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Review Paper

A Critical Review on Characterization Methods of SMEDDS: Droplet Dynamics, Thermodynamic Stability, Lipid Digestion Models and IVIVC

Yash Patel*, Pranjali Lingalwar, Mahesh Bhagwat, Pritam Jain, Amod Patil, K. Agrawal, Nitin Haswani

R.C. Patel Institute of Pharmacy, Karwand Naka, Shirpur, Dist. Dhule (MS) India 425 405.

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ABSTRACT

Self-micro emulsifying drug delivery systems (SMEDDS) have become a crucial approach for improving the oral bioavailability of poorly water soluble BCS Class II and IV drugs by facilitating the spontaneous formation of fine oil-in-water microemulsions in gastrointestinal environments, thereby enhancing solubilization and absorption relative to traditional formulations[1], [2]. The clinical and economic success of SMEDDS is significantly dependent on rigorous characterization, as formulation performance is driven by dynamic physicochemical behaviour that determines in vivo fate and therapeutic outcomes [3]. This review critically evaluates four principal characterization domains: (i) droplet dynamics, which govern dispersion, interfacial properties, and transport phenomena; (ii) thermodynamic stability, which guarantees the resilience of the microemulsion state against physiological disturbances; (iii) in vitro lipid digestion models, which elucidate digestion-mediated solubilization and drug precipitation pathways; and (iv) in vitro in vivo correlation (IVIVC), which assesses the translational predictability of biorelevant data sets [4], [5] . In recent years, there have been methodological improvements, such as mechanistic gastrointestinal simulations and integrated digestion absorption workflows that better represent the complexity of lipid-based delivery systems [6]. However, there are still big gaps, like a lack of agreement on standardized digestion protocols, a lack of clear links between microstructural development and absorption kinetics, and a lack of clarity on how lipid excipients interact with each other [7].

INTRODUCTION

2.1 Background and Need

***Corresponding Author:** Yash Patel
Address: *Department of Pharmaceutical Quality Assurance, R.C. Patel Institute of Pharmacy, Karwand Naka, Shirpur, Dist. Dhule (MS) India 425 405..*
Email ✉: patelyash8686@gmail.com

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Oral drug delivery continues to be the most favoured method for systemic therapy because to patient adherence, cost-effectiveness, and simplicity of administration. Nonetheless, a considerable fraction of novel chemical entities has inadequate aqueous solubility and restricted permeability, traditionally classified under the Biopharmaceutics Classification System (BCS) Class II and IV, which substantially impedes oral bioavailability [8], [9]. For these drugs, dissolution or solubilization in the gastrointestinal (GI) environment is the rate-limiting step for absorption, resulting in unpredictable pharmacokinetics, dosage escalation, and therapeutic failure [10], [11].

Researchers have looked into lipid-based drug delivery systems (LBDDS) a lot to find ways to solve these problems by making drugs easier to dissolve, easier to move through the lymphatic system, and easier to absorb by changing the way the GI system works [12], [13]. Self-emulsifying and self-micro emulsifying systems have attracted significant interest within the realm of LBDDS due to their ability to spontaneously generate fine dispersions upon interaction with gastrointestinal fluids, hence overcoming the constraints of traditional solubilization methods [14], [15]. The evolutionary progression from self-emulsifying drug delivery systems (SEDDS) to self-micro emulsifying drug delivery systems (SMEDDS), and subsequently to nano-SMEDDS (S-SMEDDS) and self-nanoemulsifying drug delivery systems (SNEDDS), signifies a continuous enhancement in droplet size reduction, kinetic stability, and biorelevant performance [16].

Even though there have been many successful formulations, it has been hard to turn SMEDDS into clinically useful medications because the mechanisms behind them are not well understood. Conventional measurements like globule size and polydispersity index (PDI) offer inadequate insights into dynamic behaviour under physiological conditions. Additionally, the interaction among lipid excipients, digestion kinetics, and drug supersaturation is inadequately understood, which compromises the predictability of in vivo outcomes [17], [18]. These deficiencies carry substantial regulatory consequences, as agencies increasingly mandate mechanistic explanation for excipient selection, in vitro in vivo correlation (IVIVC), and comprehensive stability characterization to underpin quality by design (QbD) frameworks [19], [20], [21]. Consequently, sophisticated, physiologically pertinent characterization methodologies are essential to elucidate SMEDDS performance, improve predictability, and ensure product development is in accordance with regulatory standards.

2.2 Mechanism of Self-Micro emulsification

Phase behaviour and interfacial thermodynamics are the main things that control the self-micro emulsification process. When SMEDDS are added to gastrointestinal (GI) fluids, they automatically form thermodynamically stable or metastable oil-in-water microemulsions because of drops in interfacial free energy [22]. The best ratios of oil, surfactant, and co-surfactant/co-solvent, which change curvature, interfacial tension, and spontaneous dispersion kinetics, affect how well this procedure works [23].

Phase behaviours experiments reveal that when surfactants with the right hydrophilic lipophilic balance (HLB) values are mixed with co-surfactants, the system goes through bi-continuous, microemulsion, and lamellar phases. This permits nanometric droplets (<100 nm) form when the mixture is diluted [24], [25]. The interactions between the surfactant and co-surfactant make it easier for co-surfactant molecules to get into the surfactant monolayer. This makes the fluid between the two layers more flexible and less likely to bend, which helps microemulsion form [26].

When the system is mixed with water, it quickly breaks up into nanosized droplets on its own because of (i) mixing that happens because of entropy and (ii) surfactant-assisted disruption of the interface, with very little mechanical energy input [27], [28]. These droplets help drugs dissolve better by giving them a lot of surface area and keeping them in supersaturated states during the first digestion [29].

This mechanism is very much affected by GI physiology. Bile salts, phospholipids, and digestive enzymes change the size of droplets, the structure of the interface, and the ability to dissolve things by making mixed micelles and colloidal species through lipolysis [30], [31], [32], [33], [34]. The way that SMEDDS droplets and endogenous amphiphiles interact with one other change the way drugs are distributed in the aqueous, micellar, and vesicular phases, which affects absorption. So, it's important to know how self-micro emulsification works in order to forecast how well it will work in vivo and make the formulation as strong as possible.

2.3 Scope of the Review

Characterization of SMEDDS has garnered significant attention owing to its direct influence on formulation quality, mechanistic comprehension, and regulatory compliance [35]. Nonetheless, the current research mostly concentrates on formulation design and performance outcomes, while placing relatively little emphasis on the essential analytical approaches that determine the translational fate of SMEDDS in vivo [35], [36]. To overcome this gap, the present analysis delineates and critically examines four major domains of SMEDDS characterization: (i) droplet dynamics, which includes droplet size, shape, charge, and changes at the interface that happen when the droplets are in a simulated gastrointestinal (GI) environment; (ii) thermodynamic stability, which tests how well the droplets hold up against phase separation, dilution, and environmental stresses; (iii) in-vitro lipid digestion models, which show how enzymes break down lipids, how drugs precipitate, and how they dissolve; and (iv) in-vitro in-vivo correlation (IVIVC), which shows how well in-vitro data can predict in-vivo exposure and bioavailability [37], [38], [39].

