

An Insightful Study on SMEDDS Challenges and Potential Strategies

Bhavani B^{1*}, B.V.S.S.Subhadra², J.Divya Bhavani³, M.Surya Kiran⁴, M.Jyothsna⁵, P. Nookaratnam⁶, G.Venkataramana.⁷

Abstract

Self-microemulsifying drug delivery systems (SMEDDS) have gained attention as an effective approach to enhance the bioavailability of poorly water-soluble drugs. They are innovative lipid-based formulations designed to enhance the solubility, bioavailability, and therapeutic efficacy of poorly water-soluble drugs. The development of SMEDDS involves systematic selection of components based on solubility and emulsification efficiency, followed by optimization of ratios using pseudo-ternary phase diagrams. The resulting formulations are evaluated for droplet size, zeta potential, self-emulsification efficiency, and thermodynamic stability to ensure efficacy and reproducibility. SMEDDS can be conveniently encapsulated in soft or hard gelatin capsules, providing a patient-friendly oral delivery platform. Nevertheless, they are not without drawbacks, such as drug precipitation in vivo, challenges in formulation handling, restricted lymphatic absorption, absence of reliable in vitro prediction methods, and the oxidative degradation of unsaturated fatty acids. These issues limit the broader application. Incorporating polymers or precipitation inhibitors into lipid-based systems can help sustain drug supersaturation after dispersion, improving bioavailability and minimizing variability in drug exposure. Furthermore, converting liquid SMEDDS to solid form can alleviate problems related to handling and stability. The inclusion of medium-chain triglycerides (MCT) and antioxidants also helps counteract the oxidation of unsaturated fatty acids, addressing key limitations. SMEDDS represent a promising approach for overcoming the solubility and bioavailability challenges of lipophilic drugs, with potential applications in both pharmaceutical research and commercial drug development. Future advancements in component selection, nanotechnology integration, and personalized medicine are expected to further expand their utility in addressing unmet clinical needs. This review offers an in-depth exploration of SMEDDS challenges and proposes strategies to overcome them.

Keywords: Self-microemulsifying drug delivery systems, limitations, techniques, invivo studies, analytical techniques

*Author for Correspondence

Bhavani B

¹Professor & Head of the Pharmacy, Department of Pharmaceutical Sciences and Technologies, Jawaharlal Nehru Technological University, Kakinada, Andhra Pradesh, India

²⁻⁷Student, Department of Pharmaceutical Sciences and Technologies, Jawaharlal Nehru Technological University, Kakinada, Andhra Pradesh, India

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INTRODUCTION

A significant proportion of new pharmaceutical compounds, nearly 40%, exhibit poor water solubility, posing challenges in their formulation [1]. Common approaches to addressing this issue include: (a) micronization of crystalline solids, (b) amorphous solid dispersions, and (c) lipid-based formulations. Among these, lipid-microemulsion systems, particularly self-emulsifying drug delivery systems (SEDSS or SMEDDS), have gained prominence for their effectiveness in enhancing the bioavailability of poorly soluble drugs and natural compounds [2]. For instance, You et al. (2005) demonstrated a 57.7% improvement in the oral bioavailability of Oleum Curcumae wenchowensis using SEDSS [3]. Lipid-based delivery systems

include macroemulsions, microemulsions, SMEDDS, solid-lipid nanoparticles (SLNs), liposomes, and lipoplexes. Recently, much attention has focused on SMEDDS due to their reduced droplet size and high thermodynamic stability [4]. Emulsions, typically composed of droplets dispersed in a liquid medium, can be classified into oil-in-water (o/w) or water-in-oil (w/o) types, as well as multiple emulsions. The size of the droplets, generally between 1 and 10 μm , determines the emulsion's appearance, viscosity, and stability. Oil-in-water emulsions, particularly useful for pharmaceuticals, require an emulsifier that is soluble in the aqueous phase, whereas water-in-oil emulsions are stabilized by oil-phase surfactants [5]. Multiple emulsions, such as water-in-oil-in-water (w/o/w), are more complex systems where droplets contain smaller droplets of a different phase. Distinguishing between microemulsions and nanoemulsions is crucial, especially as SMEDDS convert into microemulsions after oral administration [6]. Microemulsions are isotropic and thermodynamically stable mixtures of oil, water, surfactant, and co-surfactants, formed by ultra-low interfacial tension achieved through the use of two or more emulsifiers [7]. In contrast, nanoemulsions, with droplet sizes below 100 nm, are kinetically stable but thermodynamically unstable systems [8]. Nanoemulsions require energy input for their formation, either through mechanical means or the chemical potential of the components involved. Unlike microemulsions, nanoemulsions remain stable under stress conditions such as temperature changes and dilution, while microemulsions are more sensitive to these factors [9]. Another key difference between these two types of emulsions is their formation process. For nanoemulsions, mixing surfactants with the oily phase is essential for stable droplet formation; however, for microemulsions, the order of mixing does not influence their formation. This distinction is useful for identifying and characterizing emulsions. Dynamic light scattering (DLS), commonly used to estimate droplet size, can be problematic for microemulsions since dilution can alter micelle size, whereas nanoemulsions are unaffected by dilution during size measurement. Regardless of the type of lipid formulation, an essential requirement is the ability to maintain the drug in a solubilized state within the gastrointestinal tract (GIT). If the drug precipitates, the advantages of lipid-based delivery systems are lost.

SEDDS/PRE-MICROEMULSION CONCENTRATES

Self-emulsifying drug delivery systems (SEDDS) are isotropic blends of oils, surfactants, and sometimes co-solvents that rapidly form oil-in-water (o/w) emulsions upon mild agitation or under the influence of digestive motility in the gastrointestinal (GI) tract [10]. SEDDS can be categorized based on the droplet size they produce: SMEDDS (self-microemulsifying drug delivery systems) typically result in emulsions with droplet sizes between 100 to 250 nm, while SNEDDS (self-nanoemulsifying drug delivery systems) generate droplets smaller than 100 nm as shown in the Figure 1[11]. Both SMEDDS and SNEDDS consist of oil, hydrophilic surfactants, and co-solvents, and upon exposure to aqueous media and gentle agitation in the GI tract, they spontaneously form o/w microemulsions [12]. Interestingly, the mechanism by which SMEDDS/SNEDDS form fine o/w emulsions resembles the low-energy emulsification process used to create nanoemulsions. A critical factor in the dissolution of drugs from SMEDDS is the diffusion of the drug from the oil globules into the surrounding dissolution medium, which is influenced by the concentration of surfactants and co-surfactants in the formulation [13]. The primary distinction between SEDDS and SMEDDS lies in the droplet size and clarity of the resulting emulsion. SEDDS generally produce larger, opaque emulsions with droplet sizes above 300 nm, whereas SMEDDS form smaller, transparent microemulsions with droplet sizes under 250 nm[14]. Additionally, the oil content in SMEDDS is typically less than 20%, compared to the higher oil content (40-80%) in SEDDS. Another key difference is in the surfactant hydrophilic-lipophilic balance (HLB) values: SEDDS are prepared with surfactants having an HLB < 12, while SMEDDS and SNEDDS use surfactants with an HLB > 12 [15]. When comparing SMEDDS/SNEDDS to traditional microemulsions, it has been observed that the globules formed from SMEDDS/SNEDDS tend to be larger than those formed from preformulated microemulsions of the same drug [16].

