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SOLID SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEMS IN MODERN PHARMACEUTICS: DESIGN, CHARACTERIZATION, AND CLINICAL APPLICATIONS

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ABSTRACT
Background: Approximately 40% of marketed medicines and 70% of pipeline products exhibit poor aqueous solubility, leading to inconsistent oral bioavailability and impaired efficacy. S-SMEDDS represent a revolutionary approach for converting liquids into stable solid dosage forms. **Methodology:** Methods employed to prepare S-SMEDDs include adsorption onto carriers, spray drying, hot-melt extrusion, and freeze-drying. Characterization includes assessing self-emulsifying behavior, dynamic light scattering, powder diffraction, and thermal analysis. **Results and Discussion:** Depending on the drug's characteristics, the formulation composition, and the study conditions, S-SMEDDS can increase bioavailability by two to ten times. However, for some extremely lipophilic BCS Class II and IV pharmaceuticals, significantly greater benefits (up to ~50-fold) have been documented. Several investigations have demonstrated that S-SMEDDS exhibit better physical and chemical stability than liquid systems under ICH Q1A(R2) accelerated storage conditions due to reduced lipid mobility and a lower risk of phase separation. Applications extend to the treatment of cardiovascular, oncological, and endocrine disorders with improved pharmacodynamic efficacy. The multiple absorption mechanisms in S-SMEDDS include improved solubilization, reduced precipitation, lymphotropic delivery, and inhibition of efflux pumps. They demonstrate higher chemical and physical stability, precise dosing, and better patient adherence when compared to traditional liquid counterparts. **Conclusion:** S-SMEDDS constitute an established pharmaceutical platform that overcomes the drawbacks associated with liquid lipid drug delivery systems. Their high effectiveness, manufacturability, and compatibility with novel technologies such as three-dimensional printing and artificial intelligence position them to be the foundation for precision oral drug delivery.

INTRODUCTION

Oral administration is the most convenient and non-invasive route for drug delivery and offers many advantages in terms of compliance and treatment efficacy. However, good bioavailability in oral delivery requires high drug solubility and

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dissolution in the gastrointestinal environment [1]. The epidemiological data in the pharmaceutical industry continues to show that nearly 40% of approved drugs and as much as 70% of drugs in the drug development pipeline belong to the Biopharmaceutics Classification System (BCS) Class II (low solubility, high permeability) or Class IV (low solubility, low permeability) categories. In these instances, drug solubility and membrane-crossing ability are greatly reduced, thereby limiting oral absorption [2]. All of these have important clinical implications, including poor bioavailability, high intra- and inter-individual variability, lack of dose proportionality, and diminished therapeutic efficacy [3].

Drug Delivery Systems (DDS) that involve lipids are well-known and proven methods for addressing these bioavailability issues [4]. These systems use the body's lipid digestion pathway, mimicking the fed state in the intestine by creating a lipid-rich microenvironment that promotes greater solubilization. The Lipid Formulation Classification System (LFCS) is hierarchical, with self-microemulsifying drug delivery systems (SMEDDS) at the top. Thermodynamically stable, isotropic solutions of a lipophilic drug, oils, hydrophilic surfactants (HLB > 12), and cosolvents that spontaneously form fine (100-250nm) oil-in-water microemulsions on gentle agitation in an aqueous medium are called SMEDDS [3]. The resulting large interfacial surface area yields a very bioavailable pre-dissolved dosage form that bypasses the rate-limiting dissolution step [5].

The efficacy of several commercially available SMEDDS formulations for clinical use has been established, including Neoral (cyclosporine A, Novartis), Norvir (ritonavir, AbbVie), and Sandimmune (cyclosporine, Novartis). Neoral is a typical example of a clinically useful SMEDDS formulation, resulting in lower intra-individual variability and a more linear dose-response curve than the first formulation, Sandimmune [6].

Although liquid SMEDDS formulations offer therapeutic benefits, they face significant practical challenges. Precipitation of drugs during the process of dilution in the aqueous gastrointestinal environment, especially of high-dose drugs [7]. Lipid-based excipients are susceptible to oxidative and hydrolytic degradation. The liquid component causes compatibility problems with capsule shells and limits formulation options to hard or soft gelatin capsules, as well as the development of controlled-release formulations. Also, the use of high concentrations of surfactants is essential for microemulsification, but it has been reported to cause gastrointestinal irritation and toxicity [8].

Self-microemulsifying drug delivery systems (S-SMEDDS) are solid formulations that overcome these drawbacks by encapsulating liquid lipid systems within solid matrices via carrier adsorption, spray drying, hot-melt extrusion, or lyophilization [9]. The powders, granules, or tablets produced from these parent liquid formulations retain the liquid formulation's self-emulsification properties and offer improved chemical and physical stability, dosing accuracy, higher patient acceptability, and greater flexibility in dosage form design. Later, new developments such as supersaturable S-SMEDDS, Gastroretentive formulations, and lipid-polymer hybrid systems have been further developed and can now also be used for controlled drug delivery, lymphatic targeting, inhibition of efflux pumps, or even macromolecule delivery [10].

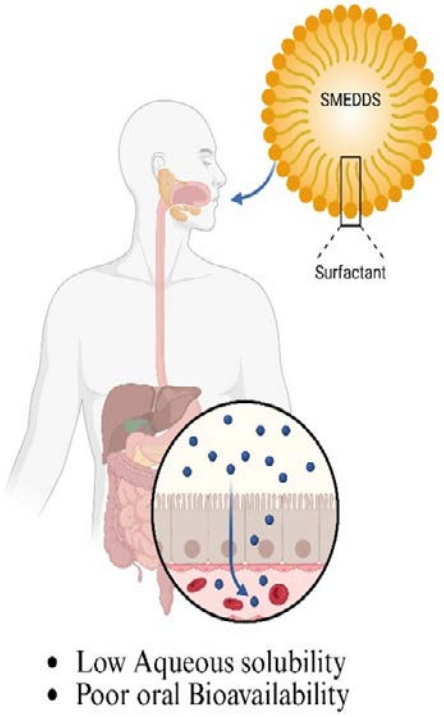

Figure 1: Role of SMEDDS in improving oral delivery. Created by authors

This extensive review includes a critical and systematic analysis of S-SMEDDS composition and formulation principles, gastrointestinal absorption mechanisms, solidification methods, physicochemical and biopharmaceutical characterization methods, preclinical & clinical pharmacokinetics & pharmacodynamics, the dynamic intellectual property landscape, and future applications in precision medicine (See Figure 1).

DESIGNING S-SMEDDS: COMPOSITION AND FORMULATION DESIGN

Systematic evaluation and selection of formulation components, including active pharmaceutical ingredients (APIs) and excipients, should be based on well-defined physicochemical principles, and such rational design of S-SMEDDS formulations is essential [11].

The selection of active pharmaceutical ingredients

Some drugs cannot be formulated into SMEDDS products. The API must have a high lipophilicity (logP>2) and be soluble in the combined oil/surfactant/limiting cosolvent system to allow for therapeutic plasma levels to be reached with a minimum dosage form volume and negligible first-pass effects. The main target population comprises BCS Class II drugs, in which permeability and absorption are the primary factors limiting bioavailability, with solubility as the remaining factor [12]. SMEDDS can also be beneficial for some BCS Class IV drugs, for which permeability can be modified by P-glycoprotein inhibition. Drugs that have been successfully formulated include atorvastatin, Cyclosporine, Itraconazole, Ketoconazole, Fenofibrate, Telmisartan, Carvedilol, Paclitaxel, Efavirenz, and Dutasteride.