This review not only summarizes methods, but also points out important gaps, such as (i) the absence of standardized gastrointestinal simulation protocols, (ii) the limited mechanistic connection between digestion kinetics and intestinal absorption, and (iii) the lack of regulatory guidance specifically for lipid-based systems. Moreover, nascent trends such as dynamic digesting platforms, hybrid in-vitro/in-silico modelling, and computationally assisted PBPK-driven IVIVC are underscored due to their capacity to improve clinical predictability and regulatory conformity [40], [41]. The scope thus reflects a complete and forward-looking view on SMEDDS characterisation, stressing analytical depth, translational relevance, and future research pathways.

3. Composition and Critical Formulation Variables of SMEDDS

3.1 Oils

Oils are the main part of SMEDDS that makes things soluble. They are also very important for drug loading capacity, micro emulsification efficiency, lipid digestion pathways, and lymphatic transport potential [42], [43]. They can be put into three main groups: long-chain triglycerides (LCTs), medium-chain triglycerides (MCTs), and semi-synthetic lipid excipients. Each group has its own physical and chemical benefits.

Long-chain triglycerides (LCTs), including soybean, sesame, and corn oils, have C14 C22 fatty acids in them. They help mixed micelles form

with bile salts and phospholipids, which makes it easier for lymphatic transport of medications that are very lipophilic (log P > 5) [44], [45], [46], [47]. This technique can get around first-pass hepatic metabolism, which makes certain actives more available in the body [48], [49]. But LCT-based solutions sometimes take longer to self-emulsify and may need larger concentrations of surfactants to get beyond interfacial resistance [50].

On the other hand, medium-chain triglycerides (MCTs), which are usually C6 C12 fractionated fats, are better at self-emulsifying because they are less viscous and have less interfacial tension. This makes the droplets smaller and speeds up the dispersion process [51]. MCTs are quickly broken down by enzymes, and most of the time they are absorbed through the portal vein instead of the lymphatic system. This could restrict the bioavailability benefits for very lipophilic compounds [52]. However, MCTs often facilitate greater apparent solubility of medicines exhibiting intermediate lipophilicity (log P 24) [52], [53].

Scientists have made semi-synthetic lipids including mono- and di-glycerides, propylene glycol esters, and polyoxyl glycerides (such Maisine®, Labrafil®, and Lauroglycol®) to help drugs dissolve better while still being able to self-emulsify [54]. They provide customized hydrophilic-lipophilic balance (HLB), regulated polarity, and enhanced miscibility with surfactants, facilitating the formation of supersaturatable SMEDDS and improving stability against precipitation caused by digestion [55].

The choice of the oil phase is based on a number of factors, such as how well the medication dissolves, how well it is absorbed, and its polarity. This shows how important it is to carefully choose excipients. Moreover, the relationship between oil chain length and lipid digestion has a big effect on drug dispersion, supersaturation, and bioaccessibility. This shows how important it is to choose the right oil when designing SMEDDS [56], [57].

3.2 Surfactants

Surfactants are essential elements of SMEDDS, facilitating the reduction of interfacial tension and the spontaneous creation of stable microemulsions following dilution in gastrointestinal fluids [58]. Their amphiphilic structure lets them line up at the oil-water interface, which lowers the free energy of dispersion and makes it easier to get droplets smaller, down to the nano- or submicron range [59]. For self-micro emulsification to work well, it usually needs surfactants with a high HLB (hydrophilic lipophilic balance) (HLB > 12) since more hydrophilicity makes it easier to make oil-in-water (o/w) systems that can be taken orally

Some examples of non-ionic surfactants that are commonly used are polyoxyethylene castor oils (like Cremophor® EL/RH40), polysorbates (like Tween® 20/80), and polyoxyl glycerides (like Labrasol®). These surfactants are better at emulsifying, dissolving, and being biocompatible than ionic surfactants [60]. Because they are non-ionic, they are less sensitive to changes in pH and ionic strength in the GI environment, which makes the formulation stronger [61]. Nonetheless, the selection of HLB remains a pivotal factor: surfactants with excessively high HLB can facilitate drug precipitation during dilution owing to rapid solvent exchange, whereas lower HLB systems may result in coarse emulsions or insufficient dispersion. So, choosing the best surfactant frequently means finding a balance between how well it works at the interface, how well it dissolves drugs, and how it acts in the body. Toxicity and rules are two big things that make it hard to choose surfactants. Some surfactants, like Cremophor® EL, have been linked to hypersensitivity reactions, complement activation, and membrane disruption effects when used in high amounts. This raises concerns about their

biocompatibility, even though they are widely used in medicine [62], [63]. Regulatory bodies have been paying more attention to excipients that have not been used in approved oral products before. This shows how important it is to have well-established safety profiles and justifiable exposure ranges [64], [65]. To overcome these constraints, novel surfactant classes such as PEG-free amphiphiles, alkyl glycerol ethers, and biobased surfactants are being explored to decrease cytotoxicity, mitigate PEG-related oxidative degradation pathways, and improve metabolic compatibility [66].

In conclusion, the choice of surfactant in SMEDDS is influenced by a complicated mix of HLB values, drug solubilization, dispersion efficiency, and toxicological limits. This shows how important it is to use rational excipient design and regulatory-aligned selection strategies when developing formulations.

3.3 Co-surfactants and co-solvents

Co-solvents and co-surfactants are added to SMEDDS formulations to change the curvature of the interface, make lipids mix better, and make drugs more soluble [67]. Ethanol, propylene glycol (PG), polyethylene glycol (PEG-400), and Transcutol® (diethylene glycol monoethyl ether) are all common pharmaceutical co-solvents. They make the solvent environment more polar, which helps dissolve medicines that are moderately lipophilic or crystalline [68], [69]. However, adding water to the dispersion will quickly weaken the solvent, which can cause the medication to become supersaturated and precipitate. This means that the ratios of the solvents must be carefully balanced [70], [71].

Co-surfactants like short-chain alcohols (ethanol, butanol) and hydrophilic glycols work by making the interface more fluid and lowering the energy needed to bend, which helps microemulsion domains form in phase diagrams [72], [73]. They also make things less thick and help with the speed of self-micro emulsification. But volatile co-solvents can evaporate while being stored, which can change the phase. Also, some co-solvents, such ethanol, have rules and stability issues when used in paediatric and chronic dose forms [74]. So, the parameters for choosing include volatility, how well it dissolves, how safe it is, and how well it works with the pathways for excipient digestion.

3.4 Drug Excipient Miscibility and Solubility Screening

The amount of drug that can be loaded into SMEDDS is mostly determined by how well the drug and lipid work together and how well the excipients can keep the drug in a molecularly dispersed state while it is being stored and dispersed [75]. The first step in screening is usually to do equilibrium solubility tests in oils, surfactants, and co-solvents to find the best solubilizing medium. This phase is very important because medications that don't dissolve well enough may solidify while they are being stored or after they have been diluted in the stomach [76].

Advanced screening methods include Hansen solubility parameters, Lipinski descriptors, and log P/log D relationships to figure out how well two substances will mix and how much they will stick to lipids [77]. New methods like temperature-modulated solubility profiling, DSC-based miscibility testing, and in-situ XRD analysis help us better understand how crystalline and amorphous materials change and how likely they are to precipitate [78], [79]. The drug's ionization state and pKa also affect how well it dissolves in lipidic and aqueous compartments. SMEDDS can help weak bases get around pH-dependent solubility problems [80].

The solubility screening stage helps choose the right excipients and lowers the risks of later formulations by finding systems that are likely to precipitate before in vitro or in vivo testing.

