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Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS): Advances in Oral Bioavailability Enhancement

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ABSTRACT

The oral delivery of poorly soluble drugs remains a major challenge in pharmaceutical development due to limited dissolution and low systemic availability, particularly for compounds belonging to Biopharmaceutics Classification System (BCS) Class II and IV. Lipid-based drug delivery systems, especially Self-Microemulsifying Drug Delivery Systems (SMEDDS), have shown considerable potential in enhancing solubilization and absorption through spontaneous formation of fine emulsions in the gastrointestinal environment. However, conventional liquid SMEDDS suffer from limitations such as instability, leakage, and precipitation upon dilution, restricting their practical application. Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS) have emerged as an advanced alternative, integrating the advantages of lipid-based formulations with the stability and convenience of solid dosage forms. Upon dispersion, S-SMEDDS rapidly reconstitute into nano-sized microemulsions, improving drug dissolution, permeability, and bioavailability. This review comprehensively discusses formulation strategies, excipient selection, and solidification techniques involved in the development of S-SMEDDS. The mechanisms of bioavailability enhancement, including improved solubilization, increased surface area, lymphatic transport, and inhibition of efflux transporters, are critically analyzed. Recent advances such as polymer-based and supersaturable systems, along with lipid–polymer hybrid approaches, are highlighted for their role in maintaining supersaturation and preventing drug precipitation. The application of Quality by Design (QbD) principles for systematic optimization and robust product development is also emphasized. Overall, S-SMEDDS represent a promising and versatile platform for enhancing oral bioavailability, with significant potential for future pharmaceutical innovation and commercialization..

Keywords: Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS); Oral bioavailability; Lipid-based drug delivery; Quality by Design (QbD)

INTRODUCTION

Oral drug delivery remains the most preferred route of administration owing to its convenience, patient compliance, cost-effectiveness, and suitability for chronic therapy [1]. However, a significant proportion of newly developed drug candidates exhibit poor aqueous solubility and limited oral bioavailability, posing a major challenge in pharmaceutical development [2]. According to the Biopharmaceutics Classification System (BCS), a large number of drugs fall under Class II and Class IV, where dissolution rate and solubility become the rate-limiting steps for absorption [3]. These limitations often lead to erratic pharmacokinetics, reduced therapeutic efficacy, and the need for higher doses, thereby increasing the risk of adverse effects[4], [5]. To address these challenges, lipid-based drug delivery systems have gained considerable attention as an effective strategy to enhance the solubility and oral absorption of poorly water-soluble drugs [6]. Among these, Self-Microemulsifying Drug Delivery Systems (SMEDDS) have emerged as a promising approach [7]. SMEDDS are isotropic

mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water microemulsions upon dilution in gastrointestinal fluids under mild agitation [8]. This spontaneous emulsification results in the formation of nano-sized droplets, significantly increasing the surface area available for drug dissolution and absorption [9], [10]. In addition, SMEDDS can enhance drug permeability, promote lymphatic transport, and reduce the impact of first-pass metabolism [7], [11].

Despite their advantages, conventional liquid SMEDDS are associated with several limitations, including poor physical stability, potential drug precipitation upon dilution, leakage from capsules, and challenges in handling, storage, and large-scale manufacturing[12], [13]. These drawbacks restrict their widespread industrial application and clinical translation[14]. To overcome these issues, recent research has focused on the development of Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS), which combine the solubilization benefits of SMEDDS with the stability and convenience of solid dosage forms[14], [15]. S-SMEDDS are typically prepared by converting liquid SMEDDS into solid intermediates using techniques such as adsorption onto porous carriers, spray drying, melt granulation, and extrusion-based processes[13], [15]. The resulting solid systems can be formulated into tablets, capsules, or granules, offering improved stability, better patient acceptability, ease of handling, and enhanced scalability [15]. Furthermore, the incorporation of polymers and advanced formulation strategies has led to the development of supersaturable and precipitation-inhibiting S-SMEDDS, which further improve drug absorption by maintaining a supersaturated state in the gastrointestinal environment.

In recent years, the integration of Quality by Design (QbD) principles and advanced optimization techniques has significantly improved the rational development of S-SMEDDS, enabling better control over critical formulation variables and ensuring consistent product performance. Additionally, emerging approaches such as lipid–polymer hybrid systems and modified-release S-SMEDDS have expanded their application across various therapeutic areas, including anticancer, antidiabetic, and central nervous system drugs [15], [16], [17], [18].[15], [16], [17], [18]., this review aims to provide a comprehensive yet concise overview of S-SMEDDS, focusing on their formulation strategies, underlying mechanisms of bioavailability enhancement, recent technological advancements, and practical considerations for industrial development. The review also highlights current challenges and future perspectives, emphasizing the growing potential of S-SMEDDS as a versatile platform for improving the oral delivery of poorly soluble drugs.

2. Fundamentals of Self-Microemulsifying Drug Delivery Systems

2.1 Components of SMEDDS

Self-Microemulsifying Drug Delivery Systems (SMEDDS) are isotropic mixtures composed of oils, surfactants, and co-surfactants or co-solvents that possess the inherent ability to spontaneously form fine oil-in-water microemulsions upon dilution in aqueous media under mild agitation, such as that provided by gastrointestinal motility[8], [19]. These systems are widely employed to enhance the solubility and oral bioavailability of poorly water-soluble drugs, particularly those belonging to BCS Class II and IV, where dissolution is the rate-limiting step in drug absorption[19], [20].