Oils: Selection and Functional Role

The oil phase is important not only for its solubilizing properties as the main solubilizing agent but also as a factor controlling drug absorption kinetics. The former, long-chain triglycerides (LCTs), such as olive oil or soybean oil, are more effective than medium-chain triglycerides (MCTs), such as Miglyol 812 or Captex 355, in maintaining drug solubilization during passage through the gastrointestinal tract and facilitating their transport into the lymph [13]. However, MCTs have better self-emulsification and dispersion properties. In current S-SMEDDS formulations, semi-synthetic modified oils such as Capmul MCM, Capmul PG-8, Labrafil M 1944CS, and Capryol 90 are preferred for their high drug-loading capacity and superior emulsification properties. The oil phase also induces endogenous biliary and pancreatic secretions, which increase solubilization of the oil phase in the gastrointestinal lumen as mixed micelles [14].

Surfactants: Selection and Mechanistic Functions

Surfactants are key ingredients in SMEDDS formulations. They reduce the oil-water interfacial tension to nearly zero, promote spontaneous emulsification, and form protective interfacial films around nascent droplets. For SMEDDS design, non-ionic surfactants with HLB values greater than 12 are preferable due to their improved emulsifying properties, lower mucosal toxicity compared with ionic surfactants, and stability at physiological pH. Castor oil polyoxyl 35 (Castor oil with HLB 12-14, Cremophor EL) and Hydrogenated Castor oil polyoxyl 40 (Castor oil with HLB 14-16, Cremophor RH40) are commonly used non-ionic surfactants that add additional benefits by inhibiting P-glycoproteins.

Nonionic surfactants, including Cremophor EL, Tween 80, and Labrasol, can improve oral drug absorption by inhibiting intestinal efflux transporters such as P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Nonetheless, there is ongoing discussion on this mechanism's clinical significance. SMEDDS are significantly diluted in gastrointestinal fluids after oral delivery, potentially reducing surfactant concentrations below those required for sustained transporter blockade.

However, localized surfactant concentrations at the oil-water interface may be high enough to alter membrane fluidity, inhibit ATP-dependent efflux, and enhance drug permeability during the early dispersion phase. Therefore, rather than transporter inhibition alone, the absorption-enhancing impact of surfactant-containing SMEDDS is probably due to a combination of increased solubilization, greater lymphatic transport, and temporary efflux transporter regulation. Alternatives to surfactants include Polysorbate 80 (Tween 80, HLB 15), Labrasol (Caprylic/Capric polyoxyl 8 glycerides), and Gelucire 44/14. Surfactant concentration must be carefully controlled; too low, and the surfactant will not emulsify sufficiently; too high, and the surfactant may be irritating to the gastrointestinal mucosa and disrupt intestinal drug permeability [15].

Cosolvents and Co-surfactants

The cosolvents can play multiple roles in S-SMEDDS formulations: improving the solubility of hydrophobic drugs in the lipid medium and reducing interfacial rigidity to facilitate microemulsion formation. Transcutol HP (diethylene glycol monoethyl ether) is known as an ideal cosolvent for hydrophobic substances. Other cosolvents used are propylene glycol, polyethylene glycol 400, and ethanol [16]. The ability to maintain drug solubility at 100–1000-fold is one of the most critical properties of cosolvents, as suboptimal solubilization in this range leads to drug precipitation in the gastrointestinal tract (GIS) (see Figure 2).

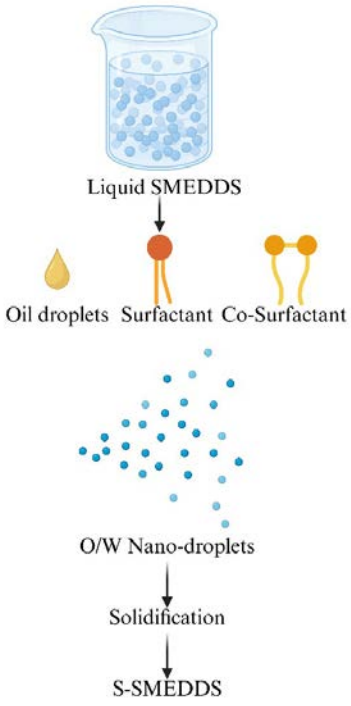

Figure 2: Schematic diagram of the formation of Solid SMEDDS from liquid SMEDDS. Created by the authors

Solid Carriers: Selection and Performance Characteristics

The use of solid carriers sets S-SMEDDS apart from liquid SMEDDS and is a crucial determinant of formulation performance [17]. Optimum carriers should have a high lipid-entrapment capacity (high capacity to contain therapeutic quantities of liquid SMEDDS), high redispersibility (good ability to disperse immediately upon contact with aqueous gastrointestinal fluids), good flowability, and sufficient mechanical strength for tableting. Carriers can be hydrophobic (Aerosil 200, Syloid XDP, Neusilin US2, Sylysia 350) or hydrophilic (mannitol, lactose, Fujicalin) [9]. The solidification capacity and drug entrapment efficiency are greater with hydrophobic silicates. Still, the size of the reconstituted droplets is larger, and the rate of drug release is slower than with hydrophilic carriers. Through capillary forces and hydrogen-bond interactions, adsorbent carriers like Aerosil® 200 physically trap lipid droplets due to their high specific surface area (>200 m^2/g) and abundance of surface silanol groups. During storage, these interactions considerably lessen lipid migration and exudation. Mannitol, on the other hand, primarily serves as a crystalline hydrophilic matrix, offering limited adsorption capacity. As a result, mannitol-based formulations primarily rely on physical entrapment rather than strong surface adsorption, which may increase the risk of lipid leakage at high liquid loading. It is important to note that in comparative pharmacokinetic studies, Atorvastatin S-SMEDDS made with a water-soluble carrier (mannitol) exhibited a relative bioavailability of 160-216%, which is better than the water-insoluble carrier (Sylysia 12). Polymeric carriers such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and Eudragit EPO act as precipitation inhibitors, preventing drug precipitation in the gastrointestinal tract and thereby improving oral bioavailability [18]. The presentation of reconstituted droplets after dispersion can be influenced by the carrier's hydrophobicity, in addition to surface area and adsorption capacity. More hydrophobic porous carriers (such as surface-modified silica materials) may improve retention of lipid components within the pore network and alter droplet liberation kinetics. In contrast, hydrophilic carriers (like mannitol) typically promote rapid wetting and release of the encapsulated lipid formulation. Effective presentation of finely dispersed droplets at the aqueous interface in the gastrointestinal tract may help maintain supersaturation and subsequent absorption by facilitating diffusion across the unstirred water layer of the intestine, a known barrier for highly lipophilic compounds [18].