3.5 Phase-Diagram Development

Pseudo ternary phase diagrams are essential to SMEDDS design because they show where microemulsions can exist dependent on the amounts of oil, surfactant/co-surfactant, and water present [81]. They make it easier to find self-micro emulsifying areas, bi- continuous structures, and liquid crystalline phases, which makes it possible to understand how emulsification works and how much excipient is needed [82]. Construction usually entails titrating surfactant/oil combinations in water and then checking for clarity, isotropy, and flowability with the naked eye or with instruments. The surfactant/co-surfactant ratio (Km value) has a big effect on phase boundaries. Higher surfactant levels make microemulsion domains bigger, but they also make cells more poisonous and irritating [83], [84]. Automated droplet analysis, rheology, polarized light microscopy, and SAXS have enhanced phase structure elucidation, supplanting subjective visual scoring [85]. Guided by phase diagrams, formulation development achieves greater stability and minimizes trial-and-error during scale-up [86].

However, this methodology assumes equilibrium conditions that fail to adequately capture dynamic gastrointestinal processes including bile salt interactions, enzymatic lipolysis, and dilution shocks highlighting a translational gap elaborated in Sections 4 and 6.

3.6 Effect of Formulation Variables

Formulation variables have an effect on the size, strength, thermodynamic stability, and bio-performance of SMEDDS formulations at different levels. Important factors are:

(i) Oil type and concentration: MCTs usually make smaller droplets that mix together more quickly, while LCTs help drugs dissolve and move through the lymphatic system but may need more surfactant [87], [88].

(ii) Surfactant grade / HLB: large-HLB surfactants (<20) help o/w dispersion and make droplets smaller, although they might cause precipitation or toxicity at large doses [89], [90], [91]. The molecular structure of surfactants (PEGylated vs. non-PEGylated) also affects how quickly and easily they can be digested.

(iii) Co-solvent ratio: Co-solvents make it easier for drugs to dissolve, but they also make it more likely that they will precipitate when they are diluted. If the proportions are too high, they may destabilize interfacial layers and make them less strong [92], [93].

(iv) Loading the drug: A lot of drugs may be too much for the excipient to dissolve, which can make lipolysis more likely to happen and cause supersaturation-driven precipitation [94], [95], [96].

Self-emulsification duration, droplet size distribution, PDI, zeta potential, and dilution stability are all performance indicators that are very sensitive to these variables. This means that optimizing excipients is necessary for consistent behaviour in vivo. It is important to note that changes to the composition affect lipid digestion patterns, mixed micelle formation, and drug partitioning. This shows a significant link between formulation composition and IVIVC results, which will be discussed in more detail in Section 7 [97], [98], [99], [100], [101].

4. Droplet Dynamics: Tools and Techniques

4.1 Droplet Size and Distribution

The size of the droplets is a key factor in how well SMEDDS works. It affects the interfacial surface area, the speed of digestion, the solubility of the medication, and the absorption profiles [102]. Dynamic light scattering (DLS), or photon correlation spectroscopy (PCS), is the most common way to figure out size and polydispersity. This is because it is sensitive in the 10 1000 nm range and can get data quickly [103]. DLS uses the

Stokes Einstein equation to figure out the hydrodynamic diameter by measuring changes in the intensity of scattered light generated by Brownian motion. DLS is used a lot, however it only works if the droplets are round. It can also be affected by artifacts from multiple scattering in samples with a lot of different sizes or concentrations [104], [105].

Nanoparticle Tracking Analysis (NTA) has developed as a supplementary technique that can concurrently assess individual droplet trajectories and size distributions, producing number-weighted data instead of intensity-weighted data, thereby offering improved resolution for polydisperse systems and heterogeneous populations [106], [107]. NTA can also measure the concentration of particles, which gives us further information about how droplets stick together and merge.

The dilution media has a big effect on the results of the measurements because ionic strength, pH, and bile salt concentrations change interfacial stability and droplet coalescence [108], [109], [110]. Surfactant-to-oil ratios similarly influence size distribution, with elevated surfactant concentrations often decreasing mean droplet diameter, while potentially enhancing toxicity or inducing precipitate upon water dilution [111]. Consequently, droplet size analysis must be conducted under both formulation and biorelevant dilution conditions to more accurately represent in vivo dynamics.

4.2 Droplet Morphology

Morphological characterization gives us information about the structure of droplets, such as their shape, the thickness of their interfaces, the organization of their interior phases, and how they group together. Transmission electron microscopy (TEM) is commonly utilized for its nanometer-scale resolution, which facilitates the imaging of droplet architecture and the differentiation between spherical microemulsions, liquid crystalline phases, or vesicular structures [112], [113]. Standard TEM, on the other hand, usually needs procedures like negative staining and drying, which can cause artifacts such droplets changing shape or collapsing because of changes in surface tension [114].

Cryogenic-TEM (cryo-TEM) solves these problems by freezing samples in liquid ethane or nitrogen, which keeps their natural hydrated shapes and lets you see scattered droplets and micellar or vesicular intermediates directly under settings that are close to normal body temperature [115], [116]. Cryo-TEM has made it possible to see temporary microstructures during the digestion of lipids and the interactions of bile salts, which has helped to connect morphology and bio-performance on a mechanistic level [117], [118].

Scanning electron microscopy (SEM) provides comprehensive topographical data; however, its use in SMEDDS is constrained by the necessity for conductive coatings and dehydration, rendering it more appropriates for solidified systems like S-SMEDDS rather than liquid microemulsions [119].

Atomic force microscopy (AFM) gives information about surface topology and nanomechanical properties by looking at how the tip interacts with the sample. It can also take pictures in liquids without staining, although it takes a long time and has a narrow field of view [120], [121].

Morphological techniques work well with DLS/NTA-based size methods because they confirm the structure, find artifacts, and help us understand how droplets change during GI transit, digestion, or solidification.

4.3 Droplet Charge and Surface Properties

The zeta potential, surface conductivity, and polydispersity index (PDI) of droplets are important measures of how stable SMEDDS is and how it interacts with GI components [122], [123].

Electrophoretic light scattering is a common way to test zeta potential, which shows how much droplets repel each other electrically. Even while SMEDDS usually use non-ionic surfactants, they can nevertheless build up surface charge by adsorbing ions, especially when bile salts, phospholipids, or lipolytic products are present in intestinal fluids [124], [125]. Higher absolute zeta potential levels (>|20| mV) are usually linked to steric or electrostatic stability. On the other hand, values that are close to neutral can make droplets more likely to come together when they are under stress [126]. PDI measures how uniform the size is, with values less than 0.2 showing that the nano-dispersions are uniform, which is good for consistent lipolysis and drug release [127]. Electrical conductivity tests also help tell the difference between oil-in-water and water-in-oil tendencies and find bicontinuous transitions during micro emulsification [128]. Recent discoveries show that surface charge affects the creation of protein corona, the flow of mucus, and the absorption of cells in the intestinal epithelium. These are all factors that are becoming more important in regulatory evaluations and have direct IVIVC relevance [129], [130], [131].