Components of SMEDDS Formulation

A self-micro emulsifying drug delivery system (SMEDDS) typically consists of four main components: drug, oil, surfactant, and co-surfactant.

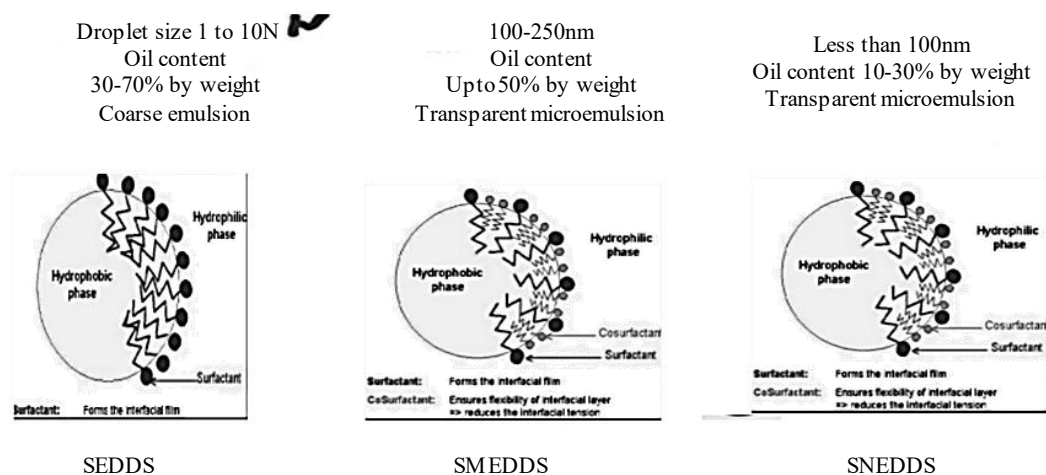


Figure 1. The schematic diagram illustrating the key differences between SEDDS, SMEDDS, and SNEDDS. The distinctions in droplet size, emulsion type, oil content, and surfactant HLB values are clearly represented.

Drug: The drug's lipophilicity and dosage are key factors to consider when developing a SMEDDS formulation. Ideally, the drug should have a low dose, a log P value greater than or equal to 2, and should not undergo extensive first-pass metabolism. Additionally, the drug must be significantly soluble in pharmaceutical lipids, surfactants, and co-solvents [17].

Oils: Oils serve as the primary lipid component in SMEDDS, aiding in drug solubilization and microemulsion formation upon dilution in aqueous media.

Commonly Used Oils:

- **Long-chain triglycerides (LCTs): e.g., castor oil, olive oil**
 - Provide high solubilization capacity for lipophilic drugs.
 - Slower digestion compared to MCTs, leading to prolonged drug release.
- **Medium-chain triglycerides (MCTs): e.g., caprylic/capric triglycerides (e.g., Miglyol 812)**
 - Faster digestion and better emulsification properties.
- **Essential oils: e.g., peppermint oil, eucalyptus oil**
 - Enhance drug permeability and provide functional benefits like anti-inflammatory effects.

Effect on Formulation

- The oil phase influences droplet size, drug solubilization, and the efficiency of microemulsion formation.
- Selection depends on the drug's lipophilicity and the required release profile

Medium-chain triglycerides (MCT), with carbon atoms ranging between 6 and 12, are directly absorbed into the systemic circulation via the portal blood, while long-chain triglycerides (LCT), with more than 12 carbon atoms, are transported through the intestinal lymphatic system. Due to their superior solvent capacity and resistance to oxidation, MCTs are commonly used in lipid-based formulations [18].

Surfactants

Surfactants lower interfacial tension, which enhances the dispersion process by forming an interfacial film. When choosing a surfactant, its hydrophilic-lipophilic balance (HLB) and concentration are crucial considerations. For high emulsifying efficiency, surfactants with an HLB greater than 12 are ideal, as they help create small oil-in-water (o/w) droplets and allow for rapid formulation dispersion in aqueous media. Non-ionic surfactants with an HLB above 12 are commonly used because they are less toxic than ionic surfactants [4, 19].

Commonly Used Surfactants:

- **Non-ionic surfactants: e.g., Tween 80 (polysorbate 80), Cremophor EL**
 - Low toxicity and good biocompatibility.
- **Ionic surfactants: e.g., sodium dodecyl sulfate (SDS)**
 - Occasionally used but can irritate biological membranes.

Properties Affecting Formulation:

- **Hydrophilic-lipophilic balance (HLB):**
 - High HLB surfactants (e.g., Tween 80) favor o/w microemulsions.
 - Low HLB surfactants favor w/o systems.
- Critical micelle concentration (CMC):

Surfactants with low CMC are more efficient in stabilizing the emulsion

Co-Surfactants

Co-surfactants provide flexibility to the interfacial layer by reducing the interfacial tension to near-zero levels. This flexibility allows for the formation of microemulsions across a broad range of compositions. Co-surfactants, typically medium-chain alcohols (C3–C8), are often employed to achieve this effect [20].

Commonly Used Co-surfactants:

- Ethanol
- Propylene glycol
- Polyethylene glycol (PEG)
- Span 20 (sorbitan monolaurate)

Effect on Formulation:

- Reduce interfacial tension further, aiding in spontaneous emulsification.
- Help to fine-tune the droplet size and improve drug solubilization.

Co-Solvents

Co-solvents are used to dissolve both the drug and excipients and to modify the system's polarity.

Commonly Used Co-solvents:

- Ethanol
- Propylene glycol
- PEG 400

Effect on Formulation:

- Enhance drug solubility in the pre-concentrate.
- Influence the phase behavior and stability of the formulation.

PRECIPITATION OF THE DRUG

Drug precipitation in vivo is a significant concern, as it can occur when the solubilization capacity of the formulation is reduced due to factors such as pH changes, dilution with bodily fluids, or the digestion of excipients. Precipitation decreases the drug's concentration in the aqueous phase, delaying or reducing its efficacy [21]. Precipitation is a complex process consisting of three steps: supersaturation, nucleation, and crystal growth.

Supersaturation

Supersaturation occurs when the solubilized drug concentration exceeds its saturation solubility, leading to the drug precipitating or crystallizing. A supersaturated system is thermodynamically unstable and tends to return to equilibrium through precipitation [17].

Nucleation

Nucleation involves the formation of small clusters of drug molecules in a supersaturated solution. These clusters act as seeds for further crystal growth. Nucleation can be spontaneous or triggered by impurities, with the former referred to as primary nucleation and the latter as secondary nucleation [22].

Crystal growth

Once nucleation occurs, the clusters grow through diffusion. The process of crystal growth is affected by physical conditions, with either growth or nucleation dominating. More growth leads to larger crystals, while ongoing nucleation results in smaller crystals [23].