MECHANISMS OF S-SMEDDS ABSORPTION IN THE GASTROINTESTINAL TRACT

To optimize S-SMEDDS formulation, it is important to understand the in vivo absorption mechanisms. The S-SMEDDS tablet or capsule is easily broken down in the stomach, and the liquid preconcentrate is rapidly released. This preconcentrate self-emulsifies in gastrointestinal fluids with gentle peristaltic agitation, yielding extremely small oil-in-water droplets, usually less than 200 nm in diameter. This dramatic reduction in droplet size results in a 1000-fold increase in the contact area between the drug and gastrointestinal fluids, thereby achieving very high bioavailability [19]. In the small intestine, pancreatic and gastric lipases will slowly break down the triglyceride oil phase to produce fatty acids and monoglycerides. These products of lipid digestion, along with endogenous bile salts, phospholipids, and cholesterol, form mixed micelles and colloidal structures (vesicles, liquid-crystalline phases) that can solubilize the drug and ferry it across the unstirred water layer adjacent to the intestinal epithelium. Subsequently, the drug diffuses to the brush border membrane, dissociates from the micellar vehicle, and enters the enterocyte [20]. For moderately lipophilic drugs (logP 2-5), absorption occurs primarily via transcellular passive diffusion. Molecules with a logP > 5 are absorbed via a separate mechanism; the absorbed fatty acids and drug molecules are

esterified in enterocytes to triglycerides, which are then packaged with apolipoproteins and transported through the intestinal lymphatics. This lymphatic pathway bypasses hepatic portal circulation and prevents first-pass hepatic metabolism, allowing for much greater systemic bioavailability. The presence of significant first-pass metabolic restrictions, such as Cyclosporine, Testosterone Undecanoate, Halofantrine, and Paclitaxel, is an important reason this pathway is particularly relevant for certain drugs [21]. Surfactants in SMEDDS, especially Cremophor EL and Polysorbate 80, inhibit P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) efflux transporters at the intestinal epithelium and also affect the activity of cytochrome P450 3A4, thus expanding net intestinal absorption. This increased bioavailability can be synergistic, beyond that attributable to improved solubilization & occurs in a transporter-mediated manner, with the aid of an excipient [22]. These factors—reduction in precipitation, increased solubilization, lymphatic delivery & inhibition of efflux transporters—can all explain the often remarkable improvements in bioavailability observed with S-SMEDDS [23].

SOLIDIFICATION TECHNIQUES

The main technical challenge in developing S-SMEDDS is the transition from a liquid to a solid formulation. There are four different approaches, each with unique processing parameters, benefits, and drawbacks. The choice of the optimal technique will be influenced by API thermal stability, the required drug-loading capacity, manufacturing scale-up, and regulatory requirements [24] (See Table 1).

The Solidification Techniques

The simplest and the least expensive solidification method is adsorption. A preconcentrate in liquid form (SMEDDS) is then added to a solid material containing an adsorbent (Aerosil 200, Neusilin US2, or Sylsyia) and continuously mixed in a planetary mixer or high shear granulator until a free-flowing product is obtained. The powder obtained may then be encapsulated in hard gelatin capsules or compressed into tablets. No organic solvents are needed for adsorption, and it is not affected by thermolabile drugs. However, there are several drawbacks, such as potential exudation of liquid ingredients during compression (sticking, capping, and changes in hardness), limited drug-loading capacity due to adsorbent saturation, and the bulk effect when a large quantity of adsorbent is needed. The study demonstrated that the adsorption method can be applied to poorly water-soluble cardiovascular drugs, as drug release from azelnidipine adsorbed on Fujicalin was extremely fast compared to the free drug & commercial tablets [25].

Spray Drying

Spray drying is a process used to convert a liquid SMEDDS into powder by atomizing a solution or suspension of the drug, excipients, and a solid carrier into the drying chamber using heated nozzles. This is because the particles can be made fine, spherical, narrow in size distribution, and have excellent flow properties when the solvent evaporates quickly. Modern spray dryers allow fine-tuned control of inlet and outlet temperatures, feed rates, atomization pressures, and particle droplet size, enabling customization of particle morphology and dissolution characteristics. This has been extended to thermolabile substances and certain biological macromolecules by operating at reduced temperatures and under vacuum. In healthy rabbits, a single formulation of spray-dried Nimodipine S-SMEDDS (comprising ethyl oleate, Labrasol, Cremophor RH40 and dextran carrier) resulted in an area under the concentration-time curve (AUC) 2.6 times greater & a maximum plasma conc. (Cmax) 6.6 times higher than conventional tablets, with equivalent pharmacokinetic profiles (See figure 3.) [26].

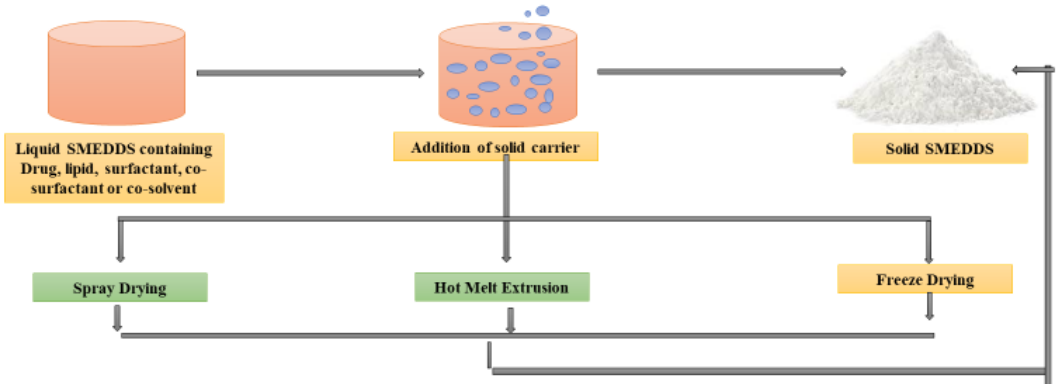

Figure 3: Solidification Technique. Created by authors

Hot Melt Extrusion (HME)

In hot-melt extrusion, a thermoplastic polymer carrier (HPMC, HPMC-AS, HPC, or PVP-VA) is melted with the drug and lipid excipients, then fed into a twin-screw extruder at elevated temperatures and pressures, and extruded into granules/pellets. The benefits of the HME process are that it is completely solvent-free, can achieve high drug loading capacity, has excellent content uniformity, and can be produced at high speed. HME products are especially beneficial for moisture-sensitive drugs, as the liquid phase is not granulated.

A representative study involved preparing Carvedilol S-SMEDDS using HME, along with HPMC-AS and HPC as carriers, to achieve pH-dependent drug release (high at pH 6.8 and low at acidic pH), thereby facilitating targeting to the intestine. Thermal stress is the major drawback of HME: drugs that have a melting point or degradation temperature below the processing temperature (80-180 degrees Celsius) are not candidates for HME [27], [28].

Freeze Drying (Lyophilization)

Lyophilization involves a series of freeze-thaw-sublimation cycles of liquid SMEDDS, often in the presence of a cryoprotectant (mannitol, trehalose, or lactose). Products produced using the resulting technology have a high residual moisture content (95-99.5 percent), which is well-suited for thermolabile drugs, proteins, and peptides. The presence of cryoprotectants helps inhibit the formation of ice crystals, which may damage the emulsification structure and promote efficient reconstitution. The dissolution and bioavailability of freeze-dried Fenofibrate S-SMEDDS 1% trehalose were found to be better than those of the marketed tablet. However, operating and equipment expenses are quite high in industrial applications [29], [30].