4.4 Droplet Dynamics Under GI Simulation

When SMEDDS enter the GI tract, they are exposed to dilution, peristaltic shear, bile salts, phospholipids, and pancreatic lipases. All of these things change the size of the droplets, the makeup of the interfaces, and the ability of the droplets to dissolve [132], [133]. In vitro digestion experiments show that droplets can develop, stick together, come together, or break apart again, depending on the content of the excipient and the rate of lipolysis [134], [135]. When triglycerides are broken down by enzymes, they turn into free fatty acids (FFAs) and monoacylglycerols. These molecules then combine with bile salts and phospholipids to form mixed micelles and vesicles that change how drugs are distributed in water, colloids, and sedimented phases [136], [137].

Recent investigations utilizing simulated intestinal fluids (FaSSIF/FeSSIF) have demonstrated that bile salt-mediated charge inversion and interfacial remodelling affect droplet stability and medication supersaturation post-digestion. Advanced analytical platforms like time-resolved DLS, SAXS, and microfluidic digestion chips have made it possible to see colloidal transformations and lipolysis kinetics in real time, giving us a better understanding of how absorption-relevant colloidal pathways work [138], [139]. These biorelevant dynamics highlight the imperative for gastrointestinal simulation, since pre-digestion droplet size alone does not adequately predict in vivo outcomes.

4.5 Critical Evaluation of Methods

Even though there has been a lot of development in the methods used to characterize droplets, there are still some big problems with them. Size estimations based on DLS are very sensitive to dilution, refractive index assumptions, and intensity-weighted bias. These factors can make larger droplets look bigger and polydispersity look smaller [140]. Morphological techniques like cryo-TEM give us detailed structural information, but they need a lot of sample preparation and don't work quickly enough for routine screening [141]. NTA provides number-weighted size and concentration data, but its sensitivity diminishes for droplets smaller than 40 nm, a size range pertinent to many modern SMEDDS [142], [143].

A significant problem is the disparity between physicochemical metrics and in vivo performance. Specifically, size, PDI, and zeta potential measured under idealized conditions do not adequately reflect lipolysis-dependent transformations, drug precipitation, or mixed colloid formation, which primarily influence absorption outcomes [144], [145], [146]. Furthermore,

the absence of established procedures for gastrointestinal simulation, encompassing enzyme activity, bile salt concentrations, and shear profiles, hinders inter-laboratory comparability and regulatory approval [147], [148]. New methods include integrated digestion-uptake systems, microfluidic GI simulators, and machine-learning models that may link changing droplet behaviours to pharmacokinetic outcomes. These are key steps toward predictive IVIVC frameworks [149], [150].

5. Thermodynamic Stability Assessment

5.1 Need for Stability Evaluation

SMEDDS create thermodynamically driven microemulsions when they are diluted, which means that the system is stable because the interfacial free energy is kept to a minimum instead of the kinetic resistance to coalescence [151]. Thermodynamic stability makes ensuring that scattered droplets stay evenly spread out and don't separate into different phases, cream, or group together when they are stored for a long time or under stress. This is important because the compatibility of excipients and the ability to maintain low interfacial tension states have a big effect on how well self- micro emulsification works, the size of the droplets, and the ability to dissolve substances [152], [153].

From a translational point of view, not enough stability can cause drug precipitation, changes in globule size, or excipient phase segregation, which can make bioavailability and IVIVC less predictable [154], [155]. Regulatory authorities are putting more and more stress on stability-centered characterisation as part of Quality by Design (QbD) frameworks for lipid-based formulations. This shows how important it is to use standardized thermodynamic analytics during development [156], [157].

5.2 Common Stability Studies

Thermodynamic stability tests usually include stress tests, thermal cycling, and freeze-thaw challenges to simulate the changes in temperature, pressure, and humidity that happen during storage, transportation, and usage in a clinical setting [158]. These tests quickly check the strength of the formulation before starting long-term ICH stability investigations.

5.2.1 Centrifugation Stress Testing

Centrifugation subjects SMEDDS dispersions to significant gravitational forces (3,000 10,000 rpm for 10 30 min) to expedite phase separation processes, underscoring their vulnerability to creaming, cracking, phase separation, or sedimentation [159]. After centrifugation, stable systems stay isotropic, but unstable systems display clear stratification. Centrifugation is very useful and quick, but it shows kinetic instability instead of real thermodynamic behaviour. This means it is a good way to screen for stability, but not a good way to forecast long-term stability [160], [161].

5.2.2 Heating Cooling Cycle

Heating cooling cycling means putting formulations through different temperature ranges (like 4 °C to 45 °C) over and over again to cause thermal stress, surfactant phase changes, and changes in solubility [162], [163]. These cycles assist find problems with excipients that happen when the temperature changes, like sorbitan ester crystallization, PEG-based surfactant phase shifts, or oil surfactant separation. The approach is especially important since systems with a lot of surfactants might have HLB variations that depend on temperature, which can vary the size of droplets and how they self-micro emulsify when they are diluted [164], [165].

5.2.3 Freeze Thaw Cycle

The freeze-thaw cycling test checks how stable something is while it is stored at temperatures

below zero, usually between −20 °C and +25 °C for 3 to 6 cycles. When freezing, ice crystals can form, which can make microemulsion precursors less stable. This can lead to interfacial film breakdown, coalescence, or drug crystallization when the mixture thaws [166], [167]. Formulations that pass freeze-thaw testing without separation or turbidity are thought to be better for cold-chain logistics or places with big changes in temperature. Recent research indicates that the incorporation of semi-synthetic lipids and non-ionic surfactants enhances freeze-thaw stability by decreasing crystallization tendency and increasing interfacial elasticity [168], [169].

5.2.4 Dilution Stability

Dilution stability tests how well SMEDDS can keep droplets together and stop phase separation after being in contact with large amounts of gastrointestinal fluid. Because SMEDDS are very diluted in vivo, quick changes in the polarity of the solvent can cause drug supersaturation, surfactant rearrangement, and droplet coalescence [170]. Typically, dilution studies are done with water, buffer solutions, FaSSIF, or FeSSIF media to mimic physiological conditions at different dilution factors. Stable systems stay clear to the eye with only small fluctuations in droplet size and PDI. Unstable systems, on the other hand, show turbidity, precipitation, or phase inversion.

Recent research has shown that formulations with a lot of co-solvents are more likely to precipitate when they are diluted because the solvents move quickly. On the other hand, lipid-rich solutions show higher buffering capacity for solubilization during simulated digestion [171], [172]. So, dilution stability is an important link between the composition of a formulation and how well it works after eating.

5.2.5 Accelerated Stability (ICH-Based)

Accelerated stability studies are performed in accordance with ICH Q1A(R2) recommendations to forecast long-term efficacy under regulated temperature and humidity conditions (e.g., 40 °C/75% RH) and to observe changes in globule size, PDI, drug crystallization, and excipient phase separation [173]. ICH frameworks were originally created for solids, but they are now being used more and more for lipid-based formulations to help with shelf-life assignment and regulatory submissions [174], [175]. Recent proposals for real-time monitoring of digested and undigested states under ICH circumstances aim to elucidate stability-driven bioavailability risks [176], indicating a transition from solely physical assessment to biopharmaceutical stability considerations.

5.3 Phase Separation, Turbidity & Robustness Index

Phase separation and turbidity measurements provide quantitative data on thermodynamic stability during progressive dilution or thermal stress. Gradual dilution studies evaluate formulation dispersion throughout 1× to 1000× medium dilutions, identifying thresholds at which visually isotropic microemulsions transform into biphasic or turbid systems [177], [178]. Light scattering or UV-visible spectrophotometry are common ways to quantify turbidity. These methods give a reliable way to measure droplet aggregation or precipitation.

