. | Valproicacid | Convulex® | Pharmacia | Antiepileptic | Soft GelatinCapsules |
| 3. | CyclosporineA/I | Neoral® | Novartis | ImmuneSuppressant | Soft GelatinCapsules |
| 4. | CyclosporineA/II | Sandimmune® | Novartis | ImmuneSuppressant | Soft Gelatin Capsules |
| 5. | Bexarotene | Targretin® | Ligand | Antineoplastic | Soft Gelatin Capsules |
| 6. | Calcitriol | Rocaltrol® | Roche | Calciumregulator | Soft Gelatin Capsules |
| 7. | Ritonavir | Norvir® | Abbott Laboratories | HIVAntiviral | Soft Gelatin Capsules |
| 8. | Sequinavir | Fortovase® | Hoffmann-LaRocheinc | HIVAntiviral | Soft Gelatin Capsules |
| 9. | Amprenavir | Agenerase® | GlaxoSmithkline | HIVAntiviral | Soft Gelatin Capsules |

**Applications of SMEDDS**

**1. SMEDDS that are super saturated (S-SMEDDS)**

GI side effects and a new class of super saturable formulations, such as super saturable SMEDDS, can result from the high surfactant content commonly found in SMEDDS formulations. (S-SMEDDS) formulations have been created to minimize the negative effects of surfactants and facilitate the quick absorption of medications that are not very soluble in water [34].

**2. Solid SMEDDS**

More drawbacks, particularly in the production process, arise from the fact that SMEDDS are typically manufactured as liquid dosage forms that can be supplied in soft gelatin capsules [35]. Adding a liquid self-emulsifying substance to a powder to produce a solid dosage form (tablet, capsules) is an alternate technique. Extrusion and super-ionization have been used to create a progesterone pellet formulation in SMEDDS that has a good in-vitro drug release (100% within 15 min. and 50% in 13 min.).

**3. SMEDDS Solubilization**

SMEDDS are often effective solubilizers of compounds with a broad range of lipophilicity due to their oftenhigh oil and surfactant content [36]. For water-soluble medications, the solubilizing capability of a w/o microemulsion is usually greater than that of an o/w microemulsion; the opposite is true for oil-soluble medications. Additionally, the composition of SMEDDS affects the solubilization [38].

**4. Sustain release from SMEDDS**

SMEDDS have a rich behavior in terms of the release of solubilized material because of the diverse variety of structures that exist within them. Because of this, hydrophobic medicines that are mostly dissolved in oil droplets in O/W micro emulsions suffer from hindered diffusion and are consequently released more slowly (depending on the O/W partitioning of the substance). Conversely, water-soluble medications release quickly and diffuse virtually unhindered, depending on the volume percentage of the dispersed phase [39]. Because of the bicontinuous nature of the microemulsion "structure," both water-soluble and oil-soluble medicines diffuse and release very quickly in micro-balanced emulsions [1]. The medication release rate is influenced by the microemulsion composition in addition to its structure.

**Conclusion**

The formulation of a 'self-micro emulsifying drug delivery system is designed to improve the oral bioavailability of drugs that are poorly soluble and have low bioavailability. It is the most suitable technique to enhance the drug's bioavailability and solubility when taking oral medication [40].' After gently stirring the mixture of oil, surfactant, and co-surfactant, the aqueous media is diluted. SMEDDS is capable of overcoming the challenges associated with future medication marketing. However, there is still much work to be done before new SMEDDS products are put on the market. This work includes bioavailability studies and the development of in-vitro, in-vivo correlation (IVIVC) and other dose forms. Researchers looking at SMEDDS, ways to increase bioavailability, and drug solubility in water can use this review article as a starting point.

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