Table 1: Comparative Overview of S-SMEDDS Solidification Techniques

Technique	Solvent Use	Thermolabile API	Drug Loading	Scale-up Ease	Relative Cost	Key Example	Ref.
Adsorption	None	Suitable	Moderate (limited by adsorbent capacity)	High	Low	Azelnidipine / Fujicalin® — faster release vs. marketed tablet	[31]
Spray Drying	Organic/ aqueous	Limited (low-temp systems extend applicability)	Good	Moderate	Moderate	Nimodipine — AUC 2.6×, Cmax 6.6× vs. conventional tablet	[32]
Hot Melt Extrusion	None	Not suitable	High	High (continuous)	Moderate	Carvedilol / HPMC-AS — controlled release at pH 6.8	[33]
Freeze Drying	Aqueous	Excellent	Good	Low	High	Fenofibrate / 1% trehalose — improved bioavailability vs. conventional tablet	[34]

PHYSICOCHEMICAL AND BIOPHARMACEUTICAL CHARACTERIZATION OF S-SMEDDS

The self-emulsification properties, properties of the reconstituted emulsion, solid-state properties, powder handling properties, in vitro drug release properties, and in vitro prediction of in vivo digestion properties are included in the comprehensive characterization of S-SMEDDS. These parameters provide important mechanistic information and enable quality-by-design (QbD) approaches for regulatory submission [35].

Sr. No.	API/Formulation Property	Recommended Technique
1	Heat-sensitive API (degradation below 60°C)	Adsorption, Freeze Drying
2	Thermally stable API (melting point >150°C)	Spray Drying, Melt Granulation
3	High liquid SMEDDS loading (>50% w/w)	Adsorption on porous carriers
4	Need for direct capsule filling	Adsorption
5	Need for tablet compression	Melt Granulation, Extrusion
6	Large-scale manufacturing	Spray Drying
7	Moisture-sensitive API	Adsorption, Melt Granulation

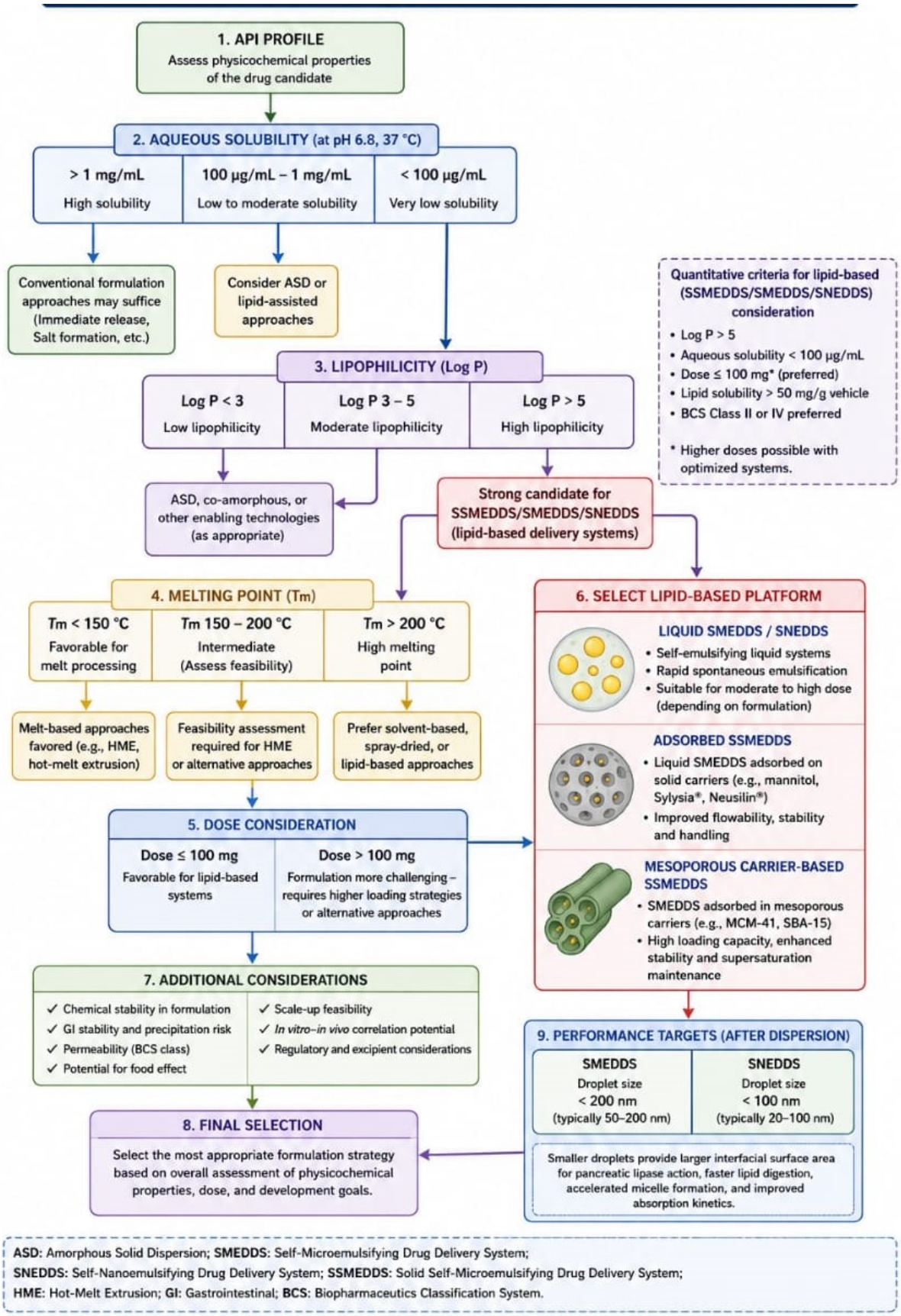

Figure 4: Quantitative framework for selecting sSMEDDS/SMEDDS/SNEDDS and other enabling strategies for poorly soluble drugs

Self-Emulsification Performance Assessment

The self-microemulsification efficiency is determined by a standardized dispersion test in which a known amount of S-SMEDDS preparation is added to 500 mL of aqueous solution and stirred at 50 rpm at 37°C. There is a five-point grading scale for emulsification speed and quality: Grade A is a clear or opalescent microemulsion formed in 60 seconds, with a gradual decrease in quality up to Grade E (oily droplets floating on the surface). Grade A or B formulations are required for good solubilizing of the drug in the gastrointestinal tract [36].

Droplet Size, Polydispersity Index, and Zeta Potential

Dynamic light scattering (DLS) was used to assess the mean droplet size of the reconstituted microemulsion, which is the most direct measure of microemulsion quality; smaller droplet sizes lead to greater interfacial area, faster drug release, and greater lipolysis [19]. S-SMEDDS formulations generally aim for less than 200nm droplets and S-SNEDDS formulations for less than 100nm droplets. Homogeneous dispersions have polydispersity indices (PDI) < 0.3. The charge of droplets and the stability of the colloidal solution can be determined by measuring the zeta potential; absolute values > 30 mV indicate good electrostatic repulsion between droplets. The zeta potential of most SMEDDS systems with non-ionic surfactants is near-neutral, and steric stabilization occurs [37].

Solid-State Characterization

The simultaneous increase in solubility & potential physical instability, due to the conversion of a crystalline form to an amorphous form, occurs during solidification. Powder X-ray Diffraction (PXRD) can clearly distinguish between crystalline and amorphous states of the drug compound, which is characterized by sharp diffraction peaks and the appearance of a broad diffraction halo. S-SMEDDS diffractograms that lack characteristic peaks of the parent drug confirm loss of crystallinity. Differential Scanning Calorimetry (DSC) can be used in conjunction with PXRD to identify glass transition temperatures, melting endotherms, and drug-excipient interactions (as reflected by shifts or the absence of the melting event). Surface morphology can be obtained from scanning electron microscopy (SEM), and nanostructure information from transmission electron microscopy (TEM). Details of molecular interactions between drugs and excipients, as well as the formation of amorphous dispersion, are provided by FTIR and Raman spectroscopy [38].