Cloud point measurements show the temperature at which non-ionic surfactants lose water by ethoxylation, which helps separate the phases. This is especially important for PEGylated systems [179], [180]. Recent research has proposed the Robustness Index (RI) to measure how well something can handle instability caused by dilution. The RI is the highest dilution ratio at which no turbidity or precipitation is seen [181]. These metrics provide systematic comparison of

formulation candidates and guide judgments concerning surfactant/co-solvent equilibrium.

These tests are important because they help tell the difference between thermodynamic stability, where the system naturally goes back to equilibrium, and kinetic stability, where emulsions stay together only because energy barriers stop them from coming together. SMEDDS take advantage of thermodynamic stability, but stress in the actual world can cause kinetic failure modes. This shows how important it is to use a combination of assessment methods.

5.4 Critical Limitations

Even though methods have improved, there are still big problems with existing thermodynamic stability assessments for SMEDDS that make them less useful for making predictions. To begin with, there is no set technique that all labs use to define acceptable cycle numbers, dilution factors, or analytical objectives. This leads to differences between studies and makes it harder to compare them. Second, traditional stability studies often overstate gastrointestinal robustness since they don't take into account bile salts, digestive enzymes, shear forces, or lipid hydrolysis, all of which are genuine mechanisms that cause destabilization in vivo [182], [183].

Third, physical stability measurements don't tell us much about biopharmaceutical stability, especially when it comes to drug precipitation during digestion, which is still a major cause of bioavailability and IVIVC failure [184], [185]. Finally, authorities don't have any precise stability guidelines for lipids right now, which makes it hard to prepare dossiers for new SMEDDS that will be sold over the world [186], [187]. As lipid-based formulations become increasingly common, we need unified frameworks that include thermodynamic, kinetic, and digestive stability to improve confidence in translation and regulation.

6. Lipid Digestion Models for SMEDDS Characterization

6.1 Rationale

When SMEDDS are taken by mouth, enzymes in the small intestine break them down into free fatty acids (FFAs), monoacylglycerols (MAGs), and colloidal species like mixed micelles, vesicles, and liquid crystals. These structures that are formed during digestion control how drugs dissolve, become supersaturated, and precipitate, which in turn affects how well they are absorbed by enterocytes [188]. Numerous biopharmaceutical investigations have shown that the magnitude and velocity of lipolysis are associated with the bioavailability of lipophilic medicines and physiologically active substances administered using lipid-based formulations [189], [190].

In vitro lipid digestion models mimic this process to show how drugs move between aqueous, pellet, and oil/colloidal phases. This gives us mechanistic information that classical dissolving testing can't give us [191], [192]. These models connect formulation design and in vivo performance by forecasting drug precipitation hazards, supersaturation windows, and solubilization capacity. All of these things have a big impact on IVIVC and regulatory assessment [193]. Lipid digestion modelling is therefore a key part of recent SMEDDS characterisation frameworks.

6.2 Types of Lipid Digestion Models

Several in vitro digestive models have been created to replicate lipid breakdown and colloidal reorganization under simulated physiological settings. These models are different in terms of how complicated they are, how much biological detail they have, and how useful they are for translation. They include:

1. pH-stat lipolysis models
2. Static buffer enzyme models
3. Dynamic gastrointestinal (GI) models

4. Hybrid in vitro in silico predictive systems pH - stat lipolysis is still the most extensively used method because it can measure lipolytic kinetics in a quantitative way. Dynamic models, on the other hand, provide more physiologically relevant hydrodynamics and secretion profiles [194]. Hybrid methodologies amalgamate in vitro digestion results with physiologically based pharmacokinetic (PBPK) frameworks or cellular absorption models, progressing towards mechanistic in vitro-in vivo correlation (IVIVC) [195].

6.2.1 pH-Stat Lipolysis Model

The pH-stat model is the best way to measure how well lipids break down in a lab. In this technique, triglyceride-rich mixtures are mixed with buffers that contain pancreatic lipase. The release of FFAs during enzymatic hydrolysis lowers the pH. To keep the pH level stable (normally between 6.5 and 7.0), a titrant (usually NaOH) is automatically added. The amount of titrant used is then used to figure out how much digestion has happened [196], [197]. This makes it possible to measure lipolysis kinetics, enzyme turnover, and total FFA release, which show how SMEDDS and other lipid carriers are broken down in the digestive system [198].

The pH-stat model also helps with drug redistribution analysis by splitting post-digestion samples into two phases:

- **Aqueous phase (solubilized drug in mixed micelles/vesicles)**
- **Pellet phase (precipitated drug or solid lipids)**
- **Oil/cream phase (residual undigested lipids)**

Quantifying drug mass in each phase yields insights into precipitation tendency, solubilization efficiency, and colloidal buffering capacity parameters indicative of absorption outcomes [199], [200]. Recent improvements include biorelevant bile salt/phospholipid mixtures, lipase colipase complexes, and simulated intestinal fluids. These make the product more clinically relevant and of more interest to regulators [201]. The model is extensively used; however, it doesn't include GI hydrodynamics or absorption interfaces. This is why static or dynamic models are often used alongside it.

6.2.2 Buffer/Enzyme-based Static Digestion Models

Static digestion models use simulated intestinal fluids (SIFs) and biological or recombinant digestive enzymes to mimic how the intestines break down food without controlling the pH. FaSSIF (fasted-state simulated intestinal fluid) and FeSSIF (fed-state simulated intestinal fluid) are two common media that contain bile salts (BS), phospholipids (PL), and buffered salts at concentrations that are relevant to biorelevant conditions [202], [203]. These models allow for the assessment of bile salt-lipid interactions, micelle/vesicle production, and the kinetics of drug solubilization during digestion [203].

Static systems do not actively titrate released FFAs like pH-stat models do. Instead, changes in pH serve as an indirect sign of lipolysis. Bile salts help with interfacial displacement, which makes droplets smaller and helps mixed micelles form that dissolve lipophilic drugs [204], [205]. Static models are easier to use and more accessible than dynamic digestion platforms, but they can't control enzymatic turnover, gastric-to-intestinal transitions, or buffer capacity. This makes them less accurate when the body is strongly fed [206], [207].

6.2.3 Dynamic Digestion Models

Dynamic models replicate gastrointestinal digestion by incorporating time-dependent pH fluctuations, secretion rates, peristaltic mixing, gastric emptying, and intestinal transit, hence providing enhanced physiological relevance. The

Dynamic Gastric Model (DGM) simulates the stomach's churning, secretion, and controlled emptying into the duodenum. This lets researchers test acid-sensitive formulations and see how food affects them [208], [209]. TIM-1 (TNO Gastro-Intestinal Model) is a more advanced system that has modular compartments for the stomach, duodenum, jejunum, and ileum. These compartments have enzyme, bile salt, and buffer perfusion, which simulates luminal fluxes and absorption across semi-permeable membranes [210].

Dynamic platforms enable concurrent evaluation of lipolysis kinetics, colloidal transformations, drug dissolution, and simulated absorption, offering enhanced understanding of lipid digestion and drug absorption mechanisms that static and pH-stat models fail to elucidate [211], [212], [213]. But these systems utilize a lot of resources, need specialist knowledge, and have a low throughput, therefore they can only be used for mechanistic research or late-stage formulation development [214], [215].