The composition of SMEDDS plays a crucial role in determining their performance. The oil phase acts as a solubilizing medium for lipophilic drugs and may also facilitate lymphatic transport, thereby bypassing hepatic first-pass metabolism[11]. Both medium-chain and long-chain triglycerides are commonly utilized, with medium-chain triglycerides offering faster emulsification and better solubilization, while long-chain triglycerides are more effective in promoting lymphatic uptake[21]. Surfactants are essential components that reduce interfacial tension between oil and aqueous phases, enabling spontaneous microemulsion formation [11]. Non-ionic surfactants with high hydrophilic–lipophilic balance are generally preferred due to their lower toxicity and improved compatibility [22]. Co-surfactants or co-solvents enhance the flexibility of the interfacial film and improve drug solubilization, facilitating efficient self-emulsification [11].

2.2 Mechanism of Self-Emulsification

The mechanism of self-emulsification is governed by a combination of thermodynamic and kinetic factors. Upon contact with gastrointestinal fluids, surfactant molecules rapidly orient at the oil–water interface, leading to a significant reduction in interfacial tension and spontaneous dispersion of the system into fine droplets[23]. The presence of co-surfactants further stabilizes the interfacial film, allowing the formation of a flexible and thermodynamically favorable microemulsion system[11], [24].

This process is largely entropy-driven and requires minimal external energy, resulting in the formation of droplets typically in the nanometer size range[23], [24]. The generation of such small droplets significantly increases the interfacial surface area, thereby enhancing drug dissolution and maintaining the drug in a solubilized state within the gastrointestinal tract[23].

2.3 Advantages of SMEDDS

SMEDDS offer several advantages in oral drug delivery systems. They significantly enhance the solubility and dissolution rate of poorly water-soluble drugs, resulting in improved and more consistent oral bioavailability[25]. The formation of nano-sized droplets provides a large surface area for drug absorption, while the lipidic nature of the system can facilitate lymphatic transport and reduce the impact of first-pass metabolism[11], [23]. Additionally, SMEDDS may inhibit efflux transporters and protect drugs from enzymatic degradation[11], [26]. Their relatively simple formulation approach compared to other nanocarrier systems further contributes to their practical applicability[11].

2.4 Limitations of Liquid SMEDDS

Despite their advantages, conventional liquid SMEDDS exhibit several limitations that restrict their widespread application[27], [28]. These include physical instability and the risk of phase separation during storage[13], [27]. Drug precipitation may occur upon dilution in gastrointestinal fluids, reducing bioavailability[13]. Leakage from soft or hard gelatin capsules is another common issue, along with difficulties in handling and storage[13], [28]. Furthermore, challenges in large-scale manufacturing and limited compatibility with solid dosage form development have driven the need for converting liquid SMEDDS into solid systems (S-SMEDDS) to improve stability, patient compliance, and industrial feasibility[12], [28].

3. Transition from SMEDDS to Solid SMEDDS (S-SMEDDS)

3.1 Rationale for Solidification

Although conventional SMEDDS have demonstrated significant potential in enhancing the solubility and oral bioavailability of poorly water-soluble drugs [27], their liquid nature presents several practical and technological limitations [12]. Issues such as leakage from capsules, incompatibility with capsule shells, poor physical stability, and difficulties in handling, storage, and transportation restrict their large-scale application and commercial viability[12], [28]. In addition, drug precipitation upon dilution in gastrointestinal fluids may compromise in vivo performance[13]. To address these challenges, the transformation of liquid SMEDDS into solid dosage forms has emerged as a promising strategy [12]. Solidification improves formulation stability and enables the development of conventional dosage forms such as tablets, capsules, and granules. It also enhances dose accuracy, ease of packaging, and shelf life, thereby improving patient acceptability and industrial feasibility [12].

3.2 Advantages of S-SMEDDS over Liquid SMEDDS

Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS) combine the advantages of lipid-based drug delivery with the technological benefits of solid dosage forms [29]. The solid form minimizes leakage issues and enhances both physical and chemical stability [15], [30]. In addition, S-SMEDDS exhibit superior handling properties, allowing easier processing, storage, and transportation [15], [30]. From a patient perspective, solid dosage forms are more convenient and acceptable, leading to improved compliance [15]. S-SMEDDS provide opportunities for modified or controlled drug release [15] and facilitate the incorporation of functional excipients such as polymers for precipitation inhibition [30]. These advantages make S-SMEDDS more suitable for large-scale manufacturing and commercialization [15]. A comparative overview of the key differences between liquid SMEDDS and S-SMEDDS is presented in Table 1.