Powder Flow Properties

Studies of dissolution in United States Pharmacopeial apparatus Type II (paddle) or Type I (basket) in biorelevant media (fasted state simulated intestinal fluid [FaSSIF], fed state simulated intestinal fluid [FeSSIF] or fasted state simulated gastric fluid [FaSSGF]) yield mechanistically relevant dissolution information. These media provide a more physiologically representative in vitro representation of the gastrointestinal tract than aqueous buffers alone. In vitro pH-stat apparatuses can be used to model lipid digestion in the intestine, containing the lipid phase, pancreatin, bile salts, and phospholipids. In the case of lipid-based formulations, these models can predict which drug dissolves and which precipitates after lipid digestion, thereby enhancing the in vitro-in vivo correlation (IVIVC) [39].

In Vitro Drug Release and Lipolysis Studies

Dissolution studies employing United States Pharmacopeial apparatus Type II (paddle) or Type I (basket) in biorelevant media—including fasted state simulated intestinal fluid (FaSSIF), fed state simulated intestinal fluid (FeSSIF), and fasted state simulated gastric fluid (FaSSGF)—provide mechanistically relevant dissolution information. These media provide a more realistic in vitro representation of the physiological gastrointestinal tract than aqueous buffers alone. Intestinal lipid digestion models incorporate the lipid phase into in vitro pH-stat apparatuses containing pancreatin, bile salts, and phospholipids. These models predict the fractions of drug dissolved and precipitated after lipid digestion, thereby improving in vitro-in vivo correlation (IVIVC) for lipid-based formulations [40]. While S-SMEDDS usually produces microemulsion droplets between 100 and 200 nm, S-SNEDDS usually produces nanoemulsion droplets smaller than 100 nm. S-SNEDDS's smaller droplet size provides pancreatic lipase with a greater interfacial surface area, which accelerates lipid digestion and mixed micelle formation. As a result, when compared to S-SMEDDS, S-SNEDDS may show faster absorption kinetics and earlier Tmax values. However, S-SMEDDS are appealing for long-term storage and industrial manufacturing because they often exhibit greater thermodynamic stability and a lower risk of Ostwald ripening. Another benefit of SNEDDS is its ability to produce droplets typically smaller than 100 nm, whereas SMEDDS typically produce droplets smaller than 200 nm. The interfacial surface area available per unit volume of formulation is significantly increased by the decrease in droplet diameter. Because pancreatic lipase-mediated digestion occurs at the oil–water

interface, SNEDDS's greater surface area can accelerate lipid hydrolysis and enzyme adsorption, thereby promoting faster formation of mixed micelles and improved drug solubilization. Additionally, drug partitioning into intestinal colloidal structures may be accelerated by the shorter diffusion distance of smaller droplets, thereby improving absorption kinetics and, in certain situations, accelerating the onset of systemic exposure. However, the extent of this effect remains formulation-dependent and depends on the type of surfactant, lipid composition, and digestive processing. However, the degree of this effect remains formulation-dependent and depends on the type of surfactant, lipid composition, and conditions of digestive processing [40].

PHARMACOKINETIC ENHANCEMENT WITH S-SMEDDS

Some of the most important pharmacokinetic aspects of S-SMEDDS efficacy include increased area under the plasma concentration-time curve (AUC), elevated maximum plasma concentration (Cmax), modified time to peak plasma concentration (Tmax), and significantly enhanced bioavailability. Pharmacokinetic improvements such as increased solubilization, decreased precipitation, lymphatic circulation, and inhibition of efflux transporters act synergistically to yield more potent, predictable, and consistent pharmacokinetic profiles compared to conventional dosage forms [41].

Bioavailability enhancement: preclinical and clinical evidence

The atypical antipsychotic Iloperidone, which undergoes extensive first-pass metabolism and exhibits poor aqueous solubility, was formulated as S-SMEDDS using Capmul MCM, Labrafac WL 1349, Lauroglycol 90, and polyethylene glycol 600 solidified onto Neusilin US2. Pharmacokinetic investigation in rats demonstrated that AUC increased by 3.80-fold and 2.19-fold relative to the coarse and tablet suspensions, respectively. Maximum effect time was 15min with S-SMEDDS compared to coarse suspension with reversal of MK-801-induced hyperlocomotion [42]. The antiretroviral agent Efavirenz, which undergoes extensive first-pass metabolism, was developed as a cationic S-SMEDDS formulation using Peceol, Polysorbate 80, Labrafac Lipophile WL-1349, and the cationic lipid Octadecylamine, with Syloid XDP as the solidifying agent [24]. Increased electrostatic interactions between the positively charged formulation surface and the negatively charged intestinal mucosa resulted in an extended residence time. An increase in oral bioavailability of up to 4.12-fold over the Efavirenz suspension was observed at equivalent doses [43]. Relugolix (RLGL), a gonadotropin-releasing hormone antagonist, presents dual challenges of poor solubility and P-glycoprotein substrate characteristics. An RLGL-S-SMEDDS formulation containing ethyl oleate (26 percent), Solutol HS15 (49 percent), Transcutol HP (25 percent), and hydrophilic silica-200 as a carrier demonstrated an in vitro release of 86 percent of the total drug, compared to only 3.6 percent from the RLGL suspension in phosphate-buffered saline at pH 6.8. RLGL-S-SMEDDS uptake by Caco-2 cell lines was threefold higher compared to free RLGL. In vivo rat pharmacokinetics revealed a 1.9-fold increase in oral bioavailability with RLGL-S-SMEDDS compared with the RLGL suspension. For Atorvastatin calcium (ATV), comparative evaluation of S-SMEDDS using water-soluble carrier (mannitol)—designated S(M)-SMEDDS—and water-insoluble carrier (Sylysia)—designated S(S)-SMEDDS—demonstrated that optimized liquid SMEDDS achieved 345 percent oral bioavailability compared to plain ATV suspension in rats. S(M)-SMEDDS oral bioavailability was 216 percent, while S(S)-SMEDDS achieved 160 percent, demonstrating the significant influence of carrier hydrophilicity on reconstitution and absorption performance [44]. In pharmacokinetic investigations in rats, supersaturable S-SMEDDS of Valsartan with Florite 102 as the solid carrier and croscarmellose sodium as the superdisintegrant exhibited 107 percent relative bioavailability of Valsartan compared to the liquid Su-SMEDDS formulation and 222 percent relative bioavailability compared to the marketed formulation Diovan (Table 2). By decreasing water penetration into the dosage form after administration, hydrophobic carriers may have a detrimental effect on bioavailability. Diffusion across the intestinal unstirred water layer (UWL) is prolonged, and microemulsion production is delayed by limited wetting. Slower droplet dispersion can reduce the concentration gradient that drives drug transport because the UWL acts as a diffusion barrier adjacent to the epithelial surface. On the other hand, hydrophilic carriers, such as Neusilin® and porous silica, promote effective medication diffusion and absorption by facilitating quick water uptake and emulsification. Several oral formulation techniques have shown notable increases in the bioavailability of medications that are poorly soluble in water. As an illustration of the transformative potential of lipid-based delivery systems, Yi et al. reported that a spray-dried solid self-microemulsifying drug delivery system (SMEDDS) significantly increased the oral

bioavailability of model poorly soluble drugs, with improvements approaching 50-fold in some cases [45]. Furthermore, solid SMEDDS and associated lipid-based formulations enhance the oral bioavailability and pharmacodynamic performance of several poorly soluble substances, such as testosterone [9], fluvastatin [45], lovastatin [44], rosuvastatin [16,43] & *Kaempferia parviflora* extract [41]. Together, these results show that by improving solubilization, dissolution, and intestinal absorption, lipid-based formulations can result in significant increases in systemic drug exposure.

