RESEARCH PAPER

Next-Generation SEDDS: Emerging Strategies for Oral Drug Delivery

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ABSTRACT
The increasing prevalence of poorly water-soluble drug molecules continues to present significant challenges in oral drug delivery, often resulting in inadequate dissolution, variable gastrointestinal absorption, and suboptimal therapeutic performance. Self-Emulsifying Drug Delivery Systems (SEDDS) have emerged as a versatile lipid-based formulation approach capable of addressing these limitations through enhanced drug solubilization and improved bioavailability. The development of SEDDS has evolved from early lipid-based formulations and conventional emulsifying systems to advanced self-micro emulsifying drug delivery systems (SMEDDS), self-nanoemulsifying drug delivery systems (SNEDDS), supersaturable SEDDS (S-SEDDS), and intelligent hybrid delivery platforms. This progression reflects continuous advancements in pharmaceutical sciences aimed at improving formulation efficiency, stability, absorption characteristics, and therapeutic outcomes. The present review examines the historical development and scientific evolution of SEDDS, highlighting the fundamental principles that have contributed to their emergence as a prominent oral drug delivery technology. Particular emphasis is placed on the transition from conventional self-emulsifying systems to modern micro- and Nano-scale formulations, the introduction of super saturation-based strategies, and the integration of multifunctional and targeted delivery approaches. The review also discusses the scientific basis of spontaneous emulsification, the role of lipid excipients and surfactants, and the influence of technological innovations on formulation performance. Recent developments have expanded the scope of SEDDS beyond bioavailability enhancement toward intelligent and digitally enabled delivery systems. Advances in nanotechnology, hybrid carrier design, computational modeling, artificial intelligence, machine learning, and personalized pharmaceutical manufacturing are increasingly influencing formulation development and optimization. These emerging approaches offer opportunities to improve formulation predictability, reduce development timelines, and support patient-centric drug delivery strategies. The collective evidence indicates that SEDDS have undergone a remarkable transformation from simple lipid formulations into sophisticated multifunctional delivery platforms. Their ability to overcome solubility-related barriers, enhance oral absorption, and integrate emerging pharmaceutical technologies positions them as a valuable tool in contemporary drug development. Continued innovation in formulation design, advanced excipient engineering, and digital pharmaceutical technologies is expected to further expand the clinical applicability and commercial relevance of SEDDS, supporting their role in the successful delivery of future therapeutic agents.

Keywords: Self-Emulsifying Drug Delivery Systems; SEDDS; SMEDDS; SNEDDS; Supersaturable SEDDS; Lipid-Based Drug Delivery; Oral Bioavailability; Nanotechnology; Artificial Intelligence; Personalized Medicine.
How to cite this article: Sharma GS, Lokesh T, Rao VUM. Next-Generation SEDDS: Emerging Strategies for Oral Drug Delivery. Int J Drug Deliv Technol. 2026;16(61s): 603-616. DOI: 10.25258/ijddt.16.61s.65
Source of support: Nil
Conflict of interest: None

1. INTRODUCTION

Oral administration remains the most widely accepted route for drug delivery because of its convenience, patient acceptance, ease of administration, and cost-effectiveness. Despite these advantages, the successful oral delivery of many therapeutic agents continues to be constrained by poor aqueous solubility and limited gastrointestinal absorption. Over the past two decades, drug discovery programs have increasingly generated highly lipophilic molecules with complex physicochemical characteristics, resulting in a growing proportion of drug candidates exhibiting dissolution-limited bioavailability. It has been estimated that nearly 40–70% of newly discovered chemical entities and a considerable proportion of marketed pharmaceuticals suffer from poor aqueous solubility, making formulation development a major challenge in contemporary pharmaceutical research [1–4].

Poor solubility frequently leads to inadequate dissolution within gastrointestinal fluids, resulting in incomplete absorption, high pharmacokinetic variability, inconsistent therapeutic outcomes, and increased food-dependent bioavailability. These challenges are particularly relevant for drugs

belonging to Biopharmaceutics Classification System (BCS) Class II and Class IV categories, where dissolution and permeability limitations significantly affect systemic drug exposure [2,5].Conventional approaches employed to improve oral bioavailability include particle size reduction, salt formation, crystal engineering, inclusion complexation, nanocrystal technology, amorphous solid dispersions, and prodrug design. Although these strategies have demonstrated varying degrees of success, many are associated with limitations such as physical instability, recrystallization, manufacturing complexity, scale-up difficulties, and insufficient enhancement of in vivo performance [3,6].

Lipid-based drug delivery systems have emerged as an attractive alternative for overcoming these challenges. Such systems utilize physiological lipid digestion pathways to improve drug solubilization and facilitate intestinal absorption. Among the various lipid-based technologies, self-emulsifying drug delivery systems (SEDDS) have gained considerable scientific and industrial attention owing to their ability to spontaneously generate fine emulsions upon contact with gastrointestinal fluids under gentle agitation conditions [1,2]. SEDDS are generally composed of oils, surfactants, co-surfactants, and, in some cases, co-solvents, which together form isotropic mixtures capable of producing stable dispersions following aqueous dilution. This spontaneous emulsification process substantially increases the interfacial surface area available for drug release, thereby enhancing dissolution and absorption [7] as represented in Table 1.