Table 1. Comparison between Liquid SMEDDS and Solid SMEDDS (S-SMEDDS)

Parameter	Liquid SMEDDS	S-SMEDDS
Physical state	Liquid	Solid
Stability	Lower	Higher
Handling	Difficult	Easy
Patient compliance	Moderate	High
Leakage issues	Present	Absent
Manufacturing feasibility	Limited	Improved
Drug release	Rapid	Controlled/Modulated
Scalability	Challenging	More feasible

3.3 Approaches for Converting SMEDDS to S-SMEDDS

The conversion of liquid SMEDDS into solid systems can be achieved using several formulation approaches [15]. Among these, adsorption onto porous carriers is the most commonly employed method, where the liquid formulation is absorbed onto materials such as silica or magnesium aluminometasilicate to produce free-flowing powders [15], [35]. Spray drying is another widely used technique that produces solid particles with improved uniformity and stability by rapidly evaporating the solvent. Melt granulation involves incorporating SMEDDS into a molten carrier matrix followed by cooling to form granules [36]. Other techniques such as extrusion–spheronization and freeze drying have also been explored to obtain solid intermediates with desirable physicochemical properties [13], [29]. The selection of technique depends on the nature of the drug, excipients, and the desired final dosage form [37].

3.4 Industrial and Biopharmaceutical Significance

The development of S-SMEDDS represents a significant advancement in lipid-based drug delivery systems by addressing

the limitations of liquid formulations while preserving their advantages These systems retain the ability to form fine microemulsions upon dilution, thereby enhancing drug dissolution and absorption in the gastrointestinal tract. From an industrial perspective, S-SMEDDS offer improved robustness, scalability, and compatibility with conventional manufacturing processes. Their enhanced stability and ease of handling make them suitable for commercial production and long-term storage [15]. Overall, the transition from liquid SMEDDS to S-SMEDDS has expanded the applicability of self-emulsifying systems, making them a versatile and practical platform for improving the oral delivery of poorly soluble drugs [33].

5. Formulation Strategies of Solid Self-Microemulsifying Drug Delivery Systems

5.1 Selection of Excipients

The successful development of S-SMEDDS primarily depends on the appropriate selection of formulation components, as these directly influence drug solubilization, emulsification efficiency, and overall system stability [38]. The oil phase serves as a key component for dissolving lipophilic drugs and may also facilitate lymphatic transport, thereby enhancing oral bioavailability [10]. Medium-chain triglycerides are often preferred due to their superior solubilization capacity and rapid emulsification, whereas long-chain triglycerides are advantageous for promoting lymphatic uptake [11].

Surfactants play a crucial role in reducing interfacial tension and enabling spontaneous formation of microemulsions [39]. Non-ionic surfactants with high hydrophilic–lipophilic balance are generally selected because of their lower toxicity and better compatibility with biological membranes [40]. Co-surfactants or co-solvents are incorporated to enhance the flexibility of the interfacial film and improve the dispersion characteristics of the system [19]. These components also aid in maintaining drug solubility within the formulation and preventing precipitation upon dilution [41].

5.2 Selection of Solid Carriers

Solid carriers are essential for converting liquid SMEDDS into solid intermediates while preserving their self-emulsifying properties. The choice of carrier significantly affects the flow properties, compressibility, and reconstitution behavior of the final formulation. Porous carriers such as silica-based materials and magnesium aluminometasilicate are widely used due to their high surface area and adsorption capacity, allowing efficient incorporation of liquid formulations into free-flowing powders [42].

Polymeric carriers are also employed to improve the stability of the system and to inhibit drug precipitation upon dilution. These carriers can provide additional functional benefits, including sustained release and enhanced supersaturation maintenance. The compatibility between the liquid SMEDDS and the solid carrier must be carefully evaluated to ensure uniform distribution and optimal performance [13], [35], [43], [44].

5.3 Solidification Techniques

The conversion of liquid SMEDDS into solid dosage forms can be achieved using various solidification techniques, each offering specific advantages. Commonly employed methods include adsorption onto solid carriers, spray drying, melt granulation, and extrusion-based processes. These techniques differ in terms of process complexity, scalability, and impact on the physicochemical properties of the formulation [13], [45], [46]. A schematic overview of these solidification approaches is Show in Figure 1.