Factors Influencing Drug Precipitation

Drug precipitation from supersaturated solutions is a multifaceted process governed by the interactions of nucleation and crystal growth. The following factors significantly influence this process:

Degree of supersaturation

The degree of supersaturation plays a crucial role in drug precipitation. Higher supersaturation levels increase the nucleation rate, making precipitation more likely. Supersaturation can be triggered by several mechanisms, such as solvent evaporation, cooling, or chemical reactions that alter the solubility of the drug. In a supersaturated state, the solution is thermodynamically unstable and tends to revert to equilibrium through precipitation [17, 24].

Solubility

At a constant level of supersaturation, increasing solubility promotes drug nucleation by increasing the chances of intermolecular collisions, thus accelerating the nucleation process [25].

Impurities

Impurities in the solution can stimulate the nucleation process by lowering the energy barrier for nucleus formation, thereby facilitating crystal growth. Impurities reduce the critical cluster size, making nucleation more likely than in homogeneous solutions [26].

Temperature

Higher temperatures can decrease drug precipitation by weakening the interactions between the drug and any polymers present. Increased temperature generally enhances solubility, which reduces the rate of nucleation and thus delays crystal formation [27].

Solution viscosity

Viscosity plays a significant role in drug precipitation. Lower solution viscosity favors drug precipitation by allowing faster diffusion of drug molecules to the crystal nuclei. Conversely, increasing viscosity slows down drug diffusion, thereby inhibiting both nucleation and crystal growth [28].

Mechanisms to Prevent Drug Precipitation

Various mechanisms have been proposed to explain how precipitation inhibitors work, although their precise mode of action is not fully understood. The following are some potential mechanisms:

Reticulate formation

A possible mechanism involves creating a reticulated polymer network, particularly using hydroxypropyl methylcellulose (HPMC) in supersaturable SMEDDS formulations. These networks consist of cellulosic bundles that form a structure in water, which may inhibit nucleation and crystal growth by adsorbing onto the surfaces of the nuclei or crystals [29].

Hydrogen bonding

HPMC and other hydrophilic polymers can form both intra- and intermolecular hydrogen bonds with the drug, which can slow down the rate of precipitation. For example, the formation of hydrogen bonds between PVP K17 and indirubin has been shown to inhibit precipitation [30].

Spring and parachute mechanism

The “spring and parachute” mechanism is a key approach in supersaturable formulations. This approach involves formulations that initially generate a supersaturated drug concentration (spring) in the gastrointestinal tract. However, to prevent rapid precipitation, a "parachute" effect is needed, where a component of the formulation inhibits nucleation or crystal growth, allowing time for drug absorption [23,24]. Polymers like HPMC and PVP, as well as surfactants and cyclodextrins, are often used to stabilize these supersaturated states [31].

MECHANISM BY WHICH SMEDDS IMPROVE DRUG RELEASE IN THE GIT [21,23,24,29]

Self-microemulsifying drug delivery systems (SMEDDS) enhance drug release and bioavailability in the gastrointestinal (GI) tract through a combination of physicochemical and physiological mechanisms. A detailed explanation of how SMEDDS improve drug release:

Formation of Microemulsions

When SMEDDS are exposed to the aqueous environment of the GI tract, they spontaneously form fine oil-in-water (o/w) microemulsions upon mild agitation (e.g., peristalsis). The resulting microemulsion has the following advantages:

- *Increased surface area:* The nanometer-sized droplets provide a large interfacial surface area for drug dissolution and absorption.
- *Improved drug solubility:* Poorly water-soluble drugs remain dissolved in the lipid droplets, avoiding precipitation in the aqueous environment

Enhanced Drug Dissolution

SMEDDS maintain the drug in a solubilized state throughout the GI tract, bypassing the rate-limiting step of drug dissolution. This is particularly beneficial for Biopharmaceutical Classification System (BCS) Class II drugs, which are poorly soluble but highly permeable.

Protection from Degradation

Encapsulation of the drug within the lipid phase of the microemulsion protects it from chemical and enzymatic degradation in the harsh GI environment, such as:

- Acidic conditions in the stomach.
- Hydrolytic or enzymatic degradation by digestive enzymes.

Interaction with Bile Salts

The lipidic components of SMEDDS (e.g., triglycerides) stimulate bile salt secretion. Bile salts:

- *Enhance solubilization:* Form mixed micelles with the formulation, further improving drug solubilization.
- *Increase permeability:* Disrupt the intestinal epithelial cell membrane, promoting paracellular transport of the drug.

Improved Permeability

Surfactants and co-surfactants in SMEDDS temporarily enhance intestinal permeability by:

- Modifying the integrity of tight junctions.
- Facilitating transcellular or paracellular transport of the drug.

Lymphatic Transport

SMEDDS can enhance lymphatic uptake of lipophilic drugs. Key mechanisms include:

- *Lipid absorption pathway:* The long-chain triglycerides (LCTs) in SMEDDS are absorbed into the lymphatic system along with the solubilized drug.
- *Avoidance of first-pass metabolism:* Lymphatic transport bypasses the liver, increasing systemic drug availability.

Prevention of Drug Precipitation

Drugs with low aqueous solubility often precipitate in the GI tract after conventional administration. In SMEDDS:

- The combination of oils, surfactants, and co-solvents maintains the drug in a supersaturated state.
- Precipitation inhibitors (e.g., surfactants) further prevent crystallization or precipitation during intestinal transit.

Prolonged Residence Time

The surfactants in SMEDDS can increase the viscosity of the formulation and interact with mucins in the GI tract, leading to:

- Prolonged residence time in the intestinal lumen.
- Increased opportunity for drug absorption.

Modulation of Drug Release Profile

- By modifying the composition of the oil, surfactant, and co-surfactant, SMEDDS can achieve controlled or immediate drug release profiles. This flexibility allows for tailoring the drug release to match therapeutic needs.

The ability of SMEDDS to improve drug release in the GI tract lies in their capacity to:

- Enhance drug solubilization.
- Provide protection against degradation.
- Facilitate absorption through multiple pathways, including lymphatic transport.
- Prevent precipitation and sustain a high concentration gradient, driving passive diffusion.

SUPERSATURABLE SMEDDS

Supersaturable SMEDDS are designed to minimize drug precipitation in the gastrointestinal tract. These formulations contain reduced surfactant levels and include polymeric precipitation inhibitors, typically cellulosic polymers like HPMC or PVP, which help maintain a supersaturated state. Unlike supersaturated formulations, which are not thermodynamically stable and may crystallize during storage, supersaturable SMEDDS remain stable under physiological conditions [23,29].

Hydrophilic polymers, such as PVP K17, HPMC, and sodium carboxymethyl cellulose, are commonly used in these formulations to prevent precipitation. Studies show that PVP K17 is particularly effective, maintaining higher drug concentrations for extended periods compared to other polymers [30]. Another advantage of supersaturable SMEDDS is the reduced amount of surfactant required, which can improve the formulation's safety and toxicity profile.

Encapsulation in HPMC or Gelatin Capsules

Many marketed SMEDDS are encapsulated in soft gelatin capsules, but these have several limitations. Issues include gelatin cross-linking, mechanical weakening of the capsule shell, and migration of solubilized components between the capsule fill and shell. Gelatin capsules also face consumer concerns related to religion and health, particularly with regards to transmissible spongiform encephalopathies [32].