Table 1. Key Biopharmaceutical Challenges Associated with Poorly Water-Soluble Drugs and the Mechanisms by Which Self-Emulsifying Drug Delivery Systems (SEDDS) Enhance Oral Bioavailability

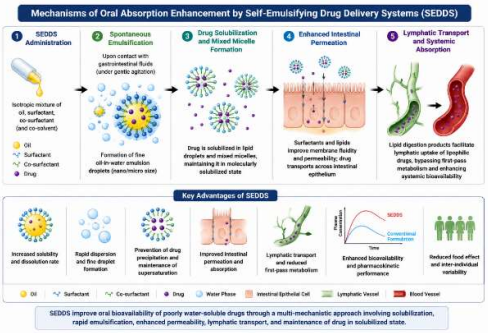
Biopharmaceutical Challenge	Impact on Oral Drug Delivery	Mechanism of Bioavailability Enhancement by SEDDS	Therapeutic Outcome
Poor aqueous solubility	Limited dissolution in gastrointestinal fluids	Maintains the drug in a pre-solubilized state within lipidic excipients	Increased apparent solubility and improved dissolution
Slow dissolution rate	Delayed drug release and absorption	Formation of fine oil-in-water dispersions with large interfacial surface area	absorption
Dissolution-limited absorption (BCS Class II drugs)	Reduced systemic drug exposure	Rapid emulsification and continuous drug presentation in dissolved form	Enhanced oral bioavailability
Combined solubility and permeability limitations (BCS Class IV drugs)	Poor therapeutic performance	Improved solubilization combined with membrane permeation enhancement	Increased drug absorption and efficacy
Drug precipitation following gastrointestinal dilution	Loss of dissolved drug fraction	Lipidic microenvironment stabilizes drug molecules after dilution	Sustained solubilization during gastrointestinal transit
Variable gastrointestinal absorption	High inter-subject pharmacokinetic variability	Consistent dispersion and improved drug distribution in intestinal fluids	Improved pharmacokinetic reproducibility
Extensive hepatic first-pass metabolism	Reduced systemic availability	Promotion of intestinal lymphatic transport for highly lipophilic drugs	Increased systemic drug exposure
Limited intestinal membrane permeation	Reduced transport across epithelial barriers	Surfactants and lipid excipients enhance membrane fluidity and	Improved intestinal uptake

		permeability	
Food-dependent bioavailability	Inconsistent therapeutic response between fed and fasted states	Maintenance of drug solubilization independent of physiological lipid intake	Reduced food effect variability
Inadequate drug loading in conventional dosage forms	Difficulty formulating highly lipophilic compounds	High solubilization capacity of oils, surfactants, and co-solvents	Increased formulation flexibility
Enzymatic degradation within the gastrointestinal tract	Reduced bioavailability of sensitive molecules	Lipid droplets may provide partial protection against gastrointestinal degradation	Improved stability of susceptible compounds
Poor absorption of highly lipophilic drugs	Incomplete uptake from gastrointestinal tract	Facilitation of mixed micelle formation and enhanced lipid digestion-mediated absorption	Increased absorption efficiency
High pharmacokinetic variability	Unpredictable therapeutic outcomes	Uniform droplet formation and reproducible gastrointestinal dispersion	More consistent plasma drug concentrations
Low therapeutic efficacy at conventional doses	Requirement for higher dosing frequency	Improved bioavailability leading to greater systemic drug levels	Enhanced therapeutic effectiveness
Challenges in delivering modern poorly soluble drug candidates	Increased formulation complexity during drug development	Multifunctional lipid-based platform adaptable to diverse drug molecules	Improved developability of new chemical entities

Abbreviations: BCS, Biopharmaceutics Classification System; SEDDS, Self-Emulsifying Drug Delivery Systems.

The success of SEDDS is attributed not only to improved drug solubilization but also to multiple complementary mechanisms that contribute to enhanced bioavailability. These include maintenance of drugs in a dissolved state during gastrointestinal transit, reduction of precipitation following dilution, enhancement of intestinal membrane permeability, stimulation of lymphatic transport, and partial avoidance of hepatic first-pass metabolism [2,8]. Furthermore, lipid digestion products generated during gastrointestinal processing contribute to the formation of mixed micellar structures capable of maintaining drug solubilization within the absorptive environment of the intestine [9] as represented in Figure 1.

Figure 1. Schematic overview of the oral absorption enhancement mechanisms of Self-Emulsifying Drug Delivery Systems (SEDDS), including spontaneous emulsification, drug solubilization, mixed micelle formation, intestinal permeation enhancement, and lymphatic transport.



The scientific foundation of SEDDS originated from early investigations into lipid formulations and self-emulsification phenomena during the latter half of the twentieth century. Initial research demonstrated that specific combinations of oils and surfactants could spontaneously disperse in aqueous media without requiring substantial external energy input. Landmark studies involving polyglycolyzed glyceride-based systems subsequently demonstrated significant improvements in the oral absorption of poorly water-soluble compounds, establishing the basis for modern self-emulsifying technologies [10].

Since then, advances in colloidal science, lipid chemistry, pharmaceutical excipients, and drug absorption mechanisms have transformed SEDDS into one of the most extensively investigated formulation platforms for bioavailability enhancement [1,11].