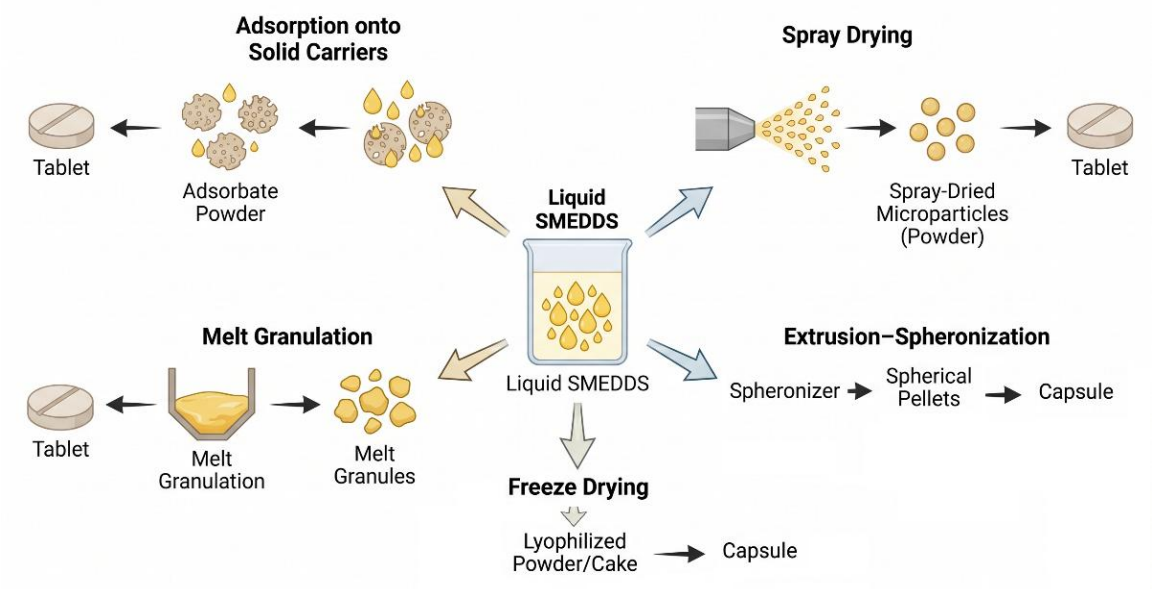

Figure 1. Solidification Techniques for Converting Liquid SMEDDS into S-SMEDDS

5.4 Critical Considerations in Formulation Development

The development of S-SMEDDS requires careful optimization of formulation variables to ensure efficient self-emulsification and drug release [22], [47]. Key factors include the ratio of oil to surfactant, the type and concentration of solid carrier, and the method of solidification [13], [32]. Improper selection or imbalance of these components may lead to poor emulsification, reduced drug loading, or instability [13], [35]. Additionally, maintaining the drug in a solubilized state after dispersion in gastrointestinal fluids is a critical challenge. The incorporation of precipitation inhibitors, particularly hydrophilic polymers, has been shown to improve the stability of supersaturated systems. The overall formulation strategy should aim to achieve a balance between stability, manufacturability, and enhanced bioavailability, ensuring consistent in vivo performance [48].

6. Mechanisms of Oral Bioavailability Enhancement

Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS) enhance oral bioavailability through a multifactorial interplay of physicochemical and physiological mechanisms. Upon exposure to gastrointestinal fluids, S-SMEDDS rapidly disperse to form fine oil-in-water microemulsions with nanoscale droplet sizes, which significantly improve drug solubilization and absorption [11], [49], [50]. The overall enhancement in bioavailability is not governed by a single pathway but rather by a combination of complementary mechanisms acting simultaneously, as illustrated in Figure 2.

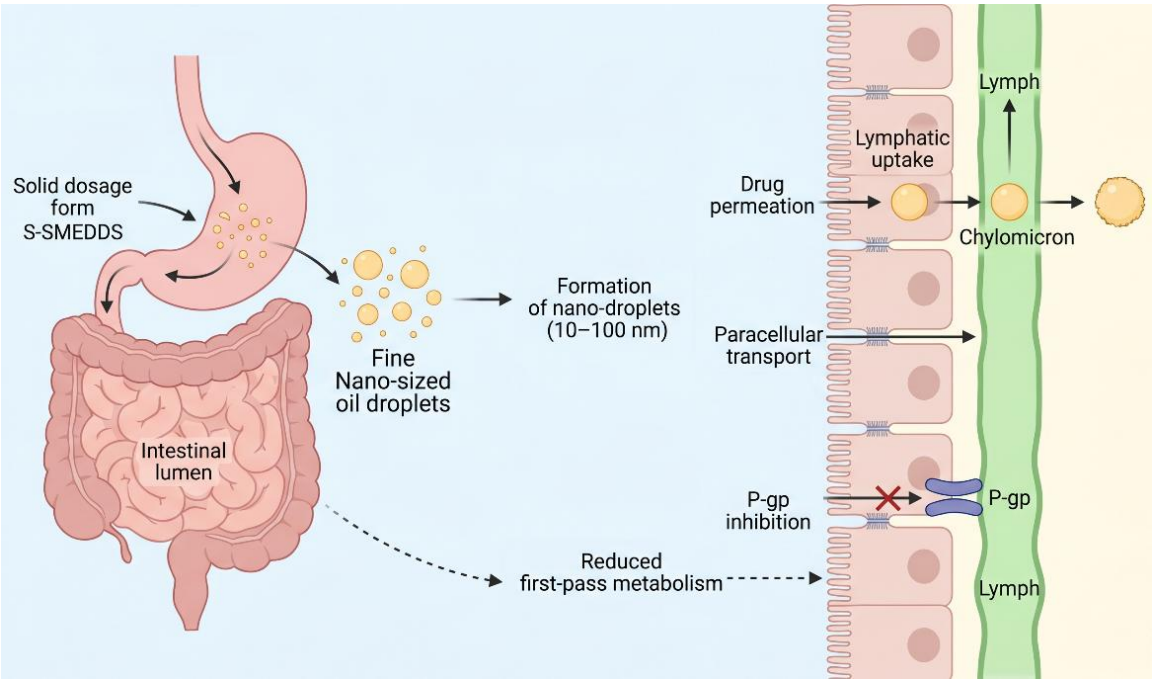

Figure 2. Mechanisms of Oral Bioavailability Enhancement by S-SMEDDS

6.1 Enhanced Drug Solubilization and Dissolution

One of the primary mechanisms responsible for improved bioavailability is the ability of S-SMEDDS to maintain the drug in a solubilized state. Lipid-based formulations dissolve lipophilic drugs within the oil phase, thereby bypassing the dissolution step, which is often the rate-limiting factor for poorly soluble drugs. Upon dispersion, the formation of microemulsions ensures that the drug remains in a dissolved form within the gastrointestinal environment, preventing precipitation and enabling continuous absorption [11], [51].