Gelatin cross-linking

The stability of soft gelatin capsules can be affected when exposed to extreme physical conditions such as high temperature, humidity, UV, gamma-radiation, and rapid drying. These factors often cause cross-linking in the gelatin shell, making it tough, rubbery, and insoluble in water. Cross-linking occurs when aldehydes form methylene bridges between amino groups in adjacent gelatin chains or within the same chain. Aldehyde impurities can result from the auto-oxidation of materials like polyethylene glycols and polyoxyethylene derivatives [33]. The rate of cross-linking is influenced by humidity, with maximum cross-linking occurring around 60-70% humidity [34]. To mitigate cross-linking, excipients

with low aldehyde content can be used, or excipients with abundant free amino groups (e.g., glycine, lysine) can act as aldehyde scavengers to compete with the gelatin chains [35]. Another approach involves masking gelatin's amino groups through covalent bonding using agents like succinic acid, although this may lead to increased permeability of the gelatin shell to volatile solvents [36].

Crystallization of solubilized components

High initial water content in the capsule shell can lead to water migration between the shell and the fill material during drying and equilibrium processes. This migration can affect the solubility of the fill contents, especially in formulations containing poorly water-soluble drugs. The extent of migration is influenced by the composition of the capsule shell, including the type and concentration of plasticizer. Crystallization can occur in soft gelatin capsules when poorly soluble compounds are encapsulated in formulations like polyethylene glycol (PEG)-based solutions. However, adding lipid-based excipients such as Gelucire 44/14 can help prevent crystallization [37]. The presence of water in lipid-based vehicles can further reduce the solubility of certain compounds by inducing hydrate formation, as seen with anhydrous testosterone [18].

Mechanical strength deterioration

The mechanical strength of gelatin capsules can degrade over time, especially in formulations containing lower molecular weight polyethylene glycols (PEG 400), which tend to draw water from the gelatin shell. This leads to a brittle and less elastic shell. To counteract this, higher molecular weight PEGs (e.g., PEG 600) or small amounts of glycerin can be used to reduce migration of water from the shell. The inclusion of glycerin helps improve the shell's elasticity and reduce brittleness during storage or exposure to cold temperatures [38,39].

Migration of solutes

Soft gelatin capsules are dynamic systems where solutes can migrate between the fill material and the gelatin shell. For instance, ethanol, commonly used as a co-solvent in formulations, can diffuse through the gelatin shell, leading to a loss of solvent and potential precipitation of the dissolved drug. To minimize solvent loss, it is advisable to use non-volatile co-solvents such as propylene glycol, or package the product in airtight materials like aluminum blisters [40].

Replacing gelatin with HPMC

Due to the issues with gelatin cross-linking and solute migration, hydroxypropyl methylcellulose (HPMC) capsules have been explored as an alternative for encapsulating supersaturable self-emulsifying drug delivery systems (SMEDDS). HPMC capsules demonstrate greater resistance to water migration than gelatin capsules and maintain drug concentrations at higher levels [41]. These properties make HPMC capsules suitable for improving the stability and bioavailability of SMEDDS formulations [42].

Storage and handling of liquid SMEDDS

Liquid SMEDDS are often encapsulated in gelatin capsules, but the interaction between the lipid formulation and the gelatin shell can lead to brittleness, shell leakage, or drug precipitation, particularly at low temperatures. To address these issues, converting liquid SMEDDS into solid dosage forms has been proposed [1]. Solid SMEDDS offer the advantages of both SMEDDS and solid formulations, such as improved stability, reproducibility, and lower manufacturing costs [43]. Solid SMEDDS formulations thus provide a more robust dosage form with better patient compliance and lower production costs [44].

SOLID DOSAGE FORMS OF SMEDDS

Dry Emulsions

Dry emulsions are powdered formulations that rapidly emulsify upon contact with water. Methods for their preparation include rotary evaporation, freeze-drying, and spray drying, with spray drying being the most commonly used technique. An oil-in-water emulsion is prepared and then spray-dried to remove the aqueous phase [45].

Capsules

Solid SMEDDS (Self-Microemulsifying Drug Delivery Systems), produced by methods like spray drying and adsorption onto solid carriers, can be encapsulated in capsule shells. This prevents issues with the interaction between liquid SMEDDS and the capsule shell [46].

Tablets

Liquid SMEDDS can be adsorbed onto porous carriers and mixed with other excipients, then compressed into tablets. This method inhibits irreversible drug precipitation in the formulation [47].

Pellets

Pellets, which are produced using extrusion/spheronization techniques, are a convenient form of SMEDDS in multiple-unit dosages [48].

Techniques for Solid SMEDDS Production

Self-Microemulsifying Drug Delivery Systems (SMEDDS) are isotropic mixtures of oils, surfactants, and co-surfactants that can spontaneously form oil-in-water microemulsions upon mild agitation and dilution in the gastrointestinal (GI) tract as shown in Figure 2. These systems enhance the solubility, bioavailability, and absorption of poorly water-soluble drugs.

Encapsulation of liquid and semisolid SMEDDS

Liquid SMEDDS can be encapsulated in capsules using processes like microspraying or banding. For semisolid SMEDDS, the process involves heating excipients above their melting point, dissolving the drug into the molten mixture, filling the capsule, and cooling to room temperature. This method is particularly effective for highly potent, low-dose drugs [1].

Spray drying

In spray drying, liquid SMEDDS is mixed with a solid carrier and atomized into fine droplets. These droplets are dried under controlled conditions to produce solid particles [49].

Adsorption onto solid carriers

Liquid SMEDDS can be adsorbed onto powders with large surface areas that can absorb significant quantities of oil. Adsorbents like Magnesium aluminometasilicate and Calcium silicate are commonly used due to their oil-absorbing capacity [50]. In the formulation of solid Self-Microemulsifying Drug Delivery Systems (SSMEDDS), several adsorbents are commonly utilized due to their unique properties and applications. Calcium Silicate is known for its inorganic nature, hydrophilicity, and high surface area, enhancing drug solubility. Amorphous Silicon Dioxide, which is non-crystalline and possesses excellent adsorption properties, serves as a thickening agent and stabilizer. Hydrophilic Fumed Silica features a very high surface area that absorbs moisture, improving the solubility and stability of lipophilic drugs. Colloidal Silicon Dioxide offers a stable dispersion and enhances bioavailability, while Hydrophobic Colloidal Silica provides low moisture absorption, enhancing flow and reducing caking in formulations. Magnesium Aluminometasilicate contributes structural stability and moisture absorption, making it suitable for various pharmaceutical applications. Lastly, Anhydrous Dibasic Calcium Phosphate acts as a calcium source with low moisture absorption, promoting good flow properties and enhancing drug release in solid formulations. Together, these adsorbents play a crucial role in optimizing the performance and stability of SSMEDDS formulations.

Melt granulation

Melt granulation involves powder agglomeration through a binder that melts at low temperatures. It offers an advantage over wet granulation by eliminating the need for liquid addition and drying steps [1].