6.2.4 Hybrid in-vitro/in-silico Digestion Models

Hybrid models combine in vitro lipolysis data with in silico computational tools (such GastroPlus®, Simcyp®, or PBPK models) to predict plasma concentration time profiles and IVIVC without having to do animal studies [216], [217], [218]. In these frameworks, digestion-induced drug precipitation, solubilization, and micellar partitioning inform absorption modules that take into account intestinal permeability, lymphatic transport, and first-pass metabolism [216], [218], [219], [220].

Recent workflows utilize machine learning (ML) to categorize formulation performance or forecast ideal excipient ratios based on digestion results, bile salt profiles, and physicochemical parameters [221]. Hybrid techniques are becoming more in line with regulatory goals in mechanistic, reductionist models that could lessen the need for in vivo animal research while still supporting QbD submissions [222].

6.3 Analysis During and After Digestion

To fully understand how drugs work, how colloids change over time, and the hazards of precipitation, you need to fully characterize them before and after digestion. These factors all affect SMEDDS performance. Some important analytical endpoints are:

• Changes in particle size: assessed using time-resolved DLS or NTA to watch for coalescence, fragmentation, or micelle formation while digestion is going on [223].

• Drug precipitation potential: assessed by measuring drug mass in pellet fractions after centrifugation, signifying supersaturation collapse [224], [225].

• Drug partitioning: usually measured by employing HPLC/UPLC-MS to separate the aqueous, pellet, and oil/cream phases and figure out how well the drug spreads out, which shows how well it can dissolve and be absorbed [226].

• Solubilization capacity and colloidal profiling: SAXS, cryo-TEM, or diffusion NMR were used to find mixed micelles, vesicles, or hexagonal liquid crystals that formed during digestion [227], [228].

These investigations yield mechanistic insights that traditional dissolution tests fail to capture. Several studies have shown that the amount of medicine that is linked to the aqueous/micellar phase is related to how well it works when taken by mouth. This supports its usage in developing IVIVC and making regulatory decisions [229], [230].

6.4 Advantages and Limitations of Lipid Digestion Models

In vitro lipid digestion models provide numerous benefits for the characterization of SMEDDS. They offer mechanistic insights into lipolysis-driven colloidal transitions, drug precipitation/supersaturation dangers, and

solubilization pathways that conventional dissolution testing does not elucidate [230]. Additionally, digestive models enable researchers to measure drug partitioning among aqueous, pellet, and colloidal phases, which are factors that have established correlations with oral bioavailability and IVIVC development [231], [217], [218], [228]. The capacity to include biorelevant bile salt/phospholipid compositions facilitates the simulation of fasting and fed states, as well as food-effect evaluations, hence augmenting translational relevance for lipid-based systems.

But there are still some big problems. First, the composition of enzymes and the concentrations of bile salts differ significantly between laboratories, leading to methodological variability that compromises clinical correlation and inter-study comparability [217]. Second, static and pH-stat models do not have gastric motility, pH gradients, secretion dynamics, or absorption compartments, which makes it hard for them to adequately mimic physiological environments [232]. Third, dynamic models like TIM-1 or DGM are more relevant to biology, but they are also expensive, slow, and hard to use, which makes it hard for them to be used by many people [233], [234], [235]. Finally, current digestion endpoints usually show solubilization instead of absorption, which means that medicine that has settled may still dissolve in vivo, making it harder to understand and less accurate for predictions [217], [224], [236]. Lipid digestion models are more effective when integrated with cellular uptake systems, PBPK models, or IVIVC frameworks, rather than utilized independently.

7. In-Vitro In-Vivo Correlation (IVIVC) for SMEDDS

7.1 Meaning of IVIVC

The term "in-vitro-in-vivo correlation" (IVIVC) refers to a predictive mathematical link between an in vitro test outcome (e.g., dissolution, lipolysis, or solubilization profile) and in vivo performance measures such as plasma drug concentration, absorption rate, or bioavailability [217], [237], [238]. Classical dissolution testing is generally insufficient for SMEDDS and other lipid-based systems since performance is determined by lipid digestion, mixed micelle generation, and precipitation dynamics rather than disintegration [217], [236], [239]. Thus, an IVIVC for SMEDDS must incorporate digestion-dependent solubilization profiles and supersaturation windows to better reflect the mechanical determinants of absorption [240], [241].

Regulatory bodies acknowledge IVIVC as a valuable tool for biowaiver justification, scale-up and post-approval adjustments (SUPAC), and minimizing needless in vivo investigations. However, due to the complicated interaction between formulation and physiology, successful IVIVCs for lipid systems are uncommon, emphasizing the necessity for sophisticated modelling methodologies specific to lipid digestion behaviours [242].

7.2 Classes of IVIVC

IVIVC is divided into many categories based on correlation strength and granularity.

1. Level A (Point-to-Point Correlation) indicates a direct link between in vitro and in vivo profiles. It is the most informative category and is appropriate for bioequivalence and regulatory decision-making, but it is challenging to demonstrate for SMEDDS due to nonlinear digestion-absorption processes [232], [243].

2. Statistical moment analysis (Level B): Correlations are built using parameters such mean dissolution/absorption time. While easier to get, Level B lacks distinctiveness and cannot sustain regulatory biowaivers on its own [244], [243], [245].

3. Level C (Single-point correlation): Identifies a link between an in vitro parameter (e.g., time to

50% solubilization) and an in vivo parameter (e.g., Cmax or AUC). It has little usefulness and is rarely accepted without several Level C correlations [243], [246], [247].

4. Multiple Level C: numerous in vitro time points are associated to numerous pharmacokinetic outputs, which improves predictive value and is widely used in the evaluation of lipid-based formulations.

Multiple Level C and hybrid digestion-PBPK-based Level A correlative frameworks are emerging for SMEDDS because they combine lipolysis kinetics, solubilization capacity, and precipitation events into prediction models.

7.3 Why IVIVC is Important for SMEDDS.

Conventional dissolution testing is ineffective for SMEDDS because these systems do not undergo simple tablet dissolution; rather, there in vivo performance is dependent on a series of processes such as self-microemulsification, lipid digestion, mixed micelle formation, supersaturation, and drug precipitation or re-solubilization [22], [240], [241]. As a result, traditional in vitro release techniques fail to capture the biopharmaceutical factors that influence oral bioavailability for lipid-based carriers.

IVIVC predicts in vivo exposure based on in vitro data, minimizing the need for exploratory animal research and facilitating bioequivalence, scale-up, and regulatory filings [248]. The most useful in vitro inputs for SMEDDS include lipolysis kinetics, aqueous-phase drug concentrations, and supersaturation duration, which correlate better with enterocyte-level drug absorption than simple dissolution curves [249], [224]. Establishing IVIVC provides developers with insight into dietary effects, drug precipitation hazards, and formulation-dependent variability, allowing for reasonable formulation optimization and iterative refinement without significant in vivo testing [218], [250]. Thus, IVIVC is a critical enabling tool for Quality by Design (QbD) and regulatory science in the lipid-based formulation domain.

7.4 Approaches to Establish IVIVC for SMEDDS

Several methodological approaches have been presented to construct IVIVC frameworks specific to SMEDDS:

(i) Lipid digestion-driven IVIVC: pH-stat lipolysis, static/evolving SIF digestion, or dynamic digestion models yield FFA release profiles, micellar drug concentrations, and precipitated fractions. These can be plotted against plasma exposure to develop correlation models [251]. Because of its proximity to enterocyte uptake, the aqueous/micellar fraction is frequently used as a proxy for the absorbed fraction [241].