6.2 Increased Surface Area and Rapid Dispersion

The spontaneous formation of nano-sized droplets (typically <100 nm) significantly increases the interfacial surface area available for drug release and absorption. This enhanced surface area accelerates drug dissolution kinetics and facilitates intimate contact with the intestinal epithelium, leading to improved absorption profiles [52], [53].

6.3 Enhancement of Intestinal Permeability

Surfactants present in S-SMEDDS play a critical role in enhancing intestinal permeability. These surfactants can interact with biological membranes, increasing membrane fluidity and facilitating drug transport across epithelial cells. In some cases, surfactants may also transiently open tight junctions, enabling paracellular transport. Additionally, lipid digestion products may further promote drug absorption by altering membrane dynamics [54].

6.4 Lymphatic Transport and First-Pass Metabolism Avoidance

Lipid-based systems such as S-SMEDDS can enhance the lymphatic transport of highly lipophilic drugs. The digestion of

lipid components stimulates the formation of chylomicrons, which transport drugs via the intestinal lymphatic system rather than the portal circulation. This pathway bypasses hepatic first-pass metabolism, thereby significantly increasing systemic drug availability. The extent of lymphatic transport is influenced by factors such as lipid content and drug lipophilicity [55], [56].

6.5 Inhibition of Efflux Transporters and Metabolic Enzymes

Another important mechanism involves the inhibition of efflux transporters such as P-glycoprotein (P-gp), which typically limit drug absorption by pumping drugs back into the intestinal lumen. Surfactants and co-solvents used in S-SMEDDS formulations can inhibit P-gp activity, thereby enhancing intracellular drug accumulation and net absorption. Additionally, these systems may reduce presystemic metabolism by modulating enzymatic activity within the intestinal mucosa [48], [57].

6.6 Maintenance of Supersaturation and Precipitation Inhibition

Advanced S-SMEDDS formulations, particularly those incorporating hydrophilic polymers, can maintain the drug in a supersaturated state following dispersion. This prolonged supersaturation creates a higher concentration gradient across the intestinal membrane, which drives enhanced passive diffusion. The use of precipitation inhibitors prevents drug crystallization, ensuring sustained drug availability for absorption [58].

6.7 Synergistic Effect of Multiple Mechanisms

The overall enhancement of oral bioavailability by S-SMEDDS is the result of a synergistic interaction among these mechanisms. Improved solubilization, increased surface area, enhanced permeability, lymphatic transport, and inhibition of efflux collectively contribute to superior pharmacokinetic performance compared to conventional formulations. This multifaceted mechanism makes S-SMEDDS a highly effective and versatile platform for the oral delivery of poorly soluble drugs [11], [59].

7. Characterization of S-SMEDDS

The characterization of S-SMEDDS is a critical step in ensuring their performance, stability, and reproducibility. Since these systems combine the properties of both lipid-based formulations and solid dosage forms, their evaluation requires a comprehensive assessment of physicochemical, solid-state, and in vitro performance parameters. Proper characterization not only confirms successful solidification but also predicts in vivo behavior and bioavailability enhancement. characterization parameters and their significance are summarized in Table 2.

7.1 Preformulation Studies

Preformulation studies form the basis for the rational design of S-SMEDDS. These include solubility studies of the drug in various oils, surfactants, and co-surfactants to identify suitable excipients that provide maximum drug loading. Pseudo-ternary phase diagrams are often constructed to determine the optimal ratios of oil, surfactant, and co-surfactant required for efficient microemulsion formation. These diagrams help in identifying the self-emulsifying region and ensuring formulation robustness.

7.2 Evaluation of Self-Emulsification Performance

The self-emulsification efficiency of S-SMEDDS is evaluated by dispersing the formulation in aqueous media under gentle agitation. The time required for emulsification, clarity of the resulting dispersion, and visual appearance are assessed to determine the spontaneity and efficiency of the system. A rapid emulsification time and formation of a clear or slightly bluish dispersion indicate efficient microemulsion formation. Droplet size and polydispersity index (PDI) are key parameters that influence drug release and absorption. These are typically measured using dynamic light scattering techniques. Smaller droplet sizes with low PDI values indicate uniform distribution and better stability. Zeta potential is also determined to evaluate the surface charge and stability of the emulsion system [60].

7.3 Solid-State Characterization

Solid-state characterization is essential to confirm the physical state of the drug and its interaction with excipients after solidification. Techniques such as Differential Scanning Calorimetry (DSC) and X-ray Diffraction (XRD) are used to assess crystallinity. A reduction or absence of characteristic crystalline peaks suggests that the drug is present in an amorphous or molecularly dispersed state, which is favorable for improved dissolution. Scanning Electron Microscopy (SEM) is employed to study the surface morphology and structural characteristics of the solid particles. It provides insights into the adsorption of liquid SMEDDS onto solid carriers and the uniformity of the formulation [61].