Extrusion spheronization

This process involves mixing liquid SMEDDS with an extrusion aid, followed by adding water to form a wet mass suitable for extrusion. The extruded mass is spheronized, dried, and size-separated into uniform pellets [48].

The formulation techniques employed in the development of Self-Microemulsifying Drug Delivery Systems (SMEDDS) exhibit varying capacities for lipid exposure and drug loading, impacting the overall performance of these systems. Capsule Filling and Spray Drying both allow for a maximum lipid exposure of 99% (w/w), enabling the incorporation of a substantial amount of lipid into the formulation, while both techniques can accommodate a maximum drug loading of 50% (w/w). In contrast, the Adsorption on Solid Carrier method permits a lower maximum lipid exposure of 80% (w/w) and a significantly reduced maximum drug loading of only 10% (w/w). Both Melt Granulation and Melt Extrusion techniques allow for a maximum lipid exposure of 50% (w/w), but they differ in drug loading capabilities; Melt Granulation supports a higher maximum drug loading of 80% (w/w), while Melt Extrusion can achieve a maximum drug loading of 60% (w/w). This diversity in formulation techniques underscores the importance of selecting the appropriate method based on the desired lipid exposure and drug loading for effective SMEDDS development.

Characterization of SMEDDS

Visual evaluation

Self-emulsification can be assessed through visual observation. When SMEDDS is diluted with water, a milky and opaque appearance suggests the formation of a macroemulsion, while a clear and isotropic solution indicates a microemulsion. The visual evaluation also allows for the assessment of drug precipitation; stable formulations show no signs of precipitation. Precipitation is more likely in formulations with water-soluble cosolvents, which can be mitigated by increasing surfactant concentration [51].

Droplet size analysis

The characteristics of droplet size are primarily influenced by the type and concentration of surfactants. Microemulsions created upon dilution yield droplets with a narrow size range, which enhances drug release, absorption, and stability. Techniques like photon correlation spectroscopy and microscopy are commonly utilized for droplet size analysis. Additionally, dynamic light scattering using a Zetasizer can provide precise droplet size measurements, with samples requiring appropriate dilution before analysis [52].

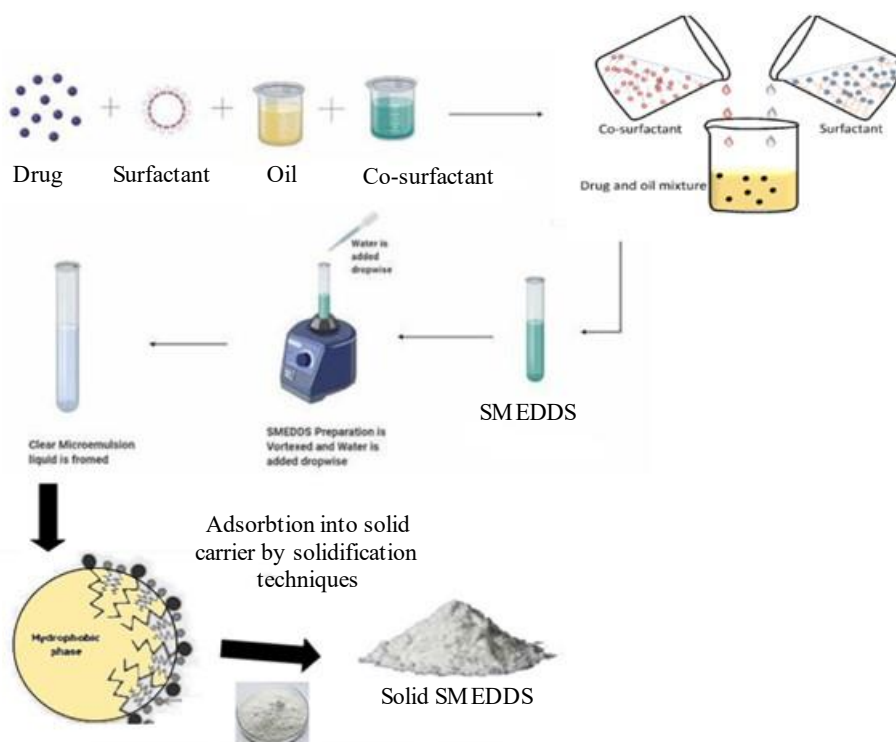


Figure 2. Solid SMEDDS preparation techniques.

Zeta potential measurement

Zeta potential is typically determined using a zeta potential analyzer or a zeta meter system. A higher zeta potential value is indicative of a more stable emulsion post-dilution. Although zeta potential values are generally negative due to free fatty acids, using cationic lipids like oleylamine results in a positive charge. Positively charged droplets are known to enhance adhesion to the gastrointestinal mucosal surface, leading to improved absorption through electrostatic interactions [53].

Time for emulsification

Self-emulsification time can be measured using a USP type II dissolution apparatus, where the formulation is added dropwise into a water-filled basket, and the transition to a clear solution is observed under paddle agitation at 50 rpm. The emulsification efficiency is influenced by the nature of the oil phase and the oil-to-surfactant ratio; higher surfactant concentrations generally lead to faster emulsification. The emulsification time can also be assessed visually by placing the formulation in a 0.1 N HCl solution and stirring to simulate gastrointestinal conditions [54].

Cloud point determination

The cloud point can be established by gradually increasing the water bath temperature of the formulation and measuring it spectrophotometrically. A decrease in transmittance indicates the cloud point, which signifies the temperature at which the transparent solution becomes cloudy. For the formulation to retain self-emulsification properties, the cloud point must be above body temperature (37°C). Higher temperatures can lead to phase separation and reduced drug solubilization due to surfactant dehydration [55].

Viscosity measurements

The viscosity of the diluted SMEDDS microemulsion can be measured using rheometers, such as Brookfield cone and plate rheometers. An increase in viscosity during titration, followed by a decrease with increased water volume, indicates the formation of O/W microemulsion from a W/O microemulsion. The microemulsion rheology can be characterized by plotting shear stress against shear rate; Newtonian behavior typically suggests the presence of small, spherical droplets [56,57].

Dilution studies

The clarity of microemulsions upon dilution can be assessed by diluting the preconcentrate in various solvents, including double-distilled water and simulated gastric fluid (SGF). If clarity is maintained across dilutions and different solvents, this indicates the absence of drug precipitation. Dilution factors of up to 100 times can simulate in vivo conditions. The pH impact can also be analyzed by diluting SMEDDS in various buffer solutions [57,58].

Refractive index

The refractive index is a measure of the isotropic nature of diluted SMEDDS. Refractive index measurements are typically conducted using refractometers, and stable formulations show no significant changes over time. The refractive index depends on the concentrations of cosurfactants and droplet size; increasing cosurfactant concentration typically decreases the refractive index [56-58].

Percentage transmittance

Percentage transmittance provides insights into the transparency of diluted SMEDDS. It is measured spectrophotometrically after dilution in water, with values nearing 100% indicating successful microemulsion formation [59,60].

Transmission electron microscopy (TEM) study

TEM is employed to analyze the structure and morphology of microemulsions formed from SMEDDS dilution. Samples are placed on a holey film grid and can be stained with agents like uranyl acetate for enhanced visualization of droplet size and shape [53].