Supersaturable S-SMEDDS: maintaining drug supersaturation in the gastrointestinal tract

The S-SMEDDS formulation of Iloperidone, which was extensively metabolized in the first pass through the gut and poorly soluble in aqueous media, used two solidified excipients: Capmul MCM and Labrafac WL 1349, and two soluble excipients: Lauroglycol 90 and polyethylene glycol 600. Pharmacokinetic studies in rats showed that the AUC was 3.80- and 2.19-fold higher for the coarse and tablet suspensions, respectively. The hyperlocomotion-reversing effects of S-SMEDDS reached a maximum after 15min, whereas a similar effect occurred in coarse suspension after 90min [45]. Efavirenz, a highly first-pass-metabolized ARV, was formulated using Peceol, Polysorbate 80, Labrafac Lipophile WL-1349, and Octadecylamine, a cationic lipid, as the solidifying agent [24]. More positive charges on the formulation surface and more negative charges on the intestinal mucosal wall led to a longer residence time. Enhancing oral bioavailability by up to 4.12-fold was achieved at the same dose level of the Efavirenz suspension [46]. The dual problems with Relugolix (RLGL) are its poor solubility and its characteristics as a P-glycoprotein substrate. The formulation prepared with RLGL-S-SMEDDS, ethyl oleate (26 percent), Solutol HS15 (49 percent), Transcutol HP (25 percent), and hydrophilic silica-200 (carrier) showed an in vitro release of 86 % of the total drug. In contrast, RLGL suspension in phosphate-buffered saline pH 6.8 released only 3.6% of the total drug. The uptake of RLGL-S-SMEDDS by Caco-2 cell lines was three-fold higher than that of free RLGL. RLGL-S-SMEDDS also resulted in a 1.9-fold increase in oral bioavailability in rats compared with the RLGL suspension [47]. Atorvastatin calcium (ATV), when compared using a water-soluble carrier (mannitol) and a water-insoluble carrier (Sylysia), indicated that the optimized liquid SMEDDS had 345 percent oral bioavailability in rats compared with the plain suspension of ATV [26]. The effect of carrier hydrophilicity on reconstitution and absorption performance was demonstrated by the oral bioavailability of 216% and 160% for S(M)-SMEDDS and S(S)-SMEDDS, respectively. The S-SMEDDS formulation of Valsartan using solid carrier Florite 102 and superdisintegrant croscarmellose sodium showed 107 percent relative bioavailability of Valsartan in rat pharmacokinetic investigations compared to the liquid S-SMEDDS formulation & 222 % relative bioavailability compared to the marketed formulation Diovan [48] (See Table 2).

Table 2: Pharmacokinetic Outcomes of Selected S-SMEDDS Formulations

Drug (Indication)	Excipients (Oil / Surfactant / Co-solvent / Carrier)	Comparator	PK Outcome	Ref.
Relugolix — prostate cancer	Ethyl Oleate / Solutol HS15 / Transcutol HP / hydrophilic-200 silica	RLGL suspension	AUC ↑ 1.9×; Caco-2 uptake ↑ 3×; In vitro release 86% vs. 3.6%	[49]
Atorvastatin Ca — dyslipidemia	Capmul MCM / Tween 20 / Tetraglycol / Mannitol (S(M)) or Sylysia® (S(S))	ATV suspension	Relative BA: liquid SMEDDS 345%; S(M) 216%; S(S) 160%	[50]
Valsartan — hypertension	Poloxamer 407 / Capmul MCM / Tween 20 / Transcutol P / Florite® PS-10 + Vivapur® 105	Diovan® powder	Relative BA: 222% vs. Diovan®; 107% vs. SuSMEDDS	[51]
Efavirenz — HIV/AIDS	Peceol / Tween 80 / Labrafac / octadecyl amine / Syloid XDP (cationic S-SMEDDS)	EFV suspension	BA ↑ 4.12-fold; reduced dose feasibility demonstrated	[52]
Iloperidone — antipsychotic	Capmul MCM / Labrafac WL 1349 / Lauroglycol 90 / PEG 600 / Neusilin US2	Coarse suspension	AUC ↑ 3.80× vs. CS; 2.61× vs. tablet suspension	[53]
Nimodipine — cerebrovascular	Ethyl oleate / Labrasol / Cremophor RH 40 / Dextran (spray-dried)	Conventional tablet	AUC ↑ 2.6×; Cmax ↑ 6.6× vs. tablet	[54]
Carbamazepine — epilepsy (Su-S-SMEDDS)	Tween 80 / PEG 400 / Cremophor EL-35 / PVP K30 (precipitation inhibitor)	Commercial tablet	BA ↑ ~5-fold vs. commercial tablet	[55]
Dutasteride — BPH (Su-S-SMEDDS)	Capryol 90 / Cremophor EL / Transcutol HP / Aerosil 200 / Soluplus	Physical mixture	Cmax and AUC ↑ 6.8- and 5.0-fold vs. physical mixture	[56]

Controlled and Site-Specific Drug Delivery

It is possible to modify the release characteristics of S-SMEDDS by modulating polymer concentration and viscosity grade [30]. In vitro dissolution studies revealed controlled 12-hour release profiles for Sirolimus S-SMEDDS containing HPMC 100LV and K4M; higher grades of HPMC (K15M and K100M) resulted in extremely thick gel layers that slowed drug release. The release profile of HPMC 100LV changed from burst release (95 percent in two hours) to smooth extended release (30 percent) as the content increased from 0 percent to 15 percent [30]. Gastroretentive S-SMEDDS of Fenofibrate formulated with Capryol PGMC, Kolliphor RH40, Transcutol HP, Fujicalin adsorbent, and HPMC as release modifier gave 90 percent drug release in 12 hours using a viscosity gradient approach (0.1K to 100K) [57].

PHARMACODYNAMIC EVIDENCE AND THERAPEUTIC APPLICATIONS

In addition to their pharmacokinetic effects, S-SMEDDS formulations offer substantive advantages across various therapeutic areas. Improved bioavailability directly leads to increased therapeutic response at the same or lower dose, decreased dose-response variation, and/or decreased adverse effect burden.

Cardiovascular and Antihyperlipidemic Applications

In the present study, Rosuvastatin calcium S-SMEDDS with carrier (Capryol 90, Kolliphor EL, Transcutol HP, Florite RE) showed a highly significant ($p < 0.001$) decrease in serum total cholesterol, triglycerides, LDL cholesterol, and an increase in HDL cholesterol. The use of Capmul PG8, Labrasol, Transcutol P, and Syloid XDP to formulate Lovastatin S-SMEDDS was shown to increase its bioavailability by 2.57-fold compared to coarse suspension and exhibited measurable antihyperlipidemic effects as early as 2 hrs after dosing, in contrast to 4 hrs for coarse suspension, a clinically significant acceleration of the onset of lipid-lowering effect. The Fluvastatin S-SMEDDS had a 3.00-fold higher bioavailability compared to the liquisolid & suspension comparators, extending its lipid-lowering effect from 6 to 12 hrs [58].