7.4 In Vitro Dissolution and Drug Release Studies

In vitro dissolution studies are conducted to evaluate the release behavior of the drug from S-SMEDDS in simulated gastrointestinal fluids. These studies are crucial for predicting in vivo performance and assessing the effectiveness of the formulation in enhancing drug release. Compared to conventional dosage forms, S-SMEDDS typically exhibit faster and more complete drug release due to the formation of microemulsions upon dispersion. The use of biorelevant media can provide more accurate insights into the in vivo behavior of the formulation. Additionally, dissolution profiles can be used to establish correlations with pharmacokinetic performance [51], [62].

Table 2.Characterization Parameters for S-SMEDDS and Their Significance

Parameter	Method/Technique	Significance
Solubility studies	Shake flask method	Selection of suitable excipients
Phase diagram	Ternary phase diagram	Identification of microemulsion region
Self-emulsification time	Visual observation	Efficiency of emulsification
Droplet size	Dynamic light scattering	Influences absorption and stability
Polydispersity index (PDI)	DLS	Uniformity of droplet distribution
Zeta potential	Electrophoretic mobility	Stability of emulsion
DSC	Thermal analysis	Drug crystallinity
XRD	Diffraction analysis	Solid-state characterization
SEM	Microscopy	Surface morphology
Dissolution studies	USP apparatus	Drug release behavior

8. Recent Advances in Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS)

In recent years, significant progress has been made in the design and development of Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS) to overcome the limitations of conventional lipid-based formulations. Modern approaches focus on improving formulation stability, preventing drug precipitation, enhancing supersaturation, and enabling controlled drug release. These advances have expanded the applicability of S-SMEDDS across a wide range of poorly soluble drugs and therapeutic areas.

8.1 Polymer-Based S-SMEDDS and Precipitation Inhibition

One of the most notable advancements in S-SMEDDS is the incorporation of hydrophilic polymers to inhibit drug precipitation upon dilution in gastrointestinal fluids. Conventional SMEDDS often face the challenge of drug precipitation due to dilution-induced supersaturation. The integration of polymers such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and Soluplus® helps maintain the drug in a supersaturated state for an extended duration. These polymers act by forming intermolecular interactions with drug molecules, thereby inhibiting nucleation and crystal growth. This results in prolonged drug solubilization and improved absorption. Polymer-based S-SMEDDS, often referred to as supersaturable systems, have shown significant improvement in oral bioavailability compared to conventional formulations [63].

8.2 Supersaturable S-SMEDDS (S-SuSMEDDS)

Supersaturable S-SMEDDS represent a refined approach designed to achieve high drug loading while minimizing the concentration of surfactants. These systems generate a transient supersaturated state upon dispersion, which provides a strong driving force for drug absorption. The inclusion of precipitation inhibitors ensures that this supersaturated state is maintained long enough for effective drug uptake. S-SuSMEDDS not only reduce the potential toxicity associated with high surfactant levels but also improve formulation stability and patient safety. This approach has gained considerable attention for drugs with extremely low aqueous solubility [64], [65].

8.3 Lipid–Polymer Hybrid Systems

The development of lipid–polymer hybrid S-SMEDDS has further enhanced formulation versatility. These systems combine the solubilization capacity of lipids with the stability and functional properties of polymers. The hybrid approach enables better control over drug release profiles and enhances the stability of supersaturated systems. In such systems, polymers can form a matrix or coating around the lipid droplets, providing sustained release and preventing rapid drug precipitation. This strategy is particularly useful for achieving controlled or targeted drug delivery while maintaining improved bioavailability [66].

8.4 Advanced Solidification and Nanostructured Systems

Recent innovations in solidification techniques have led to the development of nanostructured S-SMEDDS with improved physicochemical properties. Techniques such as spray drying and melt extrusion have been optimized to produce uniform particles with enhanced flowability, compressibility, and stability. Nanostructured solid systems provide a higher surface area and improved dispersion characteristics, leading to faster emulsification and better drug release. Additionally, the use of functional excipients and engineered carriers has improved the efficiency of drug loading and retention [67].

8.5 Modified and Controlled Release S-SMEDDS

Another important advancement is the development of modified-release S-SMEDDS, which enable controlled or sustained drug delivery. By incorporating suitable polymers or matrix-forming agents, it is possible to modulate the release rate of the drug while retaining the solubilization advantages of SMEDDS. These systems are particularly beneficial for drugs requiring prolonged therapeutic action or reduced dosing frequency. Controlled-release S-SMEDDS also help maintain consistent plasma drug concentrations, thereby improving therapeutic outcomes and minimizing side effects [68].

8.6 Integration of Quality by Design (QbD) Approaches

The application of Quality by Design (QbD) principles has significantly improved the systematic development of S-SMEDDS. By identifying critical material attributes and process parameters, researchers can optimize formulations using statistical tools such as Design of Experiments (DoE). This approach ensures robust and reproducible formulations with predictable performance. QbD-based development also facilitates regulatory compliance and accelerates the translation of laboratory-scale formulations to industrial production. The integration of risk assessment tools and design space concepts further enhances formulation reliability [69].