Differential scanning calorimetry (DSC)

DSC is used to characterize microemulsions by analyzing peaks corresponding to water in the formulation. Pure water serves as a reference, exhibiting a sharp peak at approximately -17°C , indicative of its freezing point (Podlogar et al., 2021). Lower temperature peaks suggest water in a bound state within the microemulsion, while higher concentrations shift the peak upwards [53].

NMR techniques

Nuclear Magnetic Resonance (NMR) techniques evaluate the structure of microemulsions formed after SMEDDS dilution. The PGSE method allows the study of component diffusion within the microemulsion, revealing transitions between microemulsion phases. The self-diffusion coefficients of the components inform on the microemulsion type, such as O/W or W/O [61].

Small angle X-Ray and neutron scattering methods

Small angle X-ray scattering techniques characterize the structures resulting from SMEDDS dilution. Literatures noted that varying water concentrations lead to different liquid crystalline structures, which are vital for formulation stability and drug release. Similarly, small angle neutron scattering methods can detail transitions in microemulsion structures and determine droplet size and shape [61].

Thermodynamic stability studies

Thermodynamic stability can be assessed by diluting the formulation and centrifuging to check for phase separation. Samples without phase separation undergo freeze-thaw cycles to determine visual stability; stable formulations will maintain their appearance [62].

In vitro dissolution profile

The drug release profile from SMEDDS formulations can be evaluated using various USP apparatuses at $37 \pm 0.5^{\circ}\text{C}$. The polarity of oil droplets impacts the rate of drug release, influenced by the surfactant's HLB value, molecular weight, and degree of unsaturation in the lipid phase [53].

Stability assessment

Stability studies following ICH guidelines involve testing formulations encapsulated in gelatin capsules for appearance, color, drug content, pH, and dissolution profile over time. Formulations exhibiting no changes in these parameters during storage can be classified as stable [62].

LYMPHATIC UPTAKE OF SMEDDS

Lymphatic transport plays a critical role in the absorption of lipophilic drugs from SMEDDS. Lipophilic drugs can diffuse through intestinal cells and associate with chylomicrons, which are secreted into lymphatic circulation rather than portal circulation. This bypasses the liver and first-pass metabolism, enhancing systemic drug exposure. The lymphatic system is also an important transport pathway for immunomodulatory and chemotherapeutic drugs, as it is the primary route for the metastasis of solid tumors and the spread of certain viruses like HIV and SARS. Lymphatic uptake is influenced by factors like particle size, composition, and surface charge. Drugs with a high log P value (>5) and significant solubility in long-chain triglycerides ($>50\text{ mg/mL}$) are more likely to be transported via the lymphatic system. However, the correlation between lipophilicity, triglyceride solubility, and lymphatic transport is not always consistent, and further research is required to develop predictive models [53,63].

Evaluation using animal models

Animal models, particularly rats, are commonly used to study lymphatic drug transport. The process involves cannulating the lymphatic duct to measure drug levels directly. This allows researchers to compare drug absorption via the lymphatic system to portal blood absorption [64]. However, complications such as cannula blockage can make this method challenging. Alternatively, pharmacological approaches using inhibitors like Pluronic-L81 have been developed to assess lymphatic transport without the need for cannulation. These inhibitors block chylomicron flow, providing indirect measures of lymphatic transport's impact on bioavailability [65].

Lack of effective in vitro tests

One of the main obstacles to the commercialization of SMEDDS is the lack of effective in vitro tests that accurately simulate in vivo conditions. Dissolution tests in aqueous media often fail to predict the performance of lipid-based systems due to the low solubility of many drugs in water. The development of more sophisticated dissolution media that better reflect the gastrointestinal environment is necessary to improve the predictive accuracy of these tests.

Assessment of Lipid-Based Formulations Using In Vitro Lipolysis

The development of self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) primarily focus on enhancing drug solubility, evaluating in vitro emulsification efficiency, and determining the particle size of the dispersion once diluted in aqueous media. Recent advancements have introduced in vitro dispersion tests and lipid digestion models, which simulate the gastrointestinal environment to predict the in vivo behavior of poorly water-soluble drugs. Traditional dissolution tests measure the drug's dissolution from its solid form into simple or biorelevant media. However, lipid-based formulations require a focus on the drug's precipitation rate and extent over time rather than solubilization since the drug is already in a solubilized state within the formulation [66]. One model for evaluating lipid digestion is the lipid digestion model, used to predict the effectiveness of SEDDS/SMEDDS formulations. This process involves adding lipid-based formulations to digestive buffers containing bile salts, and initiating lipid digestion by adding pancreatic lipase. This leads to the release of fatty acids, which cause a temporary decrease in pH. A pH controller regulates this drop through the addition of sodium hydroxide, allowing for the quantification of the digestion process. The rate at which sodium hydroxide is added reflects the extent of digestion, assuming a stoichiometric reaction between fatty acids and sodium hydroxide. Throughout digestion, samples are centrifuged to separate the digested products into phases: a poorly dispersed oil phase, a highly dispersed aqueous phase, and a precipitated pellet phase. Measuring the mass of the drug in the aqueous phase indicates how much drug remains solubilized and does not precipitate in vivo, offering a reliable method to predict in vivo performance of lipophilic formulations [66]. An investigation into the distribution and solubilization of dexamethasone and griseofulvin across different lipid systems (long-chain triglycerides, medium-chain triglycerides, and short-chain triglycerides) in the in vitro lipolysis model, followed by in vivo evaluation, concluded that medium-chain triglycerides led to higher drug solubilization in the aqueous phase (>95%), while long-chain triglycerides and short-chain triglycerides resulted in lower solubilization levels [67].

Dynamic Gastric Model (DGM)

The Dynamic Gastric Model (DGM), developed by the Institute of Food Research in the UK, represents the first dynamic in vitro model of the human stomach, mimicking the digestive process by transforming food into chyme. The DGM comprises a main body and antrum, replicating gastric secretion and contractions. The composition of secretions matches in vivo conditions, with enzymatic digestion occurring via gastric lipase and pepsin. As the ingested material undergoes acid, enzymatic, and mechanical digestion, samples are collected at intervals for droplet size analysis [68].

Oxidation and Polymorphism of Lipids in SEDDS/SMEDDS Formulation

Lipid oxidation

Lipid excipients containing unsaturated fatty acids are prone to oxidation, with the degradation rate proportional to the degree of unsaturation. Polyethylene glycol (PEG) and polyoxyethylene-based materials undergo auto-oxidation in the presence of oxygen, generating reactive organic peroxides and hydrogen peroxide. Impurities such as peroxides, metal ions, and photochemical sensitizers like chlorophyll and riboflavin accelerate this process, leading to the formation of degradation products, including alcohols, aldehydes, and acids, which contribute to rancid lipid odors. To mitigate oxidation, antioxidants like tertiary-butyl hydroquinone (TBHQ), as well as free radical quenchers such as α -tocopherol and butylated hydroxyanisole (BHA), can be added to the formulation. Hard gelatin capsules, which offer low oxygen permeability, can also protect lipid formulations from oxidation. Incorporating nitrogen into the capsule's headspace during production further enhances this protection [69].