Oncology Applications

The study showed that the Paclitaxel-loaded SMEDDS, using Ganoderma lucidum spore oil as the lipid phase, exhibited high antitumor activity in colorectal cancer models by inducing mitochondrial-mediated apoptosis, inhibiting metastatic cell migration, and demonstrating synergistic immunomodulatory effects. Interestingly, the formulation reduced systemic toxicity compared with conventional Paclitaxel injection preparations, suggesting that the drug was delivered more specifically and at a lower dose to normal tissues.

Gefitinib S-SMEDDS exhibited increased cytotoxicity against cancer cell lines compared with Gefitinib alone at the same concentration, owing to enhanced intracellular uptake via transcellular absorption and inhibition of efflux pumps. The mitochondria-targeting ability of piperine-conjugated SMEDDS nanoparticles with enhanced caspase-3 activity was demonstrated for the first time in direct pharmacodynamic studies in carcinoma cells, which showed significant inhibition of cell growth resulting from improved intracellular delivery of piperine by the SMEDDS nanoparticles [59], [60].

Endocrinology and Metabolic Applications

Once orally administered, Canagliflozin (CFZ) S-SMEDDS with Lauroglycol FCC, Polysorbate 80, Transcutol P, and Neusilin US2 showed a dominant inhibition of the sodium-glucose cotransporter-2 (SGLT2) pathway in an in vivo diabetic rat model. This increased bioavailability was correlated with greater complete and sustained SGLT2-mediated glucose excretion compared with the plain drug. It was believed to result from synergistic pharmacokinetic effects (higher plasma exposure) and pharmacodynamic effects (earlier Tmax and sustained AUC). In diabetic complications, UA SMEDDS was found to be more bioavailable and pharmacologically more active than UA suspension, and to significantly lower blood glucose, glycated hemoglobin, and inflammatory biomarkers in streptozotocin-induced diabetic rats [61].

Anti-Infective and Immunosuppressive Applications

Pharmacodynamic evaluations of polyethylene glycol-based suppositories against parasites indicated they had lower antimalarial activity than Artemether-Lumefantrine S-SMEDDS, suggesting that S-SMEDDS could be utilized in various dosage forms.

There was a significant decrease in intra-individual pharmacokinetic variability with cyclosporine A when administered as Neoral (liquid SMEDDS) compared with Sandimmune (conventional formulation), and improved dose proportionality in transplant recipients with SMEDDS compared with conventional cyclosporine formulations (see Table 3) [62].

Table 3: Pharmacodynamic Outcomes of S-SMEDDS Across Therapeutic Areas

Drug (Disease Area)	S-SMEDDS Key Excipients	Pharmacodynamic Outcome	Pharmacokinetic	Ref.
Rosuvastatin Calcium (Hyperlipidemia)	Capryol 90, Kolliphor® EL, Transcutol HP, Florite® RE	Significant reduction ($p<0.001$) in TC, TG, LDL-C, VLDL-C; increase in HDL-C vs. plain drug	Enhanced Bioavailability (BA)	[63]
Lovastatin (Hyperlipidemia)	Capmul PG8, Labrasol, Transcutol P, Syloid XDP	Lipid-lowering effect at 2 h vs. 4 h for coarse suspension; faster therapeutic onset	2.57× BA vs. coarse suspension	[64]
Fluvastatin (Hyperlipidemia)	Sefsol-218 Cremophor RH40 Propylene glycol	Extended lipid-lowering duration: 12 h (S-SMEDDS) vs. 6 h (LS/suspension)	3.00× BA vs. suspension	[65]
Paclitaxel + GLSO (Colorectal cancer)	Ganoderma lucidum spore oil (GLSO)	Apoptosis induction; metastasis suppression; T-lymphocyte immunomodulation; reduced systemic toxicity vs. IV PTX	Oral delivery enabled	[66]
Gefitinib (Cancer)	Oleic acid, Tween 80, Propylene glycol	Greater in vitro cytotoxicity vs. plain gefitinib at equivalent concentration	Improved intracellular delivery	[67]
Canagliflozin (Type 2 Diabetes)	Lauroylglycol FCC, Tween 80, Transcutol P, Neusilin US2	Predominant SGLT-II inhibition; more sustained urinary glucose excretion vs. plain drug	Enhanced BA	[68]
Efavirenz (HIV/AIDS)	Peceol, Tween 80, Labrafac, octadecyl amine, Syloid XDP	Enhanced anti-HIV therapeutic effect; dose reduction potential	4.12× BA vs. suspension	[69]
Cyclosporine A (Transplant — Neoral®)	Cremophor EL, ethanol, corn oil glycerides (liquid SMEDDS)	Reduced intra-individual PK variability; improved dose proportionality in transplant recipients (human clinical data)	Improved consistency	[70]

STABILITY CONSIDERATIONS

Stability of the physical and chemical properties is an important factor in determining the commercial viability and clinical efficacy of S-SMEDDS formulations [36]. In addition to chemical instability resulting from oxidation of the lipids (triglycerides) to produce peroxides and secondary oxidation products, which may cause the drug to become unstable, three other major mechanisms of degradation can occur with liquid SMEDDS formulations: (1) lipid oxidation (triglyceride excipients can be degraded by oxidation when exposed to air, moisture, light and high temperature, resulting in a formulation that contains peroxides and secondary oxidation products which may cause degradation of the drug; (2) polymorphic transitions (triglyceride excipients may change into polymorphs when exposed to air, moisture, light and high temperature, altering the appearance and performance characteristics of the formulation; and (3) hydrolytic degradation of the ester bonds, resulting in a change in the efficacy of the formulation. These three mechanisms are significantly reduced when the formulation is converted to the solid state.

Scanning electron microscopy, differential scanning calorimetry, Fourier-transform infrared spectroscopy, and powder X-ray diffraction analysis of Tacrolimus S-SMEDDS showed that all drug peaks were absent from the solid matrix, indicating complete amorphization of the drug. The calculated shelf life for solid SMEDDS was 2.25 years after rapid stability testing under conditions of 40 degrees Celsius and 75 percent relative humidity for six months, a 22 percent increase due to decreased molecular mobility and oxygen inaccessibility in the solid matrix. Formulations containing 0.20% citric acid (antioxidant) showed significantly greater stability under high light, high humidity, and elevated temperatures. Citric acid acted as a free radical scavenger by blocking lipid peroxidation chain reactions [71].

Super-saturable S-SMEDDS pose an additional challenge because the drug's amorphous form must remain stable in the supersaturated system during storage without crystallizing, making their inclusion in typical formulations impractical. Intermolecular interaction between curcumin and the matrix Eudragit EPO was found to be responsible for achieving the six-month stability of Curcumin Su-S-SMEDDS at both intermediate (30 °C, 65%RH) and accelerated (40 °C, 75%RH) temperatures [72].

AI-ASSISTED FORMULATION OPTIMIZATION

Recent developments have combined Quality by Design (QbD) concepts with artificial intelligence (AI) to develop lipid-based formulations. Droplet size, emulsification efficiency, and drug-loading capacity have all been predicted from formulation variables using machine-learning methods such as Artificial

Neural Networks (ANNs) and Random Forest models. For instance, ANN-assisted optimization of lipid-based formulations has accelerated S-SMEDDS development and supported continuous production strategies by reducing the number of experimental runs while accurately predicting key quality attributes.