Over time, SEDDS technology has evolved beyond conventional formulations to encompass several advanced subclasses. Self-micro emulsifying drug delivery systems (SMEDDS) were developed to generate transparent micro emulsions with improved thermodynamic stability and enhanced absorption characteristics. Further refinement resulted in self-nanoemulsifying drug delivery systems (SNEDDS), which produce nanometric droplets capable of providing superior dissolution behavior, enhanced membrane interaction, and improved pharmacokinetic performance [12,13]. More recently, supersaturable self-emulsifying drug delivery systems (S-SEDDS) have been introduced to reduce surfactant dependence while maintaining high drug concentrations in a transient supersaturated state. In parallel, solid self-emulsifying systems have emerged as a promising approach to improve formulation stability, patient acceptability, storage characteristics, and industrial manufacturability [14–16].

The therapeutic scope of SEDDS has expanded considerably in recent years. While originally developed for highly lipophilic small-molecule drugs, contemporary research has demonstrated their potential for delivering peptides, proteins, nutraceuticals, phytoconstituents, anticancer agents, antidiabetic drugs, antiviral compounds, and central nervous system therapeutics [17–19]. Multifunctional formulations incorporating permeability enhancers, mucoadhesive polymers, enzyme inhibitors, and targeting ligands have further broadened the applicability of SEDDS to challenging therapeutic areas that were previously considered unsuitable for oral delivery [18].

Recent advances have introduced a new generation of intelligent and digitally enabled SEDDS platforms. The integration of Quality by Design (QbD) principles, Design of Experiments (DoE), artificial intelligence (AI), machine learning algorithms, and computational modeling has enabled a more systematic and predictive approach to formulation development [20–22]. These technologies facilitate optimization of formulation composition, identification of critical material attributes, prediction of performance outcomes, and establishment of robust design spaces. Furthermore, advances in lipidomics and molecular-level characterization have improved understanding of excipient–drug interactions and enabled the development of more sophisticated lipid-based delivery systems [21].

An important contemporary development is the emergence of supersaturated, hybrid, and digitally manufactured SEDDS. Recent investigations by Obaiah, Ugandar, Badarinath, and Rao highlighted the growing significance of supersaturable systems, hybrid lipid carriers, computationally optimized formulations, and three-dimensional (3D) printing technologies in advancing next-generation SEDDS platforms [22]. Such approaches offer new opportunities for personalized medicine, patient-specific dosing, improved therapeutic precision, and flexible pharmaceutical manufacturing. The incorporation of digital technologies into formulation design and production is expected to play a transformative role in future oral drug delivery systems.

Despite substantial progress, several scientific and translational challenges remain unresolved. High surfactant concentrations may cause gastrointestinal irritation, while formulation instability, precipitation during digestion, inadequate predictive in vitro–in vivo correlations, and manufacturing scale-up difficulties continue to hinder commercial translation [1,14,16]. Regulatory uncertainties associated with complex lipid formulations and limited long-term clinical evidence for many emerging SEDDS technologies further emphasize the need for continued research and development. Addressing these limitations will require interdisciplinary collaboration involving pharmaceutical scientists, formulation engineers, computational modelers, regulatory experts, and clinicians.

Given the rapid expansion of research activity and technological innovation in this field, a comprehensive and updated evaluation of SEDDS is warranted. The present review critically examines the historical evolution, formulation principles, classification systems, characterization methodologies, solidification technologies, therapeutic applications, recent technological advances, regulatory considerations, research gaps, and future directions associated with SEDDS. Particular emphasis is placed on developments reported during the last five years, including supersaturable systems, Nano-SEDDS, targeted delivery platforms, AI-assisted optimization, lipidomics-guided excipient selection, and personalized lipid-based drug delivery approaches. Through integration of fundamental principles with recent advances, this review aims to provide a contemporary perspective on the role of SEDDS in addressing the biopharmaceutical challenges of modern drug development.

2. HISTORICAL BACKGROUND OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS)

2.1 Early Development of Lipid-Based Drug Delivery Systems

The development of self-emulsifying drug delivery systems (SEDDS) represents a significant milestone in the evolution of lipid-based pharmaceutical

technologies. The concept emerged from decades of research focused on improving the oral absorption of poorly water-soluble drugs, a challenge that has consistently limited the therapeutic performance of numerous pharmacologically active compounds. Historically, formulation scientists recognized that many drug candidates with promising pharmacodynamic properties exhibited inadequate bioavailability due to poor aqueous solubility, slow dissolution rates, and extensive presystemic metabolism. These challenges prompted the exploration of lipid-based approaches capable of enhancing drug solubilization and facilitating intestinal absorption [1–3].

The origins of lipid-based drug delivery can be traced to the early use of oils and fatty substances as pharmaceutical vehicles. Long before the formal establishment of modern pharmaceutics, natural oils were employed to improve the administration and absorption of lipophilic medicinal substances. However, systematic scientific investigation into lipid-mediated drug delivery gained momentum during the latter half of the twentieth century, when advances in colloidal chemistry, surfactant science, and gastrointestinal physiology provided a mechanistic understanding of lipid digestion and absorption processes [4,5].

During the 1960s and 1970s, researchers began investigating emulsions and microemulsions as potential carriers for hydrophobic drugs. These early systems demonstrated that the incorporation of drugs into dispersed lipid phases could improve dissolution and facilitate absorption across biological membranes. Nevertheless, conventional emulsions were often characterized by physical instability, phase separation, and manufacturing complexities, limiting their pharmaceutical applicability [6]. The search for more robust and reproducible lipid-based systems ultimately led to the discovery of spontaneous emulsification phenomena, which became the scientific foundation for SEDDS development as represented in Table 2.

Table 2. Historical Milestones in the Development of Lipid-Based Drug Delivery Systems and the Evolution of Self-Emulsifying Drug Delivery Systems (SEDDS)

Period /Year	Scientific Advancement	Key Contributors/ Development	Significance in SEDDS Evolution
Pre-1950s	Use of natural oils, fats, and waxes as medicinal vehicles	Traditional pharmaceutical preparations	Established the earliest use of lipidic materials for delivery of lipophilic compounds
1950s – 1960s	Recognition of food-induced enhancement of drug absorption	Early pharmacokinetic and gastrointestinal studies	Demonstrated the influence of dietary lipids on oral bioavailability
1960s – 1970s	Development of conventional emulsions and microemulsions	Colloidal and dispersion science research	Introduced lipid-based dispersion systems for improving drug solubilization
1970s	Understanding of bile salt–lipid interactions	Gastrointestinal physiology studies	Revealed the role of mixed micelle formation in drug absorption
Late 1970s – 1980s	Advances in surfactant chemistry and interfacial science	Pharmaceutical excipient research	Provided the scientific basis for spontaneous emulsification
Early 1980s	Investigation of isotropic oil–surfactant mixtures	Formulation scientists worldwide	Demonstrated spontaneous dispersion without extensive external energy input

1994	Introduction of self-emulsifying formulations utilizing polyglycolyzed glycerides	Shah NH, Carvajal MT, Patel CI, et al.	Considered one of the landmark studies establishing modern SEDDS technology
Mid-1990s	Commercial success of cyclosporine lipid formulations	Sandimmune® and Neoral®	Validated the clinical and commercial utility of self-emulsifying systems
Late 1990s	Expansion of pharmaceutical lipid excipients	Capmul®, Labrasol®, Cremophor®, Gelucire®, Transcutol®	Facilitated rational design of optimized self-emulsifying formulations
2000–2005	Development of Self-Microemulsifying Drug Delivery Systems (SMEDDS)	Academic and industrial formulation research	Improved droplet size reduction, stability, and absorption efficiency
2005–2015	Growth of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)	Nanotechnology-driven formulation research	Enabled nano-sized droplet generation and enhanced bioavailability
2010–2020	Recognition of lymphatic transport mechanisms	Lipid digestion and absorption studies	Strengthened mechanistic understanding of bioavailability enhancement
2015–2022	Development of Solid SEDDS technologies	Spray drying, adsorption, freeze drying, hot-melt extrusion research	Improved formulation stability, scalability, and patient convenience
2018–2024	Emergence of Supersaturable SEDDS (S-SEDDS)	Supersaturation and precipitation inhibition studies	Reduced surfactant requirements while maintaining absorption enhancement
2020–2026	Development of multifunctional and hybrid SEDDS	Integration of polymers, nanoparticles, and lipid carriers	Expanded applications to targeted and controlled drug delivery
2022–2026	Adoption of Quality by Design (QbD) and Design of Experiments (DoE)	Regulatory and formulation science initiatives	Enabled systematic and robust formulation optimization
2023–2026	AI-assisted and machine learning-guided SEDDS	Computational pharmaceutical research	Facilitated predictive formulation design and

	development		accelerated development timelines
2024–2026	Lipidomics-guided excipient selection	Advanced pharmaceutical analytics	Improved understanding of excipient–drug interactions
2025–2026	Personalized and digitally manufactured SEDDS	3D printing and precision medicine approaches	Enabled patient-specific dosage forms and individualized therapy
Present and Future	Intelligent, hybrid, AI-driven, and precision SEDDS	Multidisciplinary pharmaceutical innovation	Represents the transition toward next-generation oral drug delivery systems

Abbreviations: SEDDS, Self-Emulsifying Drug Delivery Systems; SMEDDS, Self-Microemulsifying Drug Delivery Systems; SNEDDS, Self-Nanoemulsifying Drug Delivery Systems; S-SEDDS, Supersaturable Self-Emulsifying Drug Delivery Systems; QbD, Quality by Design; DoE, Design of Experiments; AI, Artificial Intelligence.

A pivotal advancement occurred in the 1980s and early 1990s when researchers demonstrated that specific combinations of oils, surfactants, and co-surfactants could spontaneously form emulsified systems upon contact with aqueous media under mild agitation conditions. This observation suggested that external mechanical energy was not always necessary to produce fine dispersions if appropriate formulation components were selected. The pioneering work of Shah and co-workers provided one of the earliest demonstrations of the pharmaceutical potential of self-emulsifying formulations. Their studies showed that polyglycolyzed glyceride-based systems significantly enhanced the dissolution and oral absorption of lipophilic drugs, thereby establishing the conceptual basis for modern SEDDS technology [7].

The commercial success of lipid-based products further accelerated interest in self-emulsifying formulations. The introduction of cyclosporine A formulations such as Sandimmune® and later Neoral® provided compelling evidence that lipid-based delivery systems could significantly improve oral bioavailability and reduce pharmacokinetic variability. Neoral®, in particular, utilized self-emulsifying principles to achieve more predictable absorption and represented a major breakthrough in the clinical application of lipid-based technologies [8,9]. These achievements demonstrated the feasibility of translating self-emulsifying concepts from laboratory research into commercially successful pharmaceutical products.

The rapid expansion of excipient technology during the 1990s and early 2000s further transformed the field. The availability of specialized lipid excipients, including medium-chain triglycerides, long-chain triglycerides, polyethylene glycol derivatives, polyglycolyzed glycerides, and advanced non-ionic surfactants, provided formulators with a broader toolkit for designing optimized self-emulsifying systems [10]. Commercial excipients such as Labrasol®, Labrafac®, Capmul®, Cremophor®, Gelucire®, and Transcutol® became widely utilized in formulation development owing to their excellent solubilization capacity and favorable emulsification characteristics [11].

At the same time, increasing knowledge of gastrointestinal lipid digestion mechanisms revealed additional advantages of SEDDS beyond simple drug solubilization. Researchers discovered that lipid digestion products interact with bile salts and phospholipids to form mixed micellar structures capable of maintaining drugs in a dissolved state throughout gastrointestinal transit. Furthermore, lipid-rich formulations were found to promote intestinal lymphatic transport, thereby bypassing hepatic first-pass metabolism and improving systemic drug exposure for highly lipophilic compounds [12,13]. These findings significantly strengthened the scientific rationale for SEDDS development.

As understanding of self-emulsification mechanisms improved, formulation strategies evolved toward generating progressively smaller droplet sizes. Conventional SEDDS were followed by self-microemulsifying drug delivery systems (SMEDDS), which produced microemulsions with enhanced stability and improved absorption characteristics. Continued advances in nanotechnology subsequently facilitated the emergence of self-nanoemulsifying drug delivery systems (SNEDDS), which generated nano-sized droplets capable of providing superior dissolution

performance, increased interfacial surface area, and enhanced intestinal permeability [14,15].

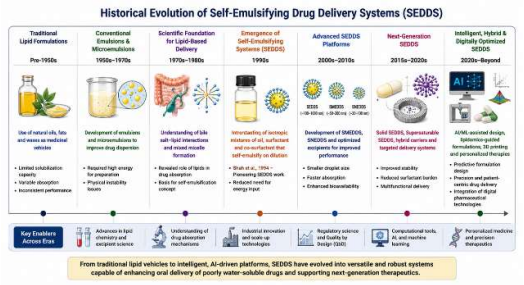
The next major phase in SEDDS evolution involved addressing limitations associated with high surfactant concentrations and liquid dosage forms. Supersaturable SEDDS (S-SEDDS) were developed to reduce surfactant requirements while maintaining high levels of drug solubilization through the incorporation of precipitation inhibitors. Simultaneously, extensive efforts were directed toward converting liquid SEDDS into solid dosage forms through techniques such as adsorption onto porous carriers, spray drying, freeze drying, melt granulation, and hot-melt extrusion. These developments led to the emergence of solid SEDDS, which combined the biopharmaceutical advantages of liquid systems with the stability, convenience, and scalability of conventional solid dosage forms [16–18].

The last decade has witnessed an unprecedented expansion in the scope and sophistication of SEDDS technology. Research has moved beyond traditional bioavailability enhancement toward multifunctional delivery platforms capable of addressing complex therapeutic challenges. Modern SEDDS have been investigated for the oral delivery of peptides, proteins, anticancer drugs, nucleic acid therapeutics, nutraceuticals, and phytopharmaceuticals. The incorporation of mucoadhesive polymers, targeting ligands, stimuli-responsive materials, and nanostructured carriers has further broadened their therapeutic applications [19,20].

Recent developments have been strongly influenced by advances in digital technologies and data-driven pharmaceutical development. The integration of Quality by Design (QbD), Design of Experiments (DoE), artificial intelligence (AI), machine learning, molecular modeling, and computational simulation has transformed the formulation development process. These tools facilitate rational excipient selection, prediction of formulation behavior, optimization of critical quality attributes, and acceleration of product development timelines [21,22]. Emerging research has also highlighted the role of lipidomics-guided excipient selection and computationally optimized self-emulsifying systems in improving formulation efficiency and translational success.

An important contemporary milestone is the evolution of SEDDS toward personalized and digitally manufactured pharmaceutical products. Recent studies by Obaiah, Ugandar, Badarinath, and Rao emphasized the growing importance of supersaturable formulations, hybrid lipid systems, three-dimensional (3D) printing technologies, and computationally optimized SEDDS in supporting precision medicine and individualized drug therapy [22]. These advances signify a transition from conventional solubilization platforms to intelligent, patient-centric drug delivery systems capable of meeting the demands of modern healthcare as represented in Figure 2.

Figure 2. Historical evolution of Self-Emulsifying Drug Delivery Systems (SEDDS) from conventional lipid formulations to modern intelligent, hybrid, and digitally optimized drug delivery platforms.



Overall, the historical progression of SEDDS reflects a continuous effort to overcome biopharmaceutical barriers associated with poorly water-soluble drugs. From early lipid formulations and microemulsions to advanced nano-enabled, AI-assisted, and personalized delivery platforms, SEDDS have undergone remarkable transformation. This evolution has established SEDDS as one of the most versatile and commercially successful lipid-based technologies in contemporary pharmaceutical science, with considerable potential for future innovation and clinical translation.

3. EVOLUTION OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS)

The evolution of Self-Emulsifying Drug Delivery Systems (SEDDS) represents one of the most significant advancements in lipid-based drug delivery. Since their introduction, SEDDS have undergone continuous transformation driven by the need to improve oral bioavailability, reduce formulation-related limitations, enhance patient compliance, and address increasingly complex therapeutic challenges. The progression from conventional self-emulsifying formulations to intelligent, digitally optimized, and personalized delivery systems reflects the integration of advances in colloidal science, nanotechnology, pharmaceutical engineering, computational modeling, and materials science.

The evolutionary pathway of SEDDS can be broadly classified into several developmental generations, each characterized by distinct formulation architectures, droplet size distributions, mechanisms of absorption enhancement, and therapeutic applications. These developments have collectively expanded the scope of SEDDS from simple solubilization systems to multifunctional platforms capable of targeted delivery, controlled release, and precision therapeutics [1–4] as represented in Table 3.

Table 3. Comparative Evolution of SEDDS Generations Highlighting Formulation Composition, Droplet Size Range, Principal

Advantages, Limitations, and Therapeutic Applications

SEDDS Generation	Typical Formulation Composition	Droplet Size Range After Dilution	Principal Advantages	Major Limitations	Representative Therapeutic Applications
Conventional SEDDS	Oils (long-chain or medium-chain triglycerides) and surfactants	Typically >200 nm	Improved drug solubilization; simple formulation design; ease of manufacturing; enhanced oral absorption compared with conventional dosage forms	Larger droplet size; lower interfacial surface area; variable absorption; limited control over drug release	Lipophilic small-molecule drugs, immunosuppressants, retinoids, antifungal agents
Self-Microemulsifying Drug Delivery Systems (SMEDDS)	Oils, high-HLB surfactants, and co-surfactants	Generally <100 nm	Rapid self-emulsification; transparent dispersions; enhanced dissolution and absorption; improved formulation stability	Higher surfactant requirement; potential gastrointestinal irritation at elevated surfactant levels	Antihypertensive drugs, antifungal agents, anti-inflammatory drugs, antidiabetic compounds
Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)	Optimized oils, surfactants, co-surfactants, and co-solvents	Approximately 20–200 nm	Very high surface area; improved permeability; enhanced lymphatic transport; superior bioavailability; reduced pharmacokinetic variability	Formulation complexity; stability concerns during long-term storage; potential excipient compatibility issues	Anticancer drugs, antiviral agents, immunosuppressants, CNS therapeutics, poorly soluble APIs
Supersaturable SEDDS (S-SEDDS)	Conventional SEDDS components combined with precipitation inhibitors (e.g., HPMC, PVP,	Variable, depending on formulation	Reduced surfactant burden; maintenance of transient supersaturation; improved safety profil	Risk of precipitation during gastrointestinal transit; complex optimization requi	Highly lipophilic drugs, BCS Class II compounds, high-dose poorly soluble molecules

	Soluplus ®)		e; enhanced drug loading	rements	
Solid SEDDS	Liquid SEDDS adsorbed or converted into solid carriers using adsorption, spray drying, freeze drying, melt granulation, or hot-melt extrusion	Reconstitutes to original droplet size upon dilution	Improved physical stability; enhanced patient compliance; ease of handling and storage; industrial scalability	Additional manufacturing steps; potential reduction in drug loading; excipient compatibility challenges	Tablets, capsules, pellets, sachets, oral solid dosage forms
Mucoadhesive SEDDS	SEDDS combined with mucoadhesive polymers such as chitosan, carbopol, alginate, or HPMC	Variable	Increased gastrointestinal residence time; enhanced mucosal contact; improved absorption efficiency	Potential alteration of emulsification behavior; formulation complexity	Peptide delivery, protein delivery, intestinal-targeted therapy
Targeted SEDDS	SEDDS modified with ligands, antibodies, peptides, aptamers, or receptor-specific molecules	Variable	Site-specific drug delivery; improved therapeutic selectivity; reduced systemic toxicity	Complex manufacturing; regulatory challenges; higher development cost	Oncology, inflammatory disorders, CNS diseases, precision therapeutics
Hybrid SEDDS	Combination of SEDDS with polymers, nanoparticles, liposomes, nanostructured lipid carriers, or other advanced materials	Variable, often nano-sized	Multifunctional delivery; controlled release; improved stability; enhanced therapeutic efficacy	Increased formulation complexity; scale-up challenges	Cancer therapy, gene delivery, peptide therapeutics, advanced drug delivery systems
AI-Assisted and Digital SEDDS	Computationally optimized formulations incorporating QbD,	Formulation-dependent	Accelerated formulation development; predictive optimization;	Dependence on high-quality datasets; need for model	Personalized medicine, precision drug delivery, next-generation pharmaceutic

	DoE, AI, machine learning, and predictive modeling tools		reduced experimental burden; enhanced robustness	validation and regulatory acceptance	al development

Abbreviations: SEDDS, Self-Emulsifying Drug Delivery Systems; SMEDDS, Self-Microemulsifying Drug Delivery Systems; SNEDDS, Self-Nanoemulsifying Drug Delivery Systems; S-SEDDS, Supersaturable Self-Emulsifying Drug Delivery Systems; HPMC, Hydroxypropyl Methylcellulose; PVP, Polyvinylpyrrolidone; HLB, Hydrophilic–Lipophilic Balance; CNS, Central Nervous System; QbD, Quality by Design; DoE, Design of Experiments; AI, Artificial Intelligence; API, Active Pharmaceutical Ingredient.

3.1 Conventional SEDDS

Conventional Self-Emulsifying Drug Delivery Systems represent the earliest generation of self-emulsifying formulations. These systems typically consist of oils and surfactants capable of forming coarse oil-in-water emulsions upon dilution in gastrointestinal fluids under gentle agitation provided by gastric motility [5].