Polymorphism

Lipids, such as fatty acids and their esters, exhibit polymorphism due to various modes of hydrocarbon chain packing. Lipids with a cone-like geometry assemble into micelles, while cylindrical-shaped lipids form bilayers. In some cases, lipids with smaller head groups adopt inverted phases like the inverted hexagonal phase. For example, dioleoylphosphatidylethanolamine (DOPE) transitions from a bilayer phase to an inverted hexagonal phase at elevated temperatures.

X-ray diffraction and differential scanning calorimetry (DSC) are key techniques used to study lipid polymorphism. Polymorphic changes can affect the solidification time of lipid excipients, influencing production and drug release profiles. To minimize such changes, excipients should be heated above their melting point and mixed thoroughly before encapsulation to ensure a uniform product [70].

Advantages of SMEDDS

Storage

Like macroemulsions, SMEDDS enhance the solubility of hydrophobic drugs. However, while macroemulsions can experience creaming over time, SMEDDS are thermodynamically stable, making them easier to store [71].

Stability

Unlike micro or nanoemulsions, SMEDDS do not contain water, which improves their physical and chemical stability during long-term storage. For example, SNEDDS tablets incorporating carvedilol have demonstrated enhanced stability during dilution in aqueous media, especially in the presence of cellulosic polymers [72].

Patient compliance

Most SMEDDS formulations are available in capsules or tablets, which are smaller, easy to administer, and more convenient for patients [29].

Palatability

SMEDDS formulations can be encapsulated, addressing the taste issues often associated with lipid-based formulations [73].

Effect of food

Food intake does not significantly affect drug absorption from SMEDDS formulations. For example, the absorption of itraconazole from a conventional marketed formulation (Sporanox capsule) was significantly affected by food, whereas its absorption from a self-emulsifying formulation (ITRA-GSMP capsule) was much less influenced [74].

Quick onset of action

SMEDDS promote rapid oral absorption of drugs, leading to faster onset of action. For instance, administering vitamin A as a SNEDDS capsule or tablet resulted in reduced time to peak concentration (t_{max}) and improved bioavailability compared to oily solution-filled capsules [75].

Ease of manufacturing and scale-Up

SMEDDS formulations are relatively easy to manufacture on a large scale using simple equipment like mixers with agitators and volumetric liquid-filling machines, making them economical to produce

LIMITATIONS OF SMEDDS

While SMEDDS formulations offer several advantages, they also have notable limitations that need to be addressed.

Drug precipitation on dilution

One significant limitation is drug precipitation upon dilution in gastrointestinal (GI) fluids. Ideally, SMEDDS should maintain the drug in a solubilized form within the GI tract. However, due to the

dilution effect of hydrophilic solvents, the drug tends to precipitate, negating the benefits of lipid-based formulations. To counter this, polymers are often incorporated to minimize precipitation in vivo [66].

Encapsulation in soft gelatin capsules

Most SMEDDS formulations are delivered in soft gelatin capsules, which present certain challenges. These capsules are associated with higher manufacturing costs and concerns related to transmissible spongiform encephalopathy (TSE), as well as issues with consumer preferences based on religion. Additionally, volatile co-solvents can migrate into gelatin capsule shells, causing drug precipitation. Hydroxypropyl methylcellulose (HPMC) capsules have been explored as an alternative to address these issues [7].

Storage and handling

Liquid SMEDDS formulations often face challenges related to handling, storage, and stability. A potential solution is the development of solid SMEDDS to mitigate these problems [1].

Limited lymphatic targeting

Targeting the lymphatic system offers two primary benefits: avoidance of first-pass metabolism and site-specific delivery to lymphatic organs. However, drug transport to lymphatics can vary depending on the drug's properties, such as lipophilicity and triglyceride solubility. A deeper understanding and improved predictive models are needed to enhance lymphatic targeting [76].

Lack of effective in vitro models

Another limitation is the absence of reliable in vitro models for evaluating SMEDDS and other lipid-based formulations. Traditional dissolution methods are insufficient since these formulations depend on lipid digestion within the gut. Though in vitro models simulating digestive processes have been developed, further refinement is necessary before they can be widely adopted [77].

Lipid oxidation and polymorphism

Lipid excipients, especially those containing unsaturated fatty acids, are prone to oxidation. This necessitates the inclusion of lipid-soluble antioxidants in capsule formulations. Additionally, lipid polymorphism—changes in the crystalline structure of lipids—can occur, requiring careful process control during formulation [77].

CHALLENGES TO ENCOUNTER SCALING UP SMEDDS FROM LABORATORY TO INDUSTRY SCALE PRODUCTION

Scaling up self-microemulsifying drug delivery systems (SMEDDS) from the laboratory to industrial-scale production involves several challenges. These arise due to differences in process requirements, equipment capabilities, and quality control measures. Here's a detailed look at the key challenges:

Ingredient Selection and Compatibility

- ***Ingredient variability [78]***
 - Excipients used in SMEDDS (e.g., oils, surfactants) may vary in purity, quality, and consistency across suppliers, impacting the formulation.
 - Batch-to-batch variation in excipients, particularly natural oils or essential oils, can affect microemulsion properties.
- ***Regulatory restrictions***
 - Certain excipients may not be approved for use in all regions or at the required concentrations.

Drug Loading and Solubility

- ***Solubility limits***
 - The amount of drug that can be solubilized in the formulation may vary at larger scales, requiring optimization of drug loading.

- **Supersaturation risks [79]**
 - Maintaining the drug in a supersaturated state can become more challenging at higher volumes, increasing the risk of drug precipitation.

Emulsification Efficiency [80].

- **Shear forces**
 - Spontaneous microemulsion formation at the laboratory scale may not translate effectively at larger scales due to differences in shear forces and mixing dynamics.
- **Mixing uniformity**
 - Achieving uniform mixing of oil, surfactant, and co-surfactant components across large batches is critical but challenging.

Equipment and Processing

- **Scaling mixing equipment [81]**
 - Laboratory-scale mixing techniques may not be directly scalable to industrial processes, requiring specialized equipment such as high-shear mixers or homogenizers.
- **Energy requirements**
 - The energy input needed for emulsification may differ at larger scales, affecting droplet size and stability.
- **Thermal sensitivity**
 - Certain excipients or drugs may degrade during large-scale production due to heat generated during mixing or emulsification.

Droplet Size and Stability [82]

- **Consistency of droplet size**
 - Maintaining the desired droplet size (<100 nm) for microemulsions across large batches is critical for ensuring bioavailability.
- **Phase separation risks**
 - Larger batch volumes increase the risk of phase separation during storage or processing, requiring careful control of formulation parameters.

Filling and Packaging

- **Viscosity and flow properties [83]**
 - The viscosity of SMEDDS formulations can affect their flowability during filling and packaging, especially for high-viscosity systems.
- **Material compatibility**
 - Compatibility of SMEDDS with packaging materials (e.g., bottles, capsules) must be ensured to avoid leaching or degradation.