(ii) Deconvolution-based IVIVC: Pharmacokinetic deconvolution approaches (e.g., Wagner-Nelson, Loo-Riegelman) link in vitro release/solubilization to fraction absorbed, allowing for Level B or multiple Level C IVIVC without needing point-to-point correspondence [252]. When paired with lipolysis data, deconvolution assists in determining which digestion phases (e.g., supersaturation windows) drive bioavailability.

Physiologically based pharmacokinetic (PBPK) models use lipid digestion, drug precipitation, and micellar solubilization as input functions to simulate intestine absorption and systemic exposure [253], [254]. Lipid digestion modules are currently supported by software such as GastroPlus®, Simcyp®, and PK-Sim®, allowing for virtual bioequivalence and population simulations required for regulatory submissions [241], [255], [256].

(iv) In silico/AI prediction tools: To forecast in vivo exposure or classify formulations by bioavailability tier, machine learning (ML) models were developed utilizing formulation composition, log P, pKa, lipolysis outputs, and permeability

parameters [232], [257]. These data-driven tools make IVIVC more feasible when mechanistic or clinical datasets are insufficient.

Collectively, these methods represent a change away from classic dissolution-centric IVIVC and toward digestion- and absorption-centric frameworks that are more in line with SMEDDS pharmacological processes.

7.5 Challenges in Developing IVIVC

The complicated interplay between formulation, digestion, and physiology makes developing robust IVIVC for SMEDDS an inherent challenge. First, the gastrointestinal (GI) tract has significant spatiotemporal variability in pH, bile salt concentration, phospholipid content, enzyme activity, and motility, all of which impact lipid digestion and mixed micelle production in ways that are challenging to imitate in vitro [258], [259]. Second, SMEDDS frequently cause supersaturation followed by drug precipitation during digestion, although precipitation kinetics do not always correspond with absorption outcomes because precipitates can stay amorphous or re-dissolve downstream in the intestine [240], [260]. Nonlinear absorption can also be complicated by solubilization-dependent permeability, intestinal transporter saturation, or carrier-mediated lymphatic uptake pathways for highly lipophilic molecules [40], [241], [261]. Furthermore, food effects have a major impact on lipid digestion and medication bioavailability by modifying bile salt secretion, lipid co-ingestion, and stomach emptying, making fasted vs fed condition predictions problematic for SMEDDS products [240], [241]. There is no particular regulatory guidance for lipid-based delivery systems, and current frameworks are borrowed from dissolution-based IVIVC designed for extended-release oral solids, leaving conceptual gaps for formulation scientists [231], [241]. Collectively, these characteristics explain why successful Level A IVIVCs for SMEDDS are still uncommon, necessitating mechanistic digestion-absorption modelling rather than traditional dissolving techniques.

7.6 Recent Advances

Recent research has concentrated on circumventing these constraints using mechanistic, computational, and data-driven approaches. One significant advancement is the development of mechanistic IVIVC frameworks that link in vitro digestion outputs (e.g., aqueous drug concentration, micellar solubilization, precipitation fractions) to PBPK simulations, allowing for point-to-point prediction of plasma exposure for lipid-based formulations [262], [218], [263], [264].

In parallel, AI/ML techniques for IVIVC prediction and formulation classification have gained traction, utilizing high-dimensional datasets containing physicochemical descriptors, excipient ratios, lipolysis measurements, and intestinal permeability parameters [232], [264], [265]. Such models may detect nonlinear patterns that standard regression cannot, and have been used to successfully discern bioavailability tiers in SMEDDS formulations.

Several groups have also constructed combined lipid digestion + cell-based uptake models, in which digestion effluents are directly applied to Caco-2 or organoid monolayers to determine absorption potential in physiologically relevant colloidal environments [266], [267]. Furthermore, microfluidic GI platforms and dynamic biphasic digestion-absorption assays allow real-time insight into drug transfer from digestion media to an absorptive sink, which improves predictability without the use of animals [268], [250]. Collectively, these advancements constitute a paradigm shift toward predictive, mechanistic, and regulatory-aligned IVIVC, paving the way for greater

translation of SMEDDS into clinically viable therapies.

8. Comparative Analysis of Characterization Strategies

A key question in SMEDDS evaluation is which characterisation approaches best predict in vivo bioavailability. Historically, SMEDDS development prioritized droplet dynamics (size, charge, and morphology) as main performance metrics, with the notion that smaller droplet sizes increase surface area and therefore solubilization. While droplet metrics provide useful physicochemical information, accumulating evidence shows that they are insufficient predictors of absorption because bioavailability is dependent on downstream lipid digestion, drug supersaturation, precipitation risk, and mixed micelle solubilization, which are not captured by pre-digestion droplet analysis [5], [6], [18].

Comparative studies currently suggest that lipid digestion models particularly those tracking micellar drug concentrations and precipitation kinetics correlate better with oral exposure for weakly water-soluble medicines administered via SMEDDS [269]. For example, the aqueous/micellar drug fraction during lipolysis is more significantly related to in vivo AUC than initial droplet size or zeta potential alone [270], [271]. Furthermore, digestion assays allow for a more mechanistic interpretation of dietary effects, which standard droplet methods cannot.

In terms of regulation, no single approach is currently regarded as a surrogate for in vivo absorption of lipid-based systems. According to recent FDA and EMA scientific opinions, integrated frameworks that combine droplet characterisation, digestion modelling, and PBPK/IVIVC techniques provide the most scientifically defensible strategy for product translation and QbD submissions [6], [41], [272]. This represents a transition from empirical screening to mechanistic and computational evaluation.

To emphasize the relative strengths and limitations, Table 1 presents a comparative summary of main SMEDDS characterisation approaches.

Table 1. Comparison of Major SMEDDS Characterization Strategies

Method Category	Representative Techniques	Primary Outputs	Strengths	Limitations	Bioavailability Predictive Value
Droplet Dynamics	DLS, NTA, zeta potential, TEM	Droplet size, PDI, charge, morphology	Fast, accessible, QC-friendly; detects instability	No digestion or precipitation info; static conditions	**Low Moderate** (pre-digestion only)
Thermodynamic Stability Tests	Centrifugation, thermal cycling, freeze thaw	Phase separation, turbidity, robustness index	Useful screening; identifies instability risks	Limited physiological relevance; no absorption link	**Low**
Lipid Digestion Models (Static/pH-stat)	pH-stat, FaSSIF/FeSSIF	FFA release, precipitation, micellar solubilization	Mechanistic insight; digestion-driven data	No motility or absorption; variable bile/enzyme levels	**Moderate High**
Dynamic Digestion Models	DGM, TIM-1	Digestion kinetics + simulated transit	High physiological fidelity; food-effect modelling	Low throughput; costly; technically demanding	**High**

Hybrid In-vitro/In-silico	Lipolysis + PBPK; ML models	Predicted plasma profiles; virtual BE	Enables IVIVC; reduces animal testing	Requires high-quality input data	**Very High (emerging)**

Taken collectively, the comparative landscape indicates that no single assay is sufficient to capture the full biopharmaceutical behaviour of SMEDDS. Instead, an integrated evaluation strategy is required, incorporating:

- Physicochemical characterization (droplet size, PDI, ζ-potential)
- Thermodynamic stress testing (centrifugation, thermal cycling)
- Biorelevant digestion modelling (static, pH-stat, dynamic)
- Simulation frameworks (PBPK, deconvolution, ML/AI)

Such integration provides orthogonal datasets linking formulation properties → digestion behaviour → absorption potential, improving predictability, regulatory robustness, and IVIVC feasibility [41], [273], [274]. Future regulatory guidance and harmonization efforts are expected to accelerate standardization of digestion-based assessments, enabling rational design of SMEDDS with improved clinical translatability.