8.7 Emerging Trends and Future Innovations

Emerging research in S-SMEDDS is exploring the use of advanced technologies such as artificial intelligence and machine learning for formulation optimization. These tools can predict the behavior of complex systems and reduce experimental workload. Additionally, the development of novel excipients, biodegradable carriers, and green formulation strategies is gaining attention. Targeted delivery approaches, including ligand-mediated systems and stimuli-responsive S-SMEDDS, are being investigated to improve site-specific drug delivery. These innovations are expected to further expand the potential of S-SMEDDS in modern pharmaceutical development [15], [33], [70].

9. Quality by Design (QbD) Approach in S-SMEDDS Development

9.1 Quality Target Product Profile (QTPP)

The QbD framework begins with the definition of the Quality Target Product Profile (QTPP), which outlines the desired characteristics of the final product. For S-SMEDDS, the QTPP typically includes attributes such as dosage form (e.g., tablet, capsule), route of administration (oral), drug release profile, bioavailability enhancement, stability, and patient compliance. These target characteristics serve as a foundation for guiding formulation development and ensuring that the final product meets therapeutic and regulatory requirements [71].

9.2 Critical Quality Attributes (CQAs)

Critical Quality Attributes (CQAs) are the physical, chemical, biological, or microbiological properties that must be controlled to ensure product quality. In S-SMEDDS, key CQAs include droplet size, polydispersity index, self-emulsification time, drug content, dissolution profile, and physical stability. These attributes directly influence the performance of the formulation, particularly its ability to enhance drug solubilization and absorption [72].

9.3 Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs)

Critical Material Attributes (CMAs) refer to the properties of raw materials that can impact CQAs. In S-SMEDDS, CMAs include the type and concentration of oils, surfactants, co-surfactants, and solid carriers. The physicochemical properties of these components, such as hydrophilic–lipophilic balance, viscosity, and adsorption capacity, play a significant role in determining formulation behavior. Critical Process Parameters (CPPs) are the variables associated with the manufacturing process that can affect product quality. These include mixing time, temperature, rate of addition, drying conditions (in spray drying), and granulation parameters. Proper control of CPPs is essential to ensure consistency and reproducibility during scale-up and production [73].

9.4 Risk Assessment and Experimental Design

Risk assessment is a key component of QbD that involves identifying and evaluating potential factors that may affect product quality. Tools such as Failure Mode and Effects Analysis (FMEA) and Ishikawa (fishbone) diagrams are commonly used to systematically assess risks associated with formulation variables and process parameters. Following risk identification, Design of Experiments (DoE) is employed to study the relationship between independent variables (e.g., excipient ratios, processing conditions) and dependent responses (CQAs). Experimental designs such as factorial design, Box–Behnken design, and central composite design are widely used for optimization. These statistical approaches enable efficient exploration of formulation space with minimal experimental runs [74], [75].

9.5 Design Space and Optimization

The design space is defined as the multidimensional combination of CMAs and CPPs that result in a product meeting the desired CQAs. Establishing a design space allows flexibility in manufacturing within defined limits without compromising product quality. Optimization of S-SMEDDS formulations is achieved by identifying the optimal levels of formulation variables that provide the best performance in terms of droplet size, dissolution, and stability. Graphical tools such as response surface plots and contour plots are often used to visualize the effects of variables and identify optimal conditions. The use of desirability functions further aids in selecting the most suitable formulation [76].

9.6 Regulatory and Industrial Significance

The application of QbD principles aligns with regulatory expectations outlined by international guidelines such as ICH Q8, Q9, and Q10. Regulatory agencies encourage the adoption of QbD to ensure consistent product quality and facilitate efficient review processes. For S-SMEDDS, QbD-based development enhances formulation robustness, reduces batch-to-batch variability, and simplifies scale-up from laboratory to industrial production. Moreover, the systematic understanding gained through QbD supports lifecycle management and continuous improvement of pharmaceutical products. It also reduces the likelihood of product failure and minimizes the need for post-approval changes [77].

10. Applications of S-SMEDDS

10.1 Anticancer Drug Delivery

S-SMEDDS have shown considerable promise in the delivery of anticancer agents, many of which exhibit poor aqueous solubility and low oral bioavailability. Drugs such as paclitaxel, curcumin, and docetaxel have been successfully formulated using S-SMEDDS to enhance their solubilization and systemic exposure. The ability of these systems to promote lymphatic transport is especially advantageous in cancer therapy, as it facilitates targeted delivery and reduces first-pass metabolism. Additionally, improved absorption leads to enhanced therapeutic efficacy and reduced dose-related toxicity [59].

10.2 Antidiabetic Therapy

Several antidiabetic drugs, particularly those with low solubility, benefit from formulation as S-SMEDDS. Improved dissolution and absorption result in better glycemic control and reduced variability in drug response. Lipid-based systems may also enhance intestinal permeability and prolong drug action, contributing to improved pharmacokinetic profiles. S-SMEDDS-based formulations can thus provide more consistent therapeutic outcomes in the management of diabetes mellitus [78].