LIMITATIONS AND CONTEMPORARY MITIGATIONS

While S-SMEDDS may be a more promising alternative to liquid SMEDDS, several formulation and regulatory issues are pertinent for both formulation scientists and regulatory authorities. Drug precipitation during gastrointestinal dilution remains a problem for highly lipophilic drugs at high doses, and supersaturable S-SMEDDS containing precipitation inhibitors have been shown to provide sufficient post-dose supersaturation for 2–4 hours, allowing significant drug absorption by the intestine. This intrinsic variability in the food effects of lipid-based formulations is being systematically addressed through mechanistic modeling of lipid digestion, quality-by-design (QbD) space exploration, and biorelevant dissolution testing in both fasted- and fed-state media [73].

Long-term gastrointestinal mucosal effects are a safety concern that can be directly addressed by the precipitation inhibitor-based supersaturation approach, as it allows the formulation's surfactant content to be reduced. Antioxidant excipients (alpha-tocopherol, citric acid, butylated hydroxytoluene), solid-carrier amorphous-stabilization capacity (maximum) during production (nitrogen purging), and vacuum-sealed packaging during storage are all methods used to minimize lipid oxidation and crystalline instability. Novel lipid excipients and carriers should be developed to meet all criteria for Generally Recognized as Safe (GRAS) status and the International Conference on Harmonization (ICH) Q3C and Q3D guidelines, and quality-by-design control measures should be implemented to enable predictable regulatory submissions [74].

FUTURE DIRECTIONS AND EMERGING TECHNOLOGIES

The next ten years of S-SMEDDS research are poised to make progress in many transformative fronts [40]. Three-dimensional printing technology can be used to produce patient-personalized dosage forms, such as S-SMEDDS and compartmentalized tablets containing multiple lipid compartments with programmable release kinetics, which are ideal formulations for pediatric dosages, chronic polypharmacy, and personalized medicine [40]. Data from molecular descriptors and excipient physicochemical databases are used in conjunction with machine learning and artificial intelligence to predict the optimal formulation composition, droplet dynamics, and in vivo digestion behavior. Such computational methods can significantly shorten formulation development cycles and reduce reliance on empirical testing.

Peptides and proteins, which have traditionally been inaccessible to lipid-based systems, can now be delivered orally via reverse micelle-based S-SMEDDS, lipid-polymer hybrid nanosystems, and protease-inhibitor-containing SMEDDS, which protect labile macromolecules from enzymatic degradation in the gastrointestinal tract and improve intestinal permeability. Site-selective drug delivery to the small intestine, colon, and tumor microenvironment using pH-, enzyme-, or temperature-responsive S-SMEDDS can mitigate the systemic toxicity of cytotoxic agents [40]. Hybrid nanostructures of S-SMEDDS with PLGA nanoparticles or liposomes are used to obtain dual-phase release kinetics (immediate and sustained) and to improve penetration through mucus and oxidative stability.

In recent years, sustainable manufacturing methods such as supercritical CO_2 extraction, solvent-less hot-melt extrusion, and continuous manufacturing systems have been implemented that adhere to the principles of green chemistry and enable online quality control [75].

REGULATORY CONSIDERATIONS FOR S-SMEDDS

Despite their formulation benefits, S-SMEDDS often contain high surfactant concentrations (30–70% w/w), which may raise concerns about long-term safety and gastrointestinal irritation. Regulatory bodies must thoroughly evaluate excipients for toxicity, especially when used at higher-than-usual quantities.

Excipients that are frequently used and have proven safety characteristics include:

Excipient	Regulatory Status
Capryol 90	Widely accepted pharmaceutical excipient
Labrasol	Pharmaceutical grade excipient
Cremophor EL	Approved but associated with hypersensitivity concerns
Tween 80	GRAS and pharmaceutically accepted
Medium-chain triglycerides	GRAS

GRAS excipients may be beneficial with industrial translation and regulatory approval.

CONCLUSION

Solid self-microemulsifying drug delivery systems have progressed from a mere engineering approach to address instability in liquid SMEDDS to a rational, clinically proven pharmaceutical platform for oral drug delivery. The evidence in this extensive review shows that S-SMEDDS can achieve reliable, reproducible increases in bioavailability of 1.9-fold to over 50-fold compared to conventional formulations via a multi-mechanism absorption pathway, including improved drug solubility in the GI tract, reduced drug precipitation, lymphatic delivery, and inhibition of efflux transporters. These pharmacokinetic benefits are directly reflected in clinically relevant pharmacodynamic effects such as quicker decrease in lipemia, increased anti-tumor activity, enhanced immunosuppression, and increased anti-infective activity. From simple adsorption processes to advanced formulations, including supersaturation, sustained release, gastric retention, and cationic surface modification, the versatility of S-SMEDDS in pharmaceutical formulation is apparent. In vivo clinical efficacy is linked to formulation science through rigorous characterization, including biorelevant dissolution studies, in vitro lipolysis, powder X-ray diffraction, differential scanning calorimetry, and Caco-2 cell permeability assessment. Industry recognition of S-SMEDDS' significant commercial and therapeutic value is reflected by the expanding global intellectual property landscape in the United States, Europe, and Asia. The potential of future combination with three-dimensional printing technology, artificial intelligence (AI) based formulation design, stimuli-responsive materials, and macromolecular delivery systems will solidify S-SMEDDS as a key platform in precision medicine. S-SMEDDS will become a programmable pharmaceutical system, shifting from a solubility-enhancement tool to one that enables more advanced therapeutic applications with personalized pharmacokinetic profiles and multifunctionality.

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NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Pallavi R. Kaple was responsible for comprehensive literature review, data synthesis, manuscript preparation, and critical evaluation of all published evidence. Surendra S. Agarwal contributed to research methodology design, validation of scientific content, critical revision of the manuscript for intellectual content, and supervision of the entire manuscript development process. Both authors reviewed and approved the final manuscript before submission.

DATA VERIFICATION AND SCIENTIFIC ACCURACY

To ensure consistency and scientific accuracy throughout the manuscript, all quantitative assertions, including bioavailability enhancement factors, stability improvements, characterization outcomes, and formulation performance measures, have been cross-referenced with the original literature.

DECLARATION OF USE OF AI TOOLS

The authors declare that, during manuscript preparation, the following artificial intelligence (AI) tools were used: BioRender (the latest version available in 2026) and other generative AI platforms for literature support. The AI tools were used exclusively for the following purposes: language editing and grammatical refinement, text organization and structure enhancement, and literature search assistance. In full compliance with Committee on Publication Ethics (COPE), International Committee of Medical Journal Editors (ICMJE), and Bentham Science publication policies: (a) AI tools were not designated as authors and were not employed to generate original research data, conduct independent analyses, interpret findings autonomously, or formulate scientific conclusions; all scientific reasoning, methodological decisions, data interpretation, and conclusions were developed and validated exclusively by the author(s); (b) no confidential, unpublished, proprietary, or patient-identifiable data were uploaded to AI systems; (c) all AI-assisted content was thoroughly reviewed and verified by the author(s) to ensure accuracy; and (d) AI tool utilization did not infringe copyright or intellectual property rights. All AI-assisted material was carefully reviewed, verified, critically evaluated, and edited by the author(s). The author(s) accept complete responsibility and accountability for accuracy and integrity of all data, validity of analyses and interpretations, content originality, and compliance with ethical and publication standards. This disclosure is provided in the interest of transparency and responsible reporting of AI-assisted scholarly work.

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