9. Regulatory and Quality Considerations

SMEDDS require rigorous evaluation for regulatory approval because they exhibit complicated formulation-biopharmaceutical interactions that influence safety, effectiveness, and batch-to-batch consistency. Regulatory bodies are increasingly looking for demonstrations of mechanistic understanding, control measures, and prediction in vitro models that follow Quality-by-Design (QbD) principles [250], [273], [275]. For SMEDDS, this translates into a thorough examination of droplet dynamics, thermodynamic stability, and lipid digestion behaviour, all of which have a direct impact on oral bioavailability and variability.

Although the FDA, EMA, and ICH do not currently give lipid-specific product guidelines, several regulatory publications indirectly apply to SMEDDS, including:

- FDA's Guidance on Lipid Excipients & Nanotechnology (characterization, safety, CMC requirements)
- EMA Reflection Papers on PBPK and Bioavailability/Bioequivalence (IVIVC, modelling)
- ICH Q8 Q12 (QbD, lifecycle management, risk assessment)

These frameworks emphasize critical quality attributes (CQAs) such as droplet size, PDI, zeta potential, robustness index, and digestion-driven solubilization, reinforcing the need for standardized measurement protocols [276], [269].

A significant regulatory gap is the lack of standardized procedures for lipid digestion testing and droplet analysis, which causes variation in research design, bile salt concentrations, enzyme activity, and analytical endpoints among laboratories [277], [278]. Without harmonization, comparing performance data across development phases or jurisdictions is problematic, impacting bioequivalence assessments, SUPAC revisions, and worldwide dossier submissions.

Furthermore, lipid-based formulations are under increased scrutiny for excipient safety, especially for paediatric or chronic administration, and regulators seek justification of excipient functionality, exposure limits, and metabolic fate [279], [241], [280]. Emerging regulatory interest in in vitro-in silico techniques (e.g., PBPK, virtual bioequivalence, machine learning predictors) is paving the way to minimize animal studies while improving mechanistic evaluation of SMEDDS [241].

In the future, standardized biorelevant lipolysis methods, recognized digestion-based CQAs, and better IVIVC advice for lipid systems will greatly increase regulatory predictability. International collaboration, possibly through ICH workstreams, will be required to coordinate terminology, test conditions, acceptance criteria, and data interpretation for SMEDDS and other lipid-based delivery systems [4], [40], [82]. Such advancements will hasten the transformation of novel lipid formulations into clinically significant and globally approved pharmaceuticals.

10. Future Perspectives & Research Gaps

The field of SMEDDS characterization is experiencing methodological revolution, owing to the shift toward solid SMEDDS (S-SMEDDS) and the need for biorelevant, predictive, and computationally enabled evaluation frameworks. Solidification strategies such as adsorption onto carriers, spray drying, or hot-melt extrusion improve stability, patient compliance, and manufacturability, but they also introduce new challenges in drug release, re-emulsification kinetics, and digestion coupling that are not adequately addressed by current characterization tools [281], [282] Future research should provide standardized platforms for evaluating reconstitution behaviour, lipolysis following solid-state processing, and drug re-precipitation hazards, as these will be crucial for S-SMEDDS translational success.

Another emerging opportunity is to use AI and ML-driven predictive models to forecast bioavailability and classify formulation performance early in development by leveraging large datasets encompassing formulation composition, log P/pKa, lipolysis kinetics, supersaturation windows, and permeability parameters [283]. Integrating such models with PBPK engines could result in virtual bioequivalence simulations, speedier QbD workflows, and fewer animal investigations, all of which would be consistent with evolving regulatory expectations and 3R (Replace-Reduce-Refine) principles [41], [284]. However, the lack of curated, standardized datasets continues to be a barrier to mainstream AI adoption, emphasizing the importance of shared, multi-institutional formulation databases.

Significant research gaps also exist in biorelevant in vitro digestion models, particularly in terms of dynamic secretion profiles, individual variability in bile/enzymes, and fed-state complexity, all of which influence real-world performance of lipid-based systems [6], [39]. Advances in microfluidic GI models and organ-on-chip platforms present exciting opportunities for real-time imaging of droplet evolution, phase transitions, and digestion-absorption coupling, but these systems must be validated and harmonized before being used routinely [285], [241], [286]. Furthermore, combining digestion results with intestinal cell/organoid uptake assays or in situ perfusion models may eliminate mechanistic gaps between the solubilization and absorption phases, allowing for more therapeutically appropriate IVIVC strategies [262], [231], [218], [287].

Finally, the transition of SMEDDS from laboratory to clinic is hampered by a lack of regulatory guidance, inadequate consistency of lipid digestion and droplet characterisation, and uncertainty about food effects, patient variability, and long-term safety of novel excipients. Future collaborations among industry, academia, and regulators are required to identify lipid-specific critical quality attributes (CQAs), create digestion-focused compendial methodologies, and establish PBPK-linked IVIVC frameworks specialized to lipid-based formulations. This convergence will hasten the approval of therapeutically significant pharmaceuticals and aid in the maturing of SMEDDS as a predictable and scalable enabling technology for poorly soluble medications.

CONCLUSION

The characterisation of SMEDDS is critical to promoting lipid-based administration as a clinically and commercially feasible method for poorly water-soluble medicines. Individual characterization domains, such as droplet dynamics and thermodynamic stability, as well as lipid digestion modelling and IVIVC techniques, provide complimentary insights but differ greatly in their translational relevance. Droplet-based parameters (size, charge, and shape) are useful for quick formulation screening and quality control, but they have little predictive potential for in vivo performance in isolation. Stability studies help manufacturability and storage robustness, but they fall short of capturing the digestion-driven colloidal alterations that ultimately determine absorption.

Biorelevant lipid digestion models and hybrid digestion-modelling methodologies are the most closely aligned with clinical pharmacokinetics, capturing supersaturation, precipitation, and solubilization routes in physiologically relevant medium. However, the discipline continues to have significant shortcomings, such as low standardization, laboratory-to-laboratory heterogeneity, and insufficient regulatory guidance unique to lipid systems. These problems impede IVIVC development, complicate global dossier submissions, and undermine trust in preclinical-to-clinical translation.

Taken together, the benefits and weaknesses of existing approaches highlight the need for integrated multimodal characterization frameworks that incorporate physicochemical investigations, digestive modelling, and computer simulation within a Quality-by-Design (QbD) framework. Harmonization of test settings, validation criteria, and biorelevant endpoints among academic, industry, and regulatory stakeholders is required to produce mechanistic, predictive, and globally acceptable SMEDDS characterisation standards. By embracing this convergence, the field will hasten the transition of SMEDDS from promising laboratory systems to predictable, scalable, and clinically relevant supporting technologies.

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