10.3 Central Nervous System (CNS) Drugs

The delivery of drugs targeting the central nervous system is often limited by poor solubility and restricted permeability across biological membranes. S-SMEDDS can improve the bioavailability of CNS-active drugs by enhancing solubilization and facilitating absorption. In some cases, lipid-based systems may also influence drug distribution and improve penetration across the blood–brain barrier. This makes S-SMEDDS a promising platform for the delivery of drugs used in the treatment of neurological disorders [79].

10.4 Cardiovascular and Anti-inflammatory Drugs

S-SMEDDS have been effectively used to improve the bioavailability of drugs used in cardiovascular and inflammatory conditions, such as statins and nonsteroidal anti-inflammatory drugs (NSAIDs). Enhanced dissolution and absorption lead to improved therapeutic efficacy and reduced interpatient variability. The ability to maintain consistent plasma drug levels further contributes to better disease management [80].

10.5 Herbal and Phytoconstituents

Many herbal compounds, including polyphenols and flavonoids, suffer from poor solubility and low oral bioavailability. S-SMEDDS provide an effective strategy to enhance the delivery of such phytoconstituents by improving their solubilization and stability. This has led to increased interest in the use of S-SMEDDS for nutraceutical and herbal formulations, where improved bioavailability is critical for achieving therapeutic benefits [68].

11. Challenges and Future Perspectives of S-SMEDDS

11.1 Challenges

One of the primary challenges associated with S-SMEDDS is drug precipitation upon dilution in gastrointestinal fluids. Although the system initially maintains the drug in a solubilized state, dilution and digestion processes may lead to supersaturation followed by precipitation, ultimately reducing bioavailability. This issue is particularly critical for drugs with extremely low aqueous solubility. Another significant concern is physical and chemical stability. While solidification improves stability compared to liquid SMEDDS, factors such as moisture uptake, polymorphic transitions, and drug–excipient interactions may still affect long-term stability. Ensuring consistent performance over the product shelf life remains a key challenge. Limited drug loading capacity is also a constraint, especially for highly lipophilic drugs requiring large amounts of lipid excipients. High surfactant concentrations, often necessary for efficient emulsification, may lead to gastrointestinal irritation and toxicity concerns, thereby limiting formulation flexibility. From a manufacturing perspective, scale-up and process reproducibility pose additional challenges. Techniques such as spray drying and melt granulation require precise control of process parameters to maintain uniformity and product quality. Variability during large-scale production can impact critical quality attributes, including droplet size and dissolution behavior. Furthermore, regulatory complexities associated with lipid-based formulations and novel excipients may hinder product approval. The lack of standardized guidelines for evaluating S-SMEDDS performance, particularly in relation to in vitro–in vivo correlation, adds to the difficulty in regulatory acceptance [81], [82].

11.2 Future Perspectives

Future research in S-SMEDDS is focused on overcoming existing limitations and expanding their applicability through innovative approaches. The incorporation of advanced precipitation inhibitors and functional polymers is expected to further

improve the stability of supersaturated systems and minimize drug precipitation. The integration of artificial intelligence (AI) and machine learning (ML) in formulation design represents a promising direction. These technologies can facilitate predictive modeling of formulation behavior, optimize excipient selection, and reduce experimental workload, thereby accelerating the development process. Emerging strategies involving novel lipid excipients and biodegradable carriers are gaining attention for improving safety and biocompatibility. Additionally, the development of green and sustainable formulation approaches aligns with current trends in environmentally conscious pharmaceutical manufacturing. Another important area of advancement is the design of targeted and stimuli-responsive S-SMEDDS, which can enable site-specific drug delivery and controlled release. Such systems may enhance therapeutic efficacy while minimizing systemic side effects. The application of personalized medicine approaches is also anticipated to influence the future development of S-SMEDDS. Tailoring formulations based on patient-specific factors, such as physiology and disease state, could lead to more effective and individualized therapies [33], [83].

12. Conclusion

Solid Self-Microemulsifying Drug Delivery Systems (S-SMEDDS) have emerged as a highly promising and versatile platform for enhancing the oral bioavailability of poorly water-soluble drugs. By integrating the solubilization advantages of lipid-based systems with the stability and convenience of solid dosage forms, S-SMEDDS effectively address the key limitations associated with conventional liquid SMEDDS. Their ability to spontaneously form fine microemulsions in the gastrointestinal environment enables improved drug dissolution, enhanced permeability, and increased systemic availability. The advancement of formulation strategies, particularly the incorporation of solid carriers, precipitation inhibitors, and polymer-based approaches, has significantly improved the performance and applicability of S-SMEDDS. In addition, the adoption of Quality by Design (QbD) principles has facilitated the development of robust and reproducible formulations, ensuring better control over critical quality attributes and enabling efficient scale-up for industrial production. Recent innovations, including supersaturable systems, lipid–polymer hybrids, and modified-release formulations, further highlight the evolving nature of this technology. Despite these advancements, challenges such as drug precipitation, limited drug loading, stability concerns, and regulatory complexities remain important considerations. Addressing these issues through innovative formulation approaches, advanced excipient selection, and emerging technologies such as artificial intelligence and machine learning will be crucial for the successful translation of S-SMEDDS from research to commercialization..

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