Scale-Up Validation [84]

- **Process validation**
 - Ensuring reproducibility and consistency across batches requires rigorous validation of the manufacturing process.
- **Quality control (QC)**
 - Sophisticated QC methods (e.g., droplet size analysis, zeta potential measurement) must be implemented for large-scale production.
- **Regulatory compliance**
 - Scaling up often requires adhering to Good Manufacturing Practices (GMP) and other regulatory guidelines, which can be resource-intensive.

Cost and Feasibility [85]

- **Excipients cost**
 - High-quality surfactants or oils used in SMEDDS can be expensive, increasing production costs at scale.

- **Process economics**
 - The need for specialized equipment, high energy input, and extensive QC may impact overall feasibility.

Stability Challenges [86]

- **Long-term stability**
 - Stability studies may reveal challenges such as drug precipitation, phase separation, or degradation at larger scales.
- **Temperature and Humidity Sensitivity**
 - Scaling up often involves transportation and storage under varying environmental conditions, which can affect the stability of the formulation.

Intellectual Property (IP) and Licensing [87]

- **Formulation modifications**
 - Slight modifications to the formulation during scale-up may impact patent protection or licensing agreements.
- **Technology transfer**

Transferring the process from the R&D lab to the production site requires detailed documentation and expertise.

Solutions to Address Challenges

1. **Pilot-scale studies:** Conduct intermediate-scale trials to identify and resolve potential issues before full-scale production.
2. **Process optimization:** Use tools like Design of Experiments (DoE) to optimize formulation and process parameters.
3. **Advanced equipment:** Invest in scalable technologies like high-shear mixers or microfluidizers for uniform emulsification.
4. **Rigorous quality control:** Implement real-time monitoring tools for droplet size, viscosity, and stability during production.
5. **Regulatory planning:** Engage with regulatory agencies early in the process to ensure compliance with guidelines.

By addressing these challenges systematically, SMEDDS can be successfully scaled up for industrial production while maintaining quality and efficacy.

RECENT ADVANCES IN THE DEVELOPMENT OF SMEDDS TO IMPROVE THEIR EFFECTIVENESS IN DRUG DELIVERY

Recent advances in the development of self-microemulsifying drug delivery systems (SMEDDS) have focused on improving their effectiveness in drug delivery through enhanced solubility, stability, bioavailability, and targeted delivery capabilities. Here are the notable advances and their benefits:

Incorporation of Advanced Lipids [88]

- **Lipid nanomaterials**
 - Use of lipid nanoparticles, like nanostructured lipid carriers (NLCs), enhances stability and drug loading.
 - Improved controlled release and prolonged circulation times.
- **Functional lipids**
 - Incorporation of bioactive lipids (e.g., omega-3 fatty acids) provides synergistic therapeutic effects, especially in nutraceutical SMEDDS.

Development of Solid SMEDDS [89]

- **Transformation into solid dosage forms**
 - Conversion of liquid SMEDDS into solid SMEDDS using adsorbents (e.g., silica), spray drying, or freeze-drying.

- Benefits:
 - Improved handling and stability.
 - Enhanced patient compliance (easy-to-administer tablets or capsules).
- *Examples*: SMEDDS-loaded pellets, granules, or powders.

Use of Nanotechnology [90]

- ***Nano-SMEDDS***
 - Formulations with ultra-small droplet sizes (<50 nm) improve drug solubilization and absorption.
 - Enhanced lymphatic uptake and systemic bioavailability.
- ***Surface-modified nanoemulsions***
 - Functionalized with polymers (e.g., polyethylene glycol) or targeting ligands for specific tissue delivery.

Integration with Biopolymers [91]

- ***Mucoadhesive SMEDDS***
 - Incorporation of polymers like chitosan or carbopol enhances adhesion to the intestinal mucosa, prolonging residence time and improving absorption.
- ***Stimuli-Responsive Polymers:***
 - Polymers sensitive to pH, temperature, or enzymes improve drug release in response to specific GI tract conditions.

Improved Drug Loading and Release [92]

- ***Supersaturated SMEDDS (S-SMEDDS)***
 - These formulations maintain a higher concentration of the drug in a metastable supersaturated state.
 - Precipitation inhibitors (e.g., polymers) are used to prevent crystallization.
- ***Controlled release systems***
 - Modified formulations allow for sustained or controlled drug release profiles.

Enhanced Targeting Capabilities [93]

- ***Lymphatic targeting***
 - Modifications in lipid composition (e.g., long-chain triglycerides) direct drug transport to the lymphatic system, bypassing hepatic metabolism.
 - Particularly effective for lipophilic drugs or drugs prone to first-pass metabolism.
- ***Brain delivery***
 - SMEDDS functionalized with brain-targeting ligands or surfactants like Tween 80 improve drug delivery across the blood-brain barrier (BBB).

Improved Bioavailability [94]

- ***Co-encapsulation of permeation enhancers***
 - Adding agents like bile salts or permeation enhancers improves intestinal absorption.
- ***Enzyme-inhibiting excipients***
 - Incorporation of enzyme inhibitors (e.g., protease inhibitors) protects drugs from degradation in the GI tract.

Use of Artificial Intelligence (AI) and Machine Learning [95]

- ***Optimized formulations***
 - AI-driven models help identify the ideal ratios of oils, surfactants, and co-surfactants to achieve optimal solubilization and stability.

- **Predictive modeling**
 - Machine learning predicts drug solubility, droplet size, and pharmacokinetics, reducing formulation time and costs.

Hybrid Delivery Systems [96]

- **SMEDDS-loaded microparticles or nanoparticles**
 - Combining SMEDDS with microparticle or nanoparticle carriers (e.g., mesoporous silica, polymeric nanoparticles) enhances stability and provides additional control over drug release.
- **Combination with Other Drug Delivery Systems**
 - Hybrid formulations, such as SMEDDS combined with hydrogels or nanofibers, enable localized or sustained drug release.

Focus on Natural and Biocompatible Excipients

- **Plant-based oils and surfactants**
 - Increased use of natural oils (e.g., coconut oil) and surfactants derived from plants for better biocompatibility and reduced toxicity.
- **Green formulation approaches [97]**
 - Use of eco-friendly solvents and excipients reduces the environmental impact of production.

Multi-Drug Delivery

- **Synergistic drug combinations [98]**
 - SMEDDS are increasingly used to co-deliver drugs with complementary mechanisms, enhancing therapeutic outcomes.
 - Example: Combination of anti-cancer drugs with P-glycoprotein inhibitors to overcome drug resistance.

Applications in Specialized Drug Delivery [99]

- **Paediatric and geriatric formulations**
 - Development of taste-masked, easy-to-swallow SMEDDS for improved compliance in vulnerable populations.
- **Vaccines and biologics**
 - SMEDDS are being explored for the delivery of vaccines and biologics (e.g., peptides and proteins) due to their ability to protect sensitive molecules.

CONCLUSION

Despite the growing interest in SMEDDS for delivering poorly water-soluble drugs, a gap remains between the potential of lipid-based systems and their market availability. Current SMEDDS formulations are often encapsulated in soft gelatin, leading to handling and cost challenges. The development of solid SMEDDS could address these issues, offering a stable and cost-effective alternative. Formulations must be designed to work harmoniously with physiological environments to fully realize the potential of lipid-based drug delivery systems.

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