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Advancements in Solubility and Bioavailability Enhancement of BCS Class II Drugs: A Comprehensive Review Using Quality by Design Approach for Self-Emulsifying Drug Delivery Systems

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ABSTRACT

BCS Class II drugs have poor aqueous solubility combined with high permeability, and therefore, in many cases, they cannot have effective oral bioavailability. Such restrictions introduced the need to innovate drug delivery techniques to make the drugs soluble and increase their uptake into the system. Salvaging these limitations through lipids has led to the development of a self-emulsifying drug delivery system (SEDDS) is a promising lipid-based platform that emulsifies to make fine emulsions when in contact with gastrointestinal fluids and consequently enhance the dissolution rates and lymphatic transport. This review explores an in-depth evaluation of the current development in the field of SEDDS formulation of the BCS Class II drug, with particular emphasis placed on the usage of the Quality by Design (QbD) approach. Important formulation materials such as oils, surfactants, and co-surfactants are discussed in the light of drug-lipid compatibility. Critical quality attributes (CQAs), critical material and process parameters (CMAs and CPPs), risk assessment tools and design of experiments (DoE) are also covered in this review as part of the QbD-based optimization process. Examples of case studies using anticancer, antifungal and anti-inflammatory drugs depict the therapeutic influence of SEDDS. It also talks about comparative analysis to other nanocarriers, regulatory aspects and industrial outlook. Future trends of the technology are outlined in the emerging innovations, such as the hybrid nanocarriers, the use of artificial intelligence (AI) in formulation, and the approach of personalized medicine. The purpose of this review will be to direct researchers and formulators to an efficient design and usage of SEDDS in enhancing oral drug delivery of poorly aqueous soluble drugs.

Keywords: BCS Class II drugs, SEDDS, Quality by Design, Solubility enhancement, Bioavailability, Lipid-based drug delivery, Nanoformulations, Nanocarriers.

INTRODUCTION

The Biopharmaceutics Classification System is a model that has been established to categorise drug substances depending on the rate of solubility and intestinal permeability. The BCS

class drugs are classified into four groups: Class I, Class II, Class III,and Class IV[1,2]. The classification is useful in the prediction of drug absorption and plays an imperative role in influencing formulation development and strategies fit for regulation. One of them, BCS Class II drugs poses a special challenge since although they have good permeability, their low solubility renders it a rate-limiting step in the production of sufficient bioavailability[1,3]. The erratic or incomplete absorption of BCS Class II drugs can be attributed to the poor aqueous solubility of these drugs. These medications are prone to being dissolved slowly in gastrointestinal fluids, thus reducing the rate of absorption, and there is a possibility of insufficient therapeutic effects. It is made even more difficult to formulate them by factors like lipophilicity, polymorphic behaviour, and pH-dependent solubility[4]. Also, the absorption can be varied due to food effects and gastrointestinal motility. These difficulties require the formulation of smart drug delivery approaches that will improve the rate of dissolution, ensure biocompatible, and non-fluctuation. The purpose of increasing the solubility and bioavailability of BCS Class II drugs is now on the agenda of contemporary pharmaceutical development. There is also the opportunity of improved dissolution profiles, absorption rates and therapeutic effectiveness[5]. Technologies like solid dispersions, complexation with cyclodextrins, micronization and lipid-based formulations, which have a lot of potential to overcome solubility barriers, have been exhaustively explored[6]. Lipid-based formulations, such as the SEDDS, has become one of these, since they present an enhanced solubilising ability in gastrointestinal fluids as well as the potential to avoid hepatic first-pass metabolism in certain cases, hence a greatly increased bioavailability[7,8]. This review addresses a highly topical and timely issue in pharmaceutical sciences, the integration of SEDDS with the (QbD) approach, which holds significant potential to improve formulation efficiency, ensure batch-to-batch reproducibility, and facilitate regulatory compliance. This combination will address the pressing problem of increasing the solubility and bioavailability of BCS Class II medications through a structured and scientifically supported formulation[9].

The advancements made in solubility and bioavailability enhancement strategies in specific to BCS Class II drugs, particularly, it will discuss the use of the Quality by Design (QbD) approach when practising self-emulsifying drug delivery systems[10]. This paper explores that the concepts of SEDDS, their formulation design, essential elements, and the application of QbD tools (including the risk assessment and Design of Experiments) to optimize the parameters of formulation and process. Combining evidence of new research, case studies and regulatory questions, this review aims to be a comprehensive guideline to researchers and formulators focused on the area of lipid-based nanocarrier systems of low soluble drugs.

BCS Class II Drugs: Characteristics and Limitations

BCS Class II drugs are defined by their poor aqueous solubility and high intestinal permeability. These drugs can permeate the intestinal epithelium effectively but face significant challenges in dissolving in gastrointestinal (GI) fluids. The primary physicochemical characteristic that defines this class is the intrinsic solubility being lower than the threshold required to fully dissolve the drug in a typical dose volume (250 mL water) across the physiological pH range[11,12]. Consequently, these drugs fail to achieve the desired dissolution profile, making solubility the rate-limiting step for absorption. Many Class II drugs are lipophilic, with log P values typically greater than 3, and exhibit poor wettability, which contributes to their slow dissolution[12,13]. Furthermore, the crystalline nature of these compounds tends to reduce solubility as well, due to strong intermolecular forces within the solid-state structure. In contrast, amorphous forms of drugs, although more soluble, are often thermodynamically unstable and prone to recrystallization during storage or in vivo conditions. Additionally, the dissolution rate of BCS Class II drugs is influenced by the pH of the GI tract[14,15]. Drugs which possess weak acidic properties are more soluble in higher pH (preferably in the intestine) and weakly base drugs, more soluble in the stomach. However, the Drugs may precipitate as the GI tract changes form acidic to alkaline conditions causing variations in drug absorption. Therefore, the interaction of a drugs ionization characteristics and the GI pH conditions have an important role in the characteristics of bioavailability of a drug[16].

Absorption Barriers

Although the BCS Class II drugs exhibit high permeability in the bio membranes, they experience very poor solubility that poses great obstacles to absorption. The low concentration of

the dissolved drug at the absorption site is one of the main barriers of absorption. When drug fails to dissolve in the GI fluids adequately and quickly, the concentration gradient between the GI fluids and inside of the intestinal membrane will not be created. As such, the drug will be poorly absorbed through passive diffusion. Also, BCS Class II medications are prone to precipitation of the GI tube. A drug which has been solubilised in an acidic medium of the stomach would precipitate in the more neutral and/or alkaline environment of the small intestine where most drugs are absorbed[17]. This is because of a process referred to as supersaturation and precipitation whereby the drug saturates itself thus lowering the available free drug to permeate and hence bioavailability. The interaction with food is another factor that influences poor soluble drugs absorption. In the presence of food especially high-fat foods, solubilization of lipophilic drugs may be boosted or suppressed. Food can enhance (induce) bile salt secretion, which facilitates solubilization of poorly soluble drugs they are micellar trapped, