Available online on 15.02.2026 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Check for updates

Review Article

Self-Nanoemulsifying Drug Delivery Systems in Soft Gelatin Capsules: Formulation Advances, Manufacturing Challenges, and Future Perspectives

Chinna Reddy Palem [1]*, Praveen Rao Balguri [2], Nishanth Kumar Nagamalli [1], Vamsi Krishna Lekkala [2], Sridhar Gumudevelli [2]

[1] R&D, Asphar Research Labs Pvt. Ltd., IDA, Balanagar, Hyderabad-500037; Telangana, India.

[2] Ascent Pharmaceuticals Inc., 400S.Technology Drive, Central Islip, NY 11722. USA.

Article Info:

Article History:

Received 17 Nov 2025
Reviewed 27 Dec 2025
Accepted 20 Jan 2026
Published 15 Feb 2026

Cite this article as:

Palem CR, Balguri PR, Nagamalli NK, Lekkala VK, Gumudevelli S, Self-Nanoemulsifying Drug Delivery Systems in Soft Gelatin Capsules: Formulation Advances, Manufacturing Challenges, and Future Perspectives, Journal of Drug Delivery and Therapeutics. 2026; 16(2):10-21 *DOI: http://dx.doi.org/10.22270/jddt.v16i2.7546*

For Correspondence:

Dr. Palem Chinna Reddy, Asphar Research Labs Pvt. Ltd., 3rd Floor, Plot No. 47, Industrial Development Area, Balanagar, Hyderabad - 500037, Telangana, India.

Abstract

Poor aqueous solubility remains a major barrier to the successful oral delivery of a large proportion of newly discovered drug candidates, often resulting in low and variable bioavailability. Self-nanoemulsifying drug delivery systems (SNEDDS) have emerged as a robust formulation strategy to address these limitations by forming fine oil-in-water nanoemulsions upon mild agitation in gastrointestinal fluids. When incorporated into soft gelatin capsules, SNEDDS offer additional advantages, including accurate dose delivery, improved patient compliance, and enhanced protection of labile drug substances. This review provides a comprehensive overview of self-nanoemulsifying formulations specifically designed for soft gelatin capsule filling, with emphasis on formulation principles, excipient selection, and critical quality attributes governing performance. Key aspects of SNEDDS characterization, encompassing physicochemical, in vitro, and in vivo evaluation techniques, are discussed in relation to capsule compatibility, stability, and biopharmaceutical behavior. Furthermore, industrial manufacturing considerations, scale-up challenges, and regulatory expectations relevant to SNEDDS-filled soft gelatin capsules are critically examined. Current limitations, such as capsule shell interactions, precipitation risks, and long-term stability concerns, are highlighted alongside emerging technological advances, including supersaturable systems, lipid-based excipient innovations, and predictive in vitro-in vivo correlation approaches. Overall, this review underscores the evolving role of SNEDDS in soft gelatin capsule dosage forms and outlines future prospects for their expanded application in improving the oral delivery of poorly soluble drugs.

Keywords: Self-nanoemulsifying drug delivery; Soft gelatin capsules; Nano emulsions; Stability and Regulatory considerations

INTRODUCTION

Oral administration continues to be the most preferred route for drug delivery due to its convenience, safety, cost-effectiveness, and high level of patient adherence[1,2]. Nevertheless, the therapeutic success of oral dosage forms is increasingly challenged by the poor aqueous solubility of a substantial proportion of modern drug candidates. It is widely recognized that more than 50% of newly discovered small-molecule drugs exhibit low water solubility, which frequently results in inadequate dissolution in gastrointestinal (GI) fluids, erratic absorption, and low or highly variable oral bioavailability[3,4]. These limitations are especially evident for drugs categorized under Biopharmaceutical Classification System (BCS) classes II and IV, where solubility is a critical rate-limiting step for systemic absorption [5].

Traditional formulation strategies employed to enhance oral bioavailability including salt formation, particle size reduction, use of cosolvents, permeation enhancers, and cyclodextrin inclusion complexes have demonstrated limited and drug-dependent success[6]. Many of these approaches are constrained by formulation instability, scalability challenges, or restricted applicability across diverse chemical entities. Consequently, the pharmaceutical research community has increasingly shifted its focus toward advanced drug delivery systems capable of sustaining drugs in a solubilized state throughout GI transit. In this regard, lipid-based drug delivery systems have emerged as a particularly promising platform, supported by clinical evidence that co-administration of lipophilic drugs with lipid-rich meals can significantly enhance their oral absorption[7]. The primary objective of lipid-based formulations is to maintain drug solubilization within the GI milieu, thereby improving absorption efficiency and minimizing inter- and intra-patient variability [8].

Among the various lipid-based delivery technologies, self-nanoemulsifying drug delivery systems (SNEDDS) have attracted substantial interest as a versatile and effective approach for improving the oral performance of poorly soluble drugs. SNEDDS are isotropic, thermodynamically stable mixtures comprising oils, surfactants, and co-surfactants or cosolvents that spontaneously form fine oil-in-water nanoemulsions upon exposure to aqueous environments under mild agitation, such as that encountered in the GI tract [9, 10]. The nanoemulsions generated typically possess droplet sizes below 200 nm, providing an extensive interfacial surface area that facilitates rapid drug release, enhanced dissolution, and improved absorption. The self-emulsification process is driven by favorable thermodynamic conditions, wherein the entropy gain associated with dispersion surpasses the energy required to create new interfacial surfaces [10].

A key advantage of SNEDDS lies in their formulation flexibility, allowing the selection and optimization of a broad range of lipid excipients, including medium- and long-chain triglycerides and non-ionic surfactants, to tailor drug solubility, stability, and absorption characteristics. Beyond improving dissolution behavior, SNEDDS have been shown to mitigate drug degradation within the GI tract, modulate intestinal membrane permeability, and in certain cases facilitate lymphatic transport, thereby reducing first-pass hepatic metabolism. These multifaceted mechanisms have contributed to the successful clinical translation and commercialization of several self-emulsifying and self-nanoemulsifying formulations, highlighting their industrial relevance and therapeutic potential [11, 12].

Soft gelatin capsules represent an established and highly suitable dosage form for the delivery of liquid and semi-solid SNEDDS. Encapsulation within soft gelatin shells enables accurate dose uniformity, enhances patient acceptability, and protects sensitive formulations from environmental factors such as moisture, oxygen, and light. Additionally, soft gelatin capsules offer practical advantages including ease of swallowing, rapid disintegration, and compatibility with high-throughput industrial manufacturing processes. Despite these benefits, the incorporation of SNEDDS into soft gelatin capsules introduces formulation-specific challenges, including potential interactions between fill components and the gelatin shell, risks of drug precipitation upon dilution, and concerns related to long-term physical and chemical stability [13, 14].

Although extensive literature exists on the development and application of SNEDDS for oral drug delivery, comparatively limited attention has been devoted to their integration with soft gelatin capsule technology, where formulation design, characterization, manufacturing, and regulatory considerations converge. In this context, the present review aims to provide a comprehensive and critical overview of self-nanoemulsifying formulations intended for soft gelatin capsules. Emphasis is placed on formulation principles, excipient selection, and critical quality attributes influencing product performance [15]. Furthermore, key challenges associated with capsule compatibility, stability, scale-up, and regulatory compliance are discussed alongside emerging innovations such as supersaturable SNEDDS, advanced lipid excipients, and predictive in vitro–in vivo correlation strategies. Collectively, this review highlights the evolving role of SNEDDS-filled soft gelatin capsules and their future prospects in addressing solubility-limited oral drug delivery.

FUNDAMENTALS AND FORMULATION COMPONENTS OF SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEMS

SNEDDS are lipid-based formulations developed to enhance the oral bioavailability of poorly water-soluble drugs by enabling spontaneous formation of fine oil-in-water nanoemulsions within the gastrointestinal (GI) tract. Upon exposure to aqueous media under mild agitation provided by GI motility, isotropic mixtures of oils, surfactants, and co-surfactants or co-solvents undergo self-nanoemulsification, a thermodynamically driven process characterized by marked reduction in interfacial tension and a favorable entropy gain. This results in the rapid generation of Nano-sized droplets, typically below 200 nm, without the need for external energy input. The resulting nanoemulsions provide a large interfacial surface area, promoting rapid drug release, enhanced dissolution, and improved absorption. The Type I–IV classification system provides a mechanistic link between formulation composition, dispersion behavior, and in vivo performance **Table 1**. SNEDDS are commonly positioned within the Type III category of lipid-based formulations under the Type I–IV classification system, which correlates formulation composition with the most favorable balance between solubilization efficiency, dispersion stability, and bioavailability, making it particularly suitable for soft gelatin capsule based delivery of poorly water-soluble drugs [16, 17]. Compared with conventional oral dosage forms, SNEDDS offer distinct advantages, including improved solubilization of lipophilic drugs, reduced food-effect variability, protection against chemical and enzymatic degradation, and potential enhancement of lymphatic transport, thereby mitigating first-pass metabolism. Mechanism of self-nanoemulsification and the transformation of an isotropic SNEDDS into a nanoemulsion upon GI dilution is schematically illustrated in **Figure 1**.

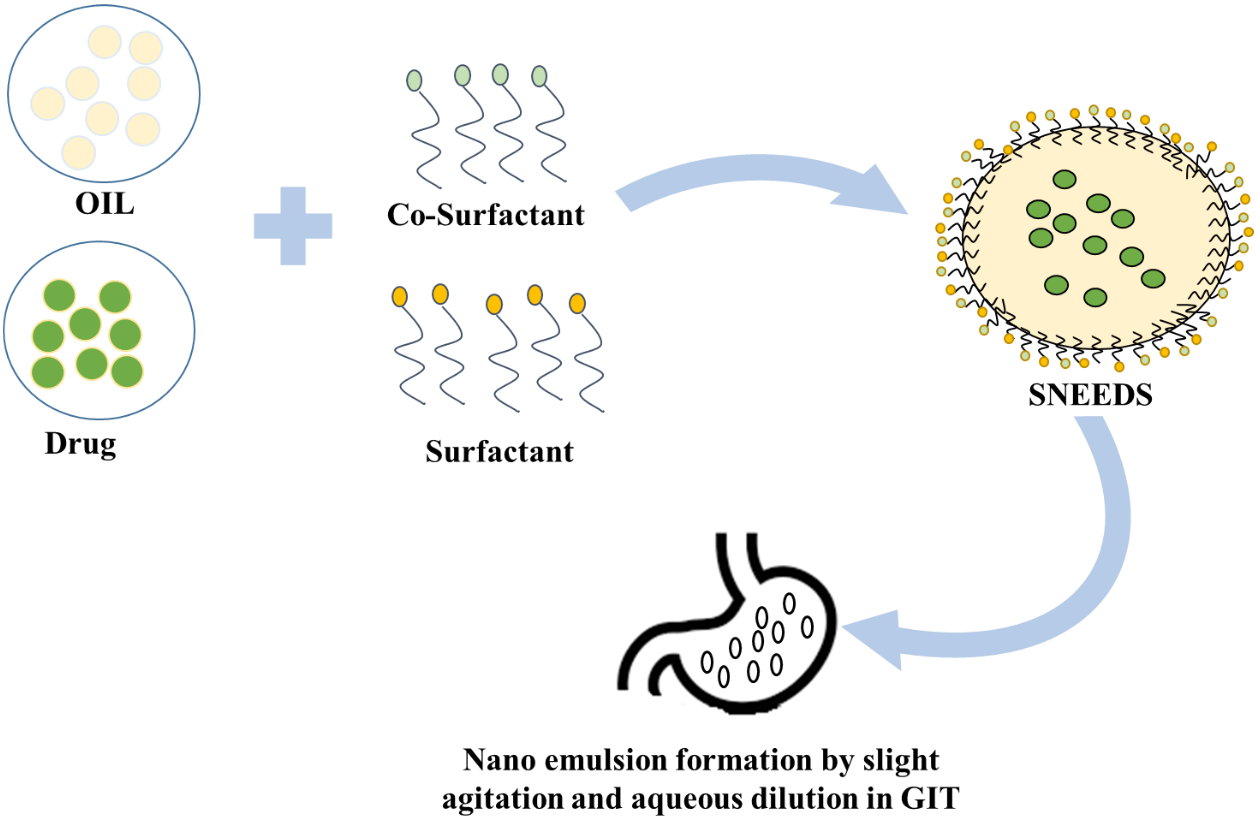

Figure 1: Illustrates the mechanism of self-Nano emulsification and the transformation of an isotropic SNEDDS into a nanoemulsion upon GI dilution

The performance of SNEDDS is critically dependent on rational selection and optimization of formulation components. **Table 2** summarizes the key components of SNEDDS, their functional roles, commonly used examples, and selection criteria. The oil phase serves as the primary solubilizing medium for lipophilic drugs, with medium-chain triglycerides generally providing superior solvent capacity and rapid emulsification, while long-chain triglycerides may facilitate lymphatic uptake and sustained absorption. Surfactants, preferably non-ionic due to their favorable safety profile, play a central role in reducing interfacial tension and stabilizing nanoemulsion droplets; their selection is guided by hydrophilic lipophilic balance (HLB) considerations to favor oil-in-water systems. Co-surfactants enhance interfacial film flexibility and emulsification efficiency, whereas co-solvents and solubilizers improve drug loading but must be carefully optimized to minimize precipitation risk upon aqueous dilution. Key nanoemulsion characteristics, including droplet size, polydispersity index (PDI), and zeta potential, are critical quality attributes influencing stability and biopharmaceutical performance. Systematic drug–excipient compatibility assessment, incorporating solubility screening, pseudo-ternary phase diagram construction, and physicochemical interaction studies, is essential for identifying robust self-nanoemulsifying regions and ensuring formulation stability [17, 18]. **Figure 2** illustrates the Type I–III categories of the Type I–IV lipid formulation classification system and delineates the roles of individual SNEDDS components in nanoemulsion formation, thereby supporting rational formulation development for oral drug delivery applications.

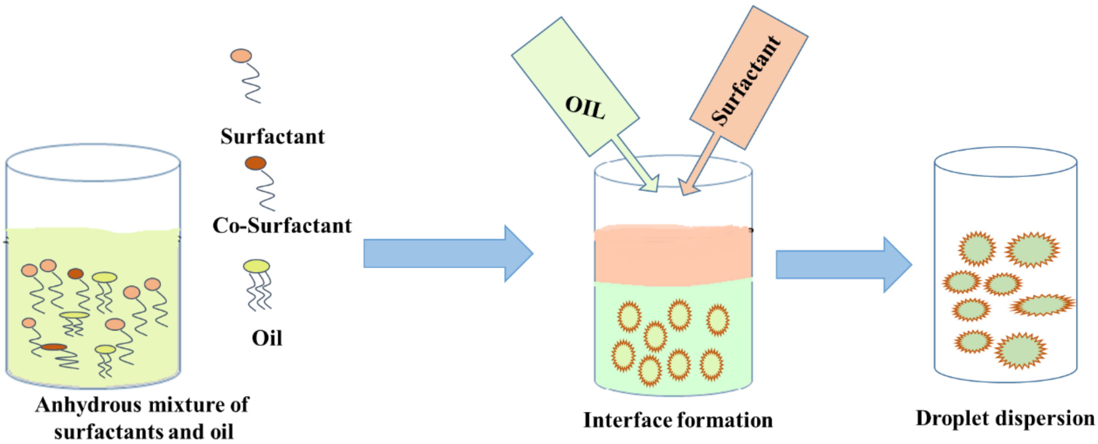

Figure 2: Type I–III Lipid Formulation Classification and Roles of SNEDDS Components in Nanoemulsion Formation

Table 1: Classification of Lipid-Based Drug Delivery Systems (Type I–IV)

Formulation type	Composition	Aqueous Dispersibility	Mechanism of drug release	Droplet size after dispersion	Advantages	Limitations	Representative systems / Relevance
Type I (Lipid Solutions)	Oils only (long-chain triglycerides, mixed glycerides); no surfactants	Poor; no spontaneous emulsification	Requires enzymatic digestion by pancreatic lipases; drug incorporated into mixed micelles	Not applicable (no emulsion formed initially)	High biocompatibility; simple composition; suitable for highly lipophilic drugs	Slow and variable absorption; highly dependent on digestion and bile secretion	Early lipid formulations; limited use in modern oral delivery
Type II (SEDDS)	Oils and lipophilic surfactants (low–medium HLB)	Moderate; forms coarse emulsions	Spontaneous emulsification followed by digestion-assisted solubilisation	Typically >200 nm	Faster dispersion than Type I; improved bioavailability	Larger droplet size still digestion dependent; limited dissolution enhancement	Self-emulsifying drug delivery systems (SEDDS)
Type IIIA	Higher oil content, hydrophilic surfactants and limited co-solvents	Good; forms fine emulsions	Rapid emulsification with partial digestion involvement	~100–250 nm	Balanced oil–surfactant composition; improved solubilisation	Moderate risk of precipitation upon dilution	Transitional systems between SEDDS and SNEDDS
Type IIIB (SNEDDS)	Lower oil content, high hydrophilic surfactants, co-surfactants/ co-solvents	Excellent; forms Nano emulsions	Spontaneous Nano emulsification; minimal dependence on digestion	<200 nm (often <100 nm)	High surface area; rapid dissolution; enhanced bioavailability; reduced food effect	High surfactant levels may cause GI irritation; precipitation risk if poorly designed	Self-nanoemulsifying drug delivery systems (SNEDDS); widely used in soft gelatin capsules
Type IV (Surfactant Systems)	Hydrophilic surfactants, co-solvents; no oil	Very high; clear dispersions	Solubilisation via micellar systems only	Micellar (<50 nm)	High drug solubilisation in formulation	High risk of drug precipitation after dilution; GI toxicity concerns	Limited standalone use; mainly for screening or hybrid systems

Table 2: Basic Components of SNEDDS Formulations

Component	Primary Role in SNEDDS	Commonly Used Examples	Selection Criteria	Formulation Remarks
Drug (Active Pharmaceutical Ingredient)	Therapeutic agent; must remain solubilized after dilution	BCS Class II & IV drugs (e.g., cyclosporine, ritonavir, curcumin, paclitaxel)	Lipophilicity (log P), dose, melting point, chemical stability	Drugs with high lipophilicity and low dose are ideal; precipitation risk must be evaluated upon aqueous dilution
Oil Phase	Solubilizes lipophilic drug; facilitates lymphatic transport	Medium-chain triglycerides (Capryol®, Miglyol® 812), Long-chain triglycerides (soybean oil, corn oil), Mixed glycerides (Maisine®, Labrafac®)	Drug solubility, digestion behavior, emulsification efficiency	MCTs provide faster emulsification; LCTs enhance lymphatic uptake but may slow dispersion
Surfactant	Reduces interfacial tension; stabilizes nanoemulsion droplets	Nonionic surfactants, Cremophor® EL, Kolliphor® RH40, Tween® 80, Labrasol®	High HLB value (≥12), safety, regulatory acceptance	Nonionic surfactants preferred for low toxicity; high levels may cause GI irritation
Co-surfactant	Enhances interfacial film flexibility; reduces droplet size	Transcutol® P, Propylene glycol monocaprylate, Lauroglycol® 90	Compatibility with surfactant and oil; ability to improve spontaneity	Optimized surfactant:co-surfactant ratio critical for stable nanoemulsions
Co-solvent / Solubilizer	Improves drug loading and formulation homogeneity	PEG 400, Propylene glycol, Ethanol (limited use)	Drug solubilization capacity; volatility; capsule compatibility	Excessive use may cause drug precipitation after dilution and shell softening
Antioxidants (optional)	Prevent lipid oxidation and drug degradation	α-Tocopherol, BHT, BHA	Oxidation sensitivity of oil/drug	Required for unsaturated oils to ensure long-term stability
Precipitation Inhibitors (optional)	Maintain supersaturation after dilution	HPMC, PVP, Soluplus®	Drug crystallization tendency	Commonly used in supersaturable SNEDDS (s-SNEDDS)
Capsule Compatibility Additives (for soft gels)	Protect gelatin shell integrity	PEGs, plasticizer-compatible excipients	Gelatin interaction profile	Avoid hygroscopic and volatile components that may cause shell brittleness or leakage

CHALLENGES AND LIMITATIONS OF SNEDDS-BASED ORAL DELIVERY

Although SNEDDS have demonstrated significant potential in improving the oral bioavailability of poorly water-soluble drugs, several formulation-specific and physiological constraints continue to limit their broader applicability. A clear understanding of these limitations is essential for rational formulation development, risk assessment, and successful translation from laboratory to clinical use.

Drug loading capacity remains a fundamental challenge in SNEDDS design, particularly for drug candidates exhibiting limited solubility in lipid excipients. Drug incorporation within SNEDDS is largely dictated by the solubilization capacity of the selected oils, surfactants, and co-solvents. High-dose drugs or compounds with insufficient lipophilicity may exceed this capacity, resulting in metastable formulations that are prone to precipitation during storage or upon dilution. Attempts to increase drug loading by elevating surfactant or co-solvent concentrations may adversely affect formulation stability, gastrointestinal tolerability, and regulatory compliance. As a result, SNEDDS are most suitable for low- to moderate-dose drugs with favorable lipid solubility profiles.

Another major limitation is the risk of drug precipitation following dilution in the gastrointestinal tract. Upon oral administration, SNEDDS encounter extensive aqueous dilution, which can substantially reduce their solvent capacity, particularly in formulations rich in hydrophilic surfactants or co-solvents. This reduction may lead to rapid drug precipitation, thereby negating the solubility and bioavailability advantages of the system. The extent of precipitation is further modulated by physiological variables such as gastrointestinal pH, bile salt secretion, and intestinal motility. Although approaches such as supersaturable SNEDDS and incorporation of precipitation inhibitors have been investigated, maintaining a stable supersaturated state in vivo remains a persistent challenge.

Food dependent variability in drug absorption also represents a significant concern for SNEDDS-based formulations. Lipid-based systems are inherently influenced by the fed or fasted state, as food intake particularly high-fat meals can alter bile secretion, gastric emptying, and lipid digestion processes. While these effects may enhance drug absorption in some cases, they can also introduce pronounced inter- and intra-subject variability. Variations in meal composition and digestive physiology may lead to inconsistent nanoemulsion formation and drug solubilization, complicating dose optimization and clinical predictability. Minimizing food-related effects therefore remains an important formulation and regulatory objective.

Finally, the encapsulation of hydrophilic or unstable drugs poses a considerable technical limitation for SNEDDS. These systems are intrinsically tailored for lipophilic compounds, whereas hydrophilic drugs generally exhibit poor solubility in lipid matrices, resulting in low encapsulation efficiency and increased likelihood of drug expulsion upon dilution. In addition, chemically or physically labile drugs may undergo degradation within the lipid environment or interact adversely with surfactants and co-solvents. Although emerging strategies, including modified SNEDDS architectures, hybrid delivery systems, and stabilizing excipients, have been explored to broaden the applicability of SNEDDS, consistent and reliable delivery of hydrophilic or unstable molecules remains challenging [19].

DESIGN, OPTIMIZATION, AND SOFT GELATIN CAPSULES AS SNEDDS DELIVERY VEHICLES

The successful development of self-nanoemulsifying drug delivery systems (SNEDDS) is founded on a rational and systematic formulation design approach that integrates excipient selection, phase behavior analysis, and evaluation of self-emulsification performance **Figure 3**. Construction of pseudo-ternary phase diagrams represents a pivotal step in this process, as it delineates the compositional domains within which spontaneous nanoemulsification occurs upon aqueous dilution. By systematically varying the ratios of oil, surfactant, and co-surfactant or co-solvent, these diagrams facilitate identification of robust self-nanoemulsifying regions capable of forming fine and kinetically stable nanoemulsions under gastrointestinal conditions. Initial screening of candidate formulations is commonly performed through qualitative and semi-quantitative self-emulsification efficiency assessments, including visual observation, dispersibility grading, and turbidity measurements following dilution under mild agitation. Further optimization focuses on droplet size reduction strategies, such as fine-tuning surfactant concentration, optimizing surfactant-to-co-surfactant ratios, and selecting lipid excipients with favorable interfacial characteristics. These refinements are essential for achieving nanoemulsions with narrow size distributions, low polydispersity indices, and resilience to variations in dilution volume, pH, and ionic strength.

Ensuring the physical and thermodynamic stability of optimized SNEDDS is critical prior to dosage form development. Formulations are therefore subjected to rigorous thermodynamic stability testing, including centrifugation, heating cooling cycles, and freeze–thaw studies, to identify and eliminate systems susceptible to phase separation, creaming, or drug precipitation. Only formulations demonstrating robustness under these stress conditions are considered suitable for further development. Among the available oral dosage forms, soft gelatin capsules have emerged as a preferred delivery vehicle for liquid and semi-solid SNEDDS due to their ability to accommodate lipid-based fills, provide accurate dose uniformity, and enhance patient acceptability. Soft gelatin capsules are primarily composed of gelatin, plasticizers such as glycerol or sorbitol, water, and minor excipients, which collectively impart flexibility, mechanical strength, and rapid disintegration. The encapsulation process involves controlled filling of the SNEDDS formulation into gelatin shells, followed by sealing and drying under carefully regulated temperature and humidity to ensure shell integrity and product consistency.

Despite their advantages, the successful integration of SNEDDS into soft gelatin capsules necessitates thorough evaluation of fill shell compatibility. Interactions between SNEDDS components particularly low-molecular-weight surfactants and co-solvents and the gelatin shell may lead to plasticizer migration, moisture imbalance, shell softening or embrittlement, and, in severe cases, capsule leakage during storage. The type and concentration of shell plasticizers play a decisive role in maintaining capsule flexibility and long-term stability, as they influence water activity and susceptibility to excipient migration. Consequently, comprehensive compatibility assessments and long-term stability studies are indispensable to ensure the physicochemical integrity of both the SNEDDS fill and the gelatin shell throughout the product shelf life. Collectively, these design and optimization considerations form the foundation for the development of SNEDDS-filled soft gelatin capsules with reliable manufacturing performance, consistent quality attributes, and predictable in vivo behavior [20].

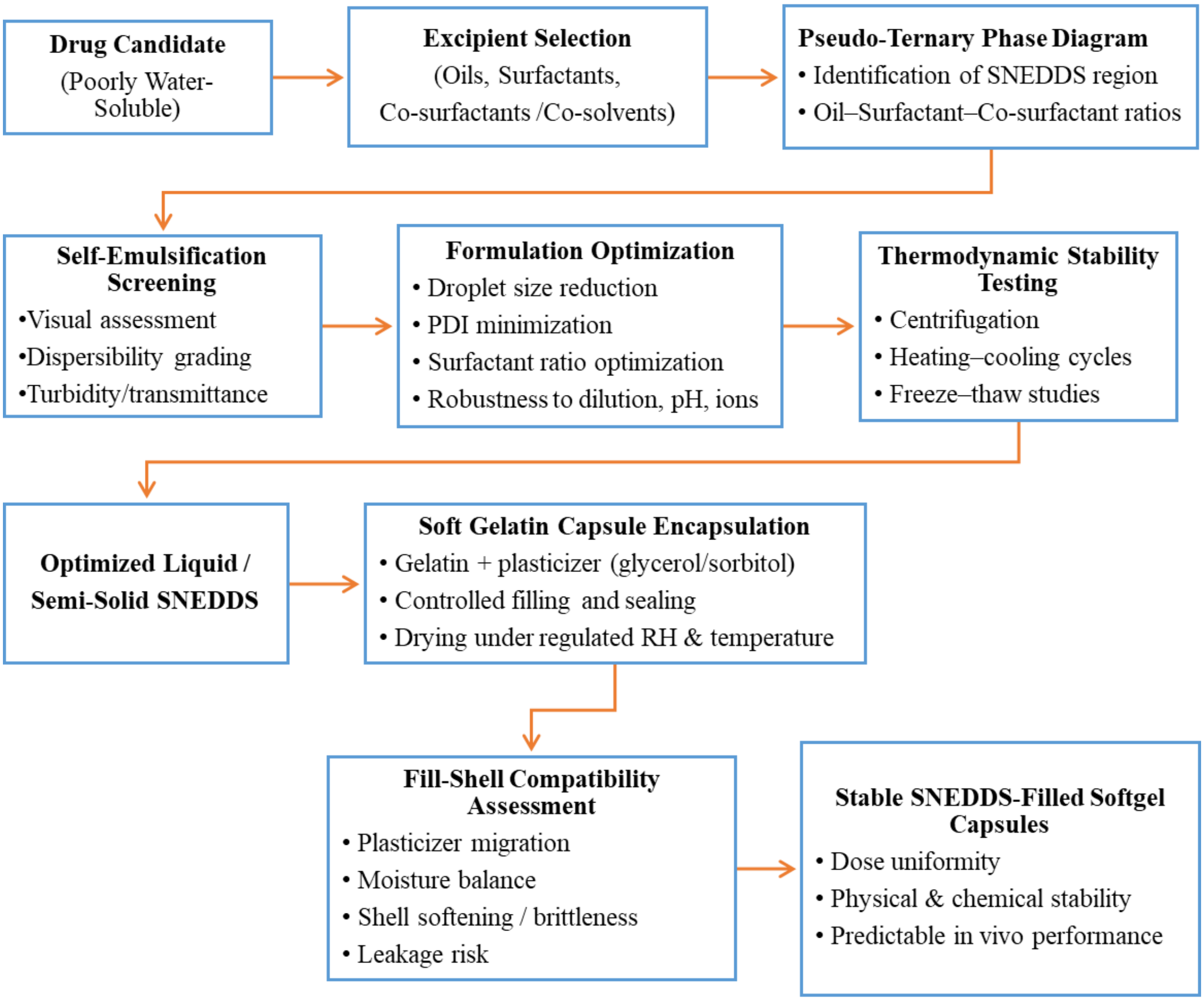

Figure 3: Schematic illustration of Design, Optimization, and Soft Gelatin Capsules as SNEDDS Delivery Vehicles

CHARACTERIZATION OF SNEDDS-FILLED SOFT GELATIN CAPSULES

Comprehensive characterization of SNEDDS encapsulated in soft gelatin capsules is essential to establish formulation performance, predict in vivo behavior, and ensure batch-to-batch reproducibility. The characterization strategy integrates evaluation of emulsification behavior, nanoemulsion physicochemical attributes, drug release performance, and intestinal permeation potential.

(i) In Vitro Emulsification and Dispersion Tests

In vitro emulsification and dispersion studies are performed to assess the ability of SNEDDS-filled soft gelatin capsules to rapidly and reproducibly form nanoemulsions under simulated gastrointestinal conditions. Typically, the capsule shell disintegration time is first evaluated in aqueous media or biorelevant dissolution fluids, followed by dispersion of the released SNEDDS under gentle agitation that mimics gastric and intestinal motility. Visual assessment, dispersibility grading, and turbidity or transmittance measurements are commonly employed to evaluate the rate and completeness of emulsification. Rapid formation of clear or slightly opalescent dispersions indicates efficient self-nanoemulsification, whereas delayed emulsification or phase separation suggests suboptimal formulation design. These tests provide early insight into the robustness of the SNEDDS system upon dilution and its suitability for oral administration.

(ii) Droplet Size, Zeta Potential, and Morphology

The physicochemical characteristics of the nanoemulsion formed after capsule dispersion play a critical role in drug absorption and stability. Droplet size and polydispersity index (PDI) are typically measured using dynamic light scattering techniques to assess the uniformity and reproducibility of the nanoemulsion. Smaller droplet sizes with narrow size distributions are associated with enhanced interfacial surface area and improved drug dissolution. Zeta potential measurements provide information on the surface charge and electrostatic stability of the droplets, which can influence aggregation behavior and shelf stability. In addition, morphological evaluation using transmission or scanning electron microscopy offers qualitative confirmation of droplet shape, size, and structural integrity. Together, these parameters serve as critical quality attributes for SNEDDS-filled soft gelatin capsules.

(iii) In Vitro dissolution and drug release kinetics

In vitro dissolution testing is employed to evaluate the drug release profile from SNEDDS-filled soft gelatin capsules and to compare performance against conventional dosage forms. Dissolution studies are commonly conducted using compendial apparatus with aqueous or biorelevant media that simulate fasted and fed state conditions. The release data are analyzed to determine dissolution rate, extent of drug release, and potential precipitation upon dilution. Application of drug release kinetic models aids in understanding the underlying release mechanisms and the influence of formulation variables. Enhanced and rapid drug release from SNEDDS formulations reflects effective maintenance of the drug in a solubilized state, which is critical for improving oral bioavailability of poorly water-soluble compounds [21].

(iv) Permeation and diffusion studies

Permeation and diffusion studies provide mechanistic insight into the ability of SNEDDS to enhance intestinal drug transport. In vitro models such as the parallel artificial membrane permeability assay (PAMPA) and Caco-2 cell monolayers are widely used to evaluate passive diffusion and cellular transport, respectively. These models help assess whether SNEDDS formulations improve membrane permeability through mechanisms such as increased drug solubilization, modulation of membrane fluidity, or surfactant-mediated effects. Permeation data are often correlated with droplet size, composition, and surfactant type to elucidate structure performance relationships. Such studies are particularly valuable for predicting in vivo absorption and supporting the development of in vitro-in vivo correlations for SNEDDS-filled soft gelatin capsules. Collectively, all these characterization approaches provide a comprehensive understanding of the performance, stability, and biopharmaceutical behavior of SNEDDS-filled soft gelatin capsules, thereby supporting their rational development and successful translation into clinically effective oral dosage forms [22].

IN VIVO PERFORMANCE, BIOAVAILABILITY, AND STABILITY CONSIDERATIONS OF SNEDDS-FILLED SOFT GELATIN CAPSULES

The in vivo performance of SNEDDS encapsulated in soft gelatin capsules is closely linked to their ability to maintain drug solubilization in the gastrointestinal tract and facilitate efficient absorption. Upon oral administration, SNEDDS rapidly disperse to form nanoemulsions that present the drug in a readily absorbable form. Enhanced absorption is primarily attributed to improved dissolution kinetics and increased interfacial surface area, which promote passive diffusion across the intestinal epithelium. In addition, certain lipid excipients particularly long-chain triglycerides can stimulate lymphatic transport, enabling partial bypass of first-pass hepatic metabolism. This absorption pathway is especially advantageous for highly lipophilic drugs and contributes to reduced interindividual variability and enhanced systemic exposure.

Pharmacokinetic evaluations consistently demonstrate that SNEDDS-filled soft gelatin capsules achieve superior oral bioavailability compared with conventional solid dosage forms such as tablets or hard gelatin capsules. Improvements are commonly reflected in higher maximum plasma concentrations (C_{max}), reduced time to reach peak concentration (T_{max}), and increased area under the plasma concentration time curve (AUC). Marketed and investigational SNEDDS-based softgel products have shown multiple-fold increases in bioavailability for poorly water-soluble drugs, underscoring the clinical relevance of this delivery platform. However, establishing a robust in vitro in vivo correlation (IVIVC) for SNEDDS remains challenging, as conventional dissolution tests may not fully capture the dynamic processes of nanoemulsion formation, lipid digestion, and bile-mediated solubilization that occur in vivo. As a result, predictive IVIVC development often requires biorelevant dissolution media and integrated in vitro and in silico modeling approaches [23, 24].

In parallel with biopharmaceutical performance, the physical and chemical stability of SNEDDS-filled soft gelatin capsules is a critical determinant of product quality and shelf life. Physical stability considerations include maintenance of nanoemulsion-forming ability, prevention of drug precipitation, and avoidance of phase separation during storage. Chemically, lipid excipients and drug substances may be susceptible to oxidation or hydrolysis, necessitating careful excipient selection and, in some cases, incorporation of antioxidants. Furthermore, shell soft-fill interactions represent a unique stability challenge for softgel-based SNEDDS.

Migration of low-molecular-weight surfactants or co-solvents into the gelatin shell can alter shell elasticity, leading to softening, brittleness, or leakage. These interactions are strongly influenced by water activity and pH, which affect gelatin crosslinking and moisture balance within the capsule. Consequently, strict control of formulation water content, shell composition, and environmental conditions is essential. Appropriate packaging and storage conditions, including moisture-barrier packaging and controlled temperature and humidity, play a pivotal role in preserving both capsule integrity and SNEDDS performance throughout the product's shelf life.

INDUSTRIAL, REGULATORY ASPECTS, AND COMMERCIAL PRODUCTS OF SNEDDS-BASED SOFT GELATIN CAPSULES

From an industrial perspective, the successful translation of SNEDDS into commercial soft gelatin capsule products **(Table 3)** depends strongly on manufacturing scalability and equipment considerations. SNEDDS are generally amenable to scale-up because they are isotropic liquid or semi-solid systems prepared using conventional mixing, heating, and homogenization equipment without the need for high-energy emulsification. However, precise control of processing parameters such as temperature, mixing speed, and order of excipient addition is essential to ensure batch-to-batch consistency. Integration of SNEDDS preparation with softgel encapsulation requires compatibility with rotary die or seamless capsule-filling technologies, as well as careful management of fill viscosity to avoid leakage, weight variation, or sealing defects at commercial production scales.

Compliance with Good Manufacturing Practice (GMP) standards presents additional quality control challenges for SNEDDS-based products. Critical quality attributes include droplet size distribution upon dilution, self-emulsification time, drug content uniformity, and stability of both the fill and gelatin shell. Unlike conventional solid dosage forms, SNEDDS require performance-based testing that captures their dynamic behavior in biorelevant environments. Stability testing must address not only chemical degradation of the drug and excipients but also physical changes such as phase separation or drug precipitation. Robust in-process controls and validated analytical methods are therefore central to regulatory acceptance and lifecycle management [11, 15].

From a regulatory standpoint, FDA and EMA pathways for lipid-based formulations generally follow established frameworks for oral drug products, although additional scrutiny is often applied to complex delivery systems such as SNEDDS. Regulatory agencies emphasize a thorough understanding of formulation composition, mechanism of action, and in vivo performance. Demonstration of bioavailability enhancement, justification of excipient levels, and assessment of food effects are typically required. The use of excipients with Generally Recognized as Safe (GRAS) status or a history of prior regulatory approval can significantly streamline development, while novel surfactants or co-solvents may necessitate additional toxicological evaluation. Safety considerations also extend to long-term exposure to high surfactant concentrations and potential interactions with gastrointestinal membranes.

Several marketed SNEDDS softgel products provide compelling clinical success stories that validate this delivery approach. Commercial formulations of lipophilic drugs, including immunosuppressants, antifungals, and lipid-soluble vitamins, have demonstrated markedly improved and more consistent bioavailability compared with earlier formulations. These products highlight the ability of SNEDDS-filled soft gelatin capsules to address solubility-limited absorption and reduce interpatient variability, thereby improving therapeutic outcomes. Lessons learned from these successes emphasize the importance of early biopharmaceutical risk assessment, careful excipient selection, and alignment between formulation design and clinical objectives. Finally, patent trends and proprietary technologies reflect sustained innovation in the SNEDDS field, with intellectual property covering novel lipid compositions, supersaturable systems, precipitation inhibitors, and specialized softgel shell technologies. Many companies leverage proprietary excipient blends or encapsulation processes to differentiate products and extend market exclusivity. Collectively, experiences from product development and commercialization underscore that the success of SNEDDS-based soft-gels relies on a holistic approach that integrates formulation science, scalable manufacturing, regulatory strategy, and clinical performance considerations from early development through market launch [25, 26].

Table 3: Marketed SNEDDS / Self-Emulsifying Oral Products

Drug / Active	Trade Name	Manufacturer Name	Dosage Form	Indication / Notes
Amprenavir	Agenerase®	Glaxo SmithKline	Soft gelatin capsule	HIV antiviral replaced by prodrug forms (PMC) and SNEDDS-related formulation; superseded by prodrug fosamprenavir (PMC)
Bexarotene	Targretin®	Ligand/Eisai	Soft gelatin capsule	Anti-cancer SNEDDS formulation (PMC)
Calcitriol	Rocaltrol®	Roche	Soft gelatin capsule	Vitamin D analog in self-emulsifying format (PMC)
Calcitriol	Rocaltrol® (alternate listing)	Validus Pharmaceuticals	Soft gelatin capsule	Secondary hyperparathyroidism and calcium regulation (MDPI)
Cyclosporine A	Gengraf®	AbbVie	Hard/Soft gelatin capsule	Bioequivalent SNEDDS variant (Pharma Excipients)
Cyclosporine A	Neoral®	Novartis	Soft gelatin capsule/oral solution	Micro emulsion/SNEDDS-type formulation with improved bioavailability (PMC) and Improved bioavailability vs Sandimmune (PMC)
Cyclosporine A	Sandimmune®	Novartis	Soft gelatin capsule	Immunosuppressant (organ transplant) (PMC)
Cyclosporine A	Sandimmune®	Novartis	Oral solution	Early self-emulsifying product for immunosuppression (PMC)
Fenofibrate	Lipirex®	Highnoon Laboratories	Hard/soft gelatin capsule	Lipid-lowering agent in SNEDDS form (Pharma Excipients)
Isotretinoin	Accutane® / Vesanoid®	Roche	Soft gelatin capsule	Dermatology and oncology uses in SNEDDS format (PMC)
Isotretinoin	Accutane®, Vesanoid®	Roche	Soft gelatin capsules	Lipid-based self-emulsifying formulation (PMC)
Lopinavir + Ritonavir	Kaletra®	AbbVie Inc	Oral solution	Initially self-emulsifying oral solution; replaced by solid dispersions (Pharma Excipients)
Ritonavir	Norvir®	Abbott Laboratories	Soft gelatin capsule	HIV protease inhibitor delivered via SNEDDS; enhanced absorption (PMC) and Enhanced lipid-based formulation for HIV treatment (PMC)
Saquinavir	Fortovase®	Hoffmann-La Roche	Soft gelatin capsule	HIV antiviral (discontinued in favor of newer formulations) (PMC) and SEDDS formulation with enhanced bioavailability; later discontinued in favor of tablet forms (PMC)
Sirolimus (Rapamycin)	Rapamune®	Wyeth–Ayerst (now Pfizer)	Oral solution	Lipid/emulsifier excipients to improve bioavailability (PMC)
Tipranavir	Aptivus®	Boehringer Ingelheim	Soft gelatin capsule	HIV protease inhibitor SNEDDS product (PMC) and SNEDDS-type lipid formulation for HIV protease inhibition (PMC)
Valproic Acid	Convulex®	Gerot Lannach	Soft gelatin capsule	Antiepileptic SNEDDS formulation (Pharma Excipients)

EMERGING TRENDS AND FUTURE PROSPECTS

Ongoing progress in SNEDDS is being shaped by innovations in excipient development, formulation strategies, and pharmaceutical manufacturing technologies, collectively broadening the applicability of lipid-based oral delivery systems. A notable emerging trend is the exploration of novel, functionally engineered excipients, including natural and semi-synthetic lipids, bio-derived surfactants, and pharmaceutically acceptable ionic liquids. Renewable natural oils, such as structured medium-chain glycerides and selected essential oils, are increasingly investigated not only for their drug solubilization efficiency but also for their favorable biocompatibility profiles and potential to enhance intestinal permeability. In parallel, ionic liquids particularly those derived from active pharmaceutical ingredients or biocompatible counterions have demonstrated promise in improving drug solubility, stabilizing supersaturated states, and modifying interfacial behavior within SNEDDS. While these materials offer substantial formulation advantages, their long-term safety, toxicity, and regulatory acceptance remain critical considerations, underscoring the importance of rational excipient selection and comprehensive risk assessment.

Advances in solid SNEDDS and supersaturated SNEDDS (s-SNEDDS) represent another key direction aimed at overcoming limitations associated with conventional liquid systems. Solidification techniques such as adsorption onto porous carriers, spray drying, hot-melt extrusion, and melt granulation enable conversion of liquid SNEDDS into solid or semi-solid intermediates that retain self-nanoemulsifying properties upon reconstitution. Supersaturated SNEDDS, typically incorporating precipitation-inhibiting polymers or polymer surfactant combinations, are designed to transiently sustain drug concentrations above thermodynamic solubility following gastrointestinal dilution, thereby increasing the driving force for absorption. In the context of soft gelatin capsule formulations, these approaches offer opportunities for enhanced drug loading, reduced surfactant content, and improved physical and chemical stability, addressing key challenges related to storage, handling, and commercial viability [11].

Future perspectives also include the development of personalized and targeted SNEDDS-based therapies, in line with the broader movement toward precision medicine. By modulating lipid composition, droplet size, and release kinetics, SNEDDS can be tailored to accommodate inter-individual physiological variability, disease-specific conditions, or altered gastrointestinal function. Moreover, the capacity of lipid-based systems to promote lymphatic uptake or site-specific absorption provides opportunities for targeted delivery and reduced first-pass metabolism. Concurrently, the integration of SNEDDS with advanced nanotechnologies and additive manufacturing platforms, such as three-dimensional (3D) printing, is gaining momentum. These technologies enable the fabrication of customized oral dosage forms with precise control over dose, geometry, and spatial distribution of SNEDDS, facilitating complex release profiles and patient-centric design. Collectively, these emerging trends highlight a future in which SNEDDS-based dosage forms become more adaptable, precise, and clinically effective, reinforcing their role as a versatile platform for the oral delivery of challenging drug candidates.

CONCLUSION

Self-nanoemulsifying drug delivery systems encapsulated in soft gelatin capsules represent a versatile and continually evolving oral delivery platform for overcoming the challenges of poor aqueous solubility and variable bioavailability of lipophilic drugs. The success of SNEDDS-filled softgels relies on rational formulation design, encompassing careful selection and optimization of lipid excipients, surfactants, and co-solvents, informed by phase behavior, nanoemulsion formation mechanisms, and biopharmaceutical considerations to ensure robust self-emulsification and consistent in vivo performance. Despite their advantages, these systems face formulation-specific limitations, including constrained drug loading, precipitation upon gastrointestinal dilution, food-dependent variability, and long-term physical and chemical stability issues, while shell–fill interactions such as excipient migration and moisture imbalance pose additional challenges that must be addressed through comprehensive preformulation studies, rigorous characterization, and stability evaluation. Recent advances, including supersaturable SNEDDS, incorporation of precipitation inhibitors, use of bio-derived or functionally engineered lipids, and conversion to solid or semi-solid intermediates, alongside biorelevant in vitro testing, in vitro–in vivo correlation strategies, and mechanistic modeling, have expanded the applicability and predictability of these systems. From an industrial and regulatory perspective, successful commercialization requires scalable manufacturing, robust quality control, and alignment with regulatory guidelines, as evidenced by marketed products demonstrating enhanced oral bioavailability, reduced interindividual variability, and clinical impact. Looking forward, the integration of quality-by-design principles, patient-centric approaches, and advanced manufacturing technologies such as digital and additive manufacturing, together with continued innovation in excipients and deeper understanding of gastrointestinal physiology, is expected to further strengthen the role of SNEDDS-filled soft gelatin capsules as a clinically relevant and adaptable solution for oral delivery of poorly soluble drugs.

Acknowledgements: The authors acknowledge Dr Sudhakar Vidiyala, President & CEO, Ascent Pharmaceuticals Inc., for his constant support and encouragement in writing this review article.

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. Palem CR, Rendla R, Nagamalli NK, Lekkala VK, Gumudevelli S, A Comprehensive Review of Current Trends and Regulatory

Frameworks in Generic Drug Development, J. Pharm. Sci 2025;1(10):16-27. https://doi.org/10.5281/zenodo.17297703

2. Palem CR, Lekkala VK, Nagamalli NK, Balguri PR, Gumudevelli S. Next-Generation Dry Powder Inhalers: Advances in Characterization and Evolving Regulatory Frameworks, J. Pharm. Sci 2025;1(9):160-177. https://doi.org/10.5281/zenodo.17168847.
3. Date AA, Desai N, Dixit R, Nagarsenker M. Self-nanoemulsifying drug delivery systems: formulation insights, applications and advances. Nanomedicine (Lond) 2010;5(10):1595-616. https://doi.org/10.2217/nnm.10.126
4. Palem CR, Gumudevelli S, Rendla R, Srinija G, Gumudevell S. Comprehensive review on the role of Dietary Acid Load in health and its effect on different types of Diabetes. International Journal of Diabetes Research 2025; 7(1): 45-53. https://www.doi.org/10.33545/26648822.2025.v7.i1a.26
5. Palem CR, Lekkala VK, Nishanth Kumar N, Venkata Santhosh P, Gumudevelli S.Scale-Up Factors in the Development and Commercial Execution of Oral Solid Dosage Forms: A Current Industry Perspective. J Pharmacol Pharm Res Volume 2024;7(1):1-14.
6. Palem CR, Chopparapu KS, Subrahmanyam PVRS, Yamsani, MR. Cyclodextrins and their Derivatives in Drug Delivery: A Review. Current Trends in Biotechnology and Pharmacy 2012; 6(3): 255-279.
7. Thatipamula RP, Palem CR, Gannu R, Mudragada S,Yamsani MR. Formulation and in vitro characterization of Domperidone loaded solid lipid nano particles and nano structured lipid carriers 2011;19(1): 23-32.
8. Holm R, Kuentz M, Alexandra-Roxana Ilie-Spiridon, Griffin BT. Lipid based formulations as supersaturating oral delivery systems: From current to future industrial applications. European Journal of Pharmaceutical Sciences 2023;189:106556. https://doi.org/10.1016/j.ejps.2023.106556
9. Parigela V,Vijayalakshmi A. Self-Nano-Emulsifying Drug-Delivery Systems: A Limelight on the Development, Advancements and Opportunities in Improving Oral Absorption. Scope 2024;14(1):1740-1755.
10. Buya AB, Beloqui A, Memvanga PB, Préat V. Self-Nano-Emulsifying Drug-Delivery Systems: From the Development to the Current Applications and Challenges in Oral Drug Delivery. Pharmaceutics 2020;12(12) :1194. https://doi.org/10.3390/pharmaceutics12121194
11. Uttreja P, Youssef AAY, Karnik I, Sanil K, Narala N, Wang H, Elkanayati RM, Vemula SK, Repka MA. Formulation Development of Solid Self-Nanoemulsifying Drug Delivery Systems of Quetiapine Fumarate via Hot-Melt Extrusion Technology: Optimization Using Central Composite Design. Pharmaceutics 2024;16(3): 324. https://doi.org/10.3390/pharmaceutics16030324 .
12. Patel UKD, Kempwade AKA, Patil VS, Hiremath RD. Formulation and Evaluation of Self-Nanoemulsifying Drug Delivery System of Clofazimine RJPS 2022;12(1):38-46. https://doi.org/10.26463/rjps.12_3_6.
13. Pouton CW. Formulation of self-emulsifying drug delivery systems. Advanced Drug Delivery Reviews, 1997;25(1),47-58. https://doi.org/10.1016/S0169-409X(96)00490-5 .
14. Gullapalli RP. Soft gelatin capsules (softgels). Journal of Pharmaceutical Sciences, 2010; 99(10):4107–4148. https://doi.org/10.1002/jps.22151.
15. Tanga S, Ramburrun P, Aucamp ME.From liquid SNEDDS to solid SNEDDS: A comprehensive review of their development and pharmaceutical applications. The AAPS Journal 2025; 28(1):10. https://doi.org/10.1208/s12248-025-01167-x
16. Feeney OM, Crum MF, McEvoy CL, Trevaskis NL, Williams HD, Pouton CW, Charman WN, Bergström CAS, Porter CJH. 50 years of oral lipid-based formulations: Provenance, progress and future perspectives. Advanced Drug Delivery Reviews 2016; 101:167–194. https://doi.org/10.1016/j.addr.2016.04.007.
17. Pouton CW, Porter CJH. Formulation of lipid-based delivery systems for oral administration: Materials, methods and strategies. Advanced Drug Delivery Reviews 2008; 60(6):625–637. https://doi.org/10.1016/j.addr.2007.10.010.
18. Singh B, Bandopadhyay S, Kapil R, Singh R, Katare O. Self-emulsifying drug delivery systems (SEDDS): formulation development, characterization, and applications. Crit Rev Ther Drug Carrier Syst. 2009;26(5):427-521. https://doi.org/10.1615/critrevtherdrugcarriersyst.v26.i5.10
19. Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, Porter CJH. Strategies to address low drug solubility in discovery and development. Pharmacological Reviews 2013; 65(1): 315–499. https://doi.org/10.1124/pr.112.005660
20. Wu F, Ma Q, Tian G, Chen K, Yang R, Shen J. Formulation and Evaluation of Solid Self-Nanoemulsifying Drug Delivery System of Cannabidiol for Enhanced Solubility and Bioavailability. Pharmaceutics. 2025; 17(3):340. https://doi.org/10.3390/pharmaceutics17030340
21. Dressman JB, Reppas. In vitro–in vivo correlations for lipophilic, poorly water-soluble drugs. European Journal of Pharmaceutical Sciences, 2000;2:S73-80. https://doi.org/10.1016/s0928-0987(00)00181-0
22. Karimi M, Mirshekari H, Moosavi Basri SM, Bahrami S, Moghoofei M, Hamblin MR. Bacteriophages and phage-inspired nanocarriers for targeted delivery of therapeutic cargos. Adv Drug Deliv Rev. 2016;106(A):45-62. https://doi.org/10.1016/j.addr.2016.03.003
23. Porter CJH, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: Optimizing the oral delivery of lipophilic drugs. Nature Reviews Drug Discovery 2007; 6(3):231–248. https://doi.org/10.1038/nrd2197.
24. Palem CR, Dudhipala NR, Battu SK, Repka MA, Yamsani MR. Development, optimization and in vivo characterization of domperidone-controlled release hot-melt-extruded films for buccal delivery. 2016, Drug Development and Industrial Pharmacy 2015;42(3):473-484. https://doi.org/10.3109/03639045.2015.1104346.
25. Rahman J, Quodbach J. Versatility on demand - The case for semi-solid micro-extrusion in pharmaceutics. Advanced Drug Delivery Reviews 2021;172:104-126. https://doi.org/10.1016/j.addr.2021.02.013
26. Palem CR, Battu SK, Maddineni S, Gannu R, Repka MA, Yamsani MR. Oral transmucosal delivery of domperidone from immediate release films produced via hot-melt extrusion technology. Pharmaceutical Development and Technology 2013:18(1):186-195. https://doi.org/10.3109/10837450.2012.693505.