The primary objective of conventional SEDDS was to maintain poorly water-soluble drugs in a dissolved state during gastrointestinal transit, thereby improving dissolution and absorption. Most early formulations utilized triglycerides, fatty acid esters, and non-ionic surfactants to facilitate spontaneous emulsification. Although these systems significantly improved bioavailability compared with conventional dosage forms, their performance was often limited by relatively large droplet sizes, incomplete dispersion, and variable absorption profiles [6].

Despite these limitations, conventional SEDDS established the fundamental principles of self-emulsification and demonstrated the feasibility of lipid-based bioavailability enhancement. Numerous early formulations of cyclosporine, retinoids, antifungal agents, and immunosuppressants successfully utilized this approach [7].

Key Characteristics of Conventional SEDDS

- Droplet size typically greater than 200 nm.
- Simple formulation architecture.
- Improved drug solubilization.
- Relatively easy manufacturing process.
- Limited droplet size control.

3.2 Self-Microemulsifying Drug Delivery Systems (SMEDDS)

The development of Self-Microemulsifying Drug Delivery Systems (SMEDDS) represented a major advancement in self-emulsifying technology. SMEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form transparent or translucent microemulsions upon dilution in aqueous media [8].

Compared with conventional SEDDS, SMEDDS generate significantly smaller droplets, generally below 100 nm, resulting in enhanced surface area and improved drug dissolution. The incorporation of co-surfactants reduces interfacial tension and increases interfacial flexibility, facilitating spontaneous formation of thermodynamically stable microemulsions [9].

The superior performance of SMEDDS has led to extensive investigation for oral delivery of antihypertensive agents, antifungal drugs, antidiabetic medications, anti-inflammatory compounds, and anticancer therapeutics. Their ability to enhance dissolution while maintaining physical stability has made SMEDDS one of the most widely studied lipid-based drug delivery systems [10].

Advantages of SMEDDS

- Rapid self-emulsification.
- Enhanced thermodynamic stability.
- Improved drug release.
- Greater absorption efficiency.
- Reduced food effects.

3.3 Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)

The emergence of nanotechnology in pharmaceutical sciences led to the development of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), which represent one of the most significant advances in SEDDS evolution. SNEDDS generate Nano-sized droplets typically ranging from 20 to 200 nm following aqueous dilution [11].

The reduced droplet size substantially increases interfacial surface area, promoting rapid drug release and enhanced membrane interaction. Furthermore, Nano-sized droplets exhibit improved kinetic stability and facilitate absorption through multiple mechanisms, including increased membrane permeability and enhanced lymphatic transport [12].

Numerous studies have demonstrated superior pharmacokinetic performance of SNEDDS compared with conventional formulations. Enhanced bioavailability has been reported for anticancer agents, antiretroviral drugs, antidiabetic compounds, immunosuppressants, and central nervous system therapeutics formulated as SNEDDS [13].

Distinctive Features of SNEDDS

- Nano-scale droplet formation.
- Enhanced dissolution rate.
- Improved permeability.
- Greater lymphatic transport potential.

- Reduced variability in absorption.

3.4 Supersaturable SEDDS (S-SEDDS)

Although conventional SEDDS, SMEDDS, and SNEDDS effectively improve drug solubilization, many formulations require high surfactant concentrations to maintain stability. Excessive surfactant levels may result in gastrointestinal irritation, toxicity concerns, and regulatory challenges. These limitations led to the development of Supersaturable Self-Emulsifying Drug Delivery Systems (S-SEDDS) [14].

S-SEDDS incorporate precipitation inhibitors such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and Soluplus® to maintain transient supersaturation following dilution. The generated supersaturated state increases the concentration gradient across the intestinal membrane and facilitates enhanced absorption before drug precipitation occurs [15].

This strategy enables significant reduction in surfactant content while preserving bioavailability enhancement. Consequently, S-SEDDS have become an important area of research for highly lipophilic and poorly soluble compounds [16].

Benefits of S-SEDDS

- Reduced surfactant concentration.
- Improved safety profile.
- Enhanced absorption efficiency.
- Better patient tolerability.
- Increased drug loading capacity.

3.5 Intelligent and Hybrid SEDDS

The next phase in SEDDS evolution involves the development of multifunctional and intelligent delivery systems capable of performing beyond simple solubilization enhancement. Hybrid SEDDS integrate lipid-based formulations with polymers, nanoparticles, liposomes, nanostructured lipid carriers, and stimuli-responsive materials to achieve enhanced therapeutic performance [17].

Mucoadhesive SEDDS represent one example of intelligent systems designed to prolong gastrointestinal residence time and improve absorption. Similarly, targeted SEDDS incorporate ligands, peptides, antibodies, or receptor-specific molecules capable of directing drugs toward specific tissues or pathological sites [18].

Hybrid formulations have demonstrated improved efficacy in cancer therapy, inflammatory disorders, peptide delivery, and central nervous system diseases. By combining multiple drug delivery mechanisms within a single platform, these systems offer enhanced therapeutic precision and reduced systemic toxicity [19].

Emerging Intelligent Features

- Targeted delivery capability.
- Mucoadhesion.
- Stimuli responsiveness.
- Controlled release.
- Enhanced tissue specificity.

3.6 Digital and AI-Assisted SEDDS

The most recent stage in SEDDS evolution is characterized by the integration of digital technologies, computational modeling, artificial intelligence (AI), machine learning (ML), and advanced manufacturing approaches. These technologies are fundamentally changing formulation development from an empirical process to a predictive and data-driven discipline [20].

Artificial intelligence algorithms are increasingly employed to predict drug–excipient compatibility, optimize formulation composition, identify critical material attributes, and establish robust design spaces. Machine learning models facilitate analysis of large formulation datasets and improve prediction of physicochemical performance, thereby reducing development timelines and experimental burden [21].

Recent investigations have also highlighted the growing role of computationally optimized SEDDS and digital pharmaceutical manufacturing. Obaiah, Ugandar, Badarinath, and Rao emphasized the potential of AI-assisted formulation development, hybrid lipid systems, supersaturated formulations, and additive manufacturing technologies to drive the next generation of self-emulsifying drug delivery systems [22].

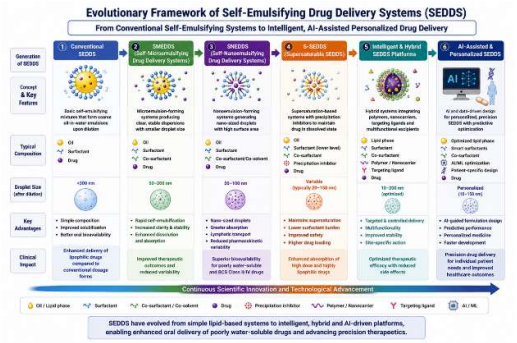
Three-dimensional (3D) printing technologies are particularly promising because they enable patient-specific dosage forms with customizable drug loading, release profiles, and therapeutic regimens. Combined with AI-driven optimization and continuous manufacturing technologies, these innovations support the broader transition toward precision medicine and personalized pharmaceutical care [22].

Future-Oriented Features

- AI-assisted formulation design.
- Machine learning optimization.
- Digital twin technology.
- Predictive modeling.
- 3D-printed personalized formulations.
- Continuous manufacturing systems.

The evolution of SEDDS demonstrates a remarkable transition from relatively simple lipid formulations to highly sophisticated drug delivery platforms incorporating nanotechnology, computational intelligence, and precision medicine concepts. This progression continues to expand the therapeutic potential of lipid-based systems and positions SEDDS as a key technology for addressing current and future challenges in oral drug delivery as represented in Figure 3.

Figure 3. Evolutionary framework of SEDDS illustrating the transition from conventional self-emulsifying systems to SMEDDS, SNEDDS, supersaturable formulations, intelligent hybrid platforms, and AI-assisted personalized drug delivery systems.



4. DISCUSSION

The development of Self-Emulsifying Drug Delivery Systems (SEDDS) represents a significant advancement in lipid-based drug delivery, driven by the need to overcome poor aqueous solubility and limited oral bioavailability of modern drug candidates. Historical evidence demonstrates that the understanding of lipid digestion, emulsification phenomena, and gastrointestinal absorption mechanisms provided the scientific foundation for the emergence of self-emulsifying formulations. The successful transition from conventional lipid vehicles to self-emulsifying systems established an effective strategy for maintaining poorly water-soluble drugs in a solubilized state and improving their absorption.

The evolution of SEDDS has been characterized by continuous technological refinement. Conventional SEDDS laid the foundation for spontaneous emulsification, while subsequent development of SMEDDS and SNEDDS enabled the generation of smaller droplets, enhanced dissolution, improved intestinal permeation, and superior bioavailability. Further advancements led to the introduction of supersaturable SEDDS, which reduced surfactant dependence while maintaining drug super saturation and absorption efficiency. More recently, hybrid and intelligent SEDDS have incorporated functionalities such as mucoadhesion, targeting capability, controlled release, and multifunctional therapeutic performance.

A major trend in contemporary SEDDS research is the integration of advanced technologies including artificial intelligence, machine learning, computational modeling, Quality by Design (QbD), and additive manufacturing. These approaches are transforming formulation development from an empirical process into a predictive, data-driven discipline capable of accelerating optimization and improving translational success. In parallel, the emergence of personalized and digitally manufactured SEDDS reflects the growing importance of precision medicine in pharmaceutical development.

Overall, the historical progression and technological evolution of SEDDS demonstrate their transformation from simple solubilisation systems into sophisticated multifunctional drug delivery platforms. Their versatility, adaptability, and ability to integrate emerging technologies position SEDDS as one of the most promising approaches for addressing current and future challenges in oral drug delivery and pharmaceutical innovation.

5. CONCLUSION

Self-Emulsifying Drug Delivery Systems (SEDDS) have evolved into a highly effective lipid-based platform for improving the oral delivery of poorly water-soluble drugs. Through continuous advancements from conventional SEDDS to SMEDDS, SNEDDS, supersaturable, solid, hybrid, and intelligent systems, these formulations have significantly enhanced drug solubilisation, absorption, and bioavailability. Their ability to overcome multiple biopharmaceutical barriers has expanded their application across a wide range of therapeutic areas.

Recent innovations involving advanced excipients, nanotechnology, Quality by Design (QbD), artificial intelligence, machine learning, and digital manufacturing have further strengthened the potential of SEDDS as next-generation drug delivery systems. Despite challenges related to stability, excipient safety, regulatory acceptance, and large-scale manufacturing, ongoing research continues to address these limitations.

Overall, SEDDS represent a versatile and continuously advancing technology with considerable potential for future pharmaceutical development. The integration of personalized medicine, computational formulation design, and emerging manufacturing technologies is expected to further enhance their clinical and commercial significance, ensuring their important role in the delivery of future therapeutic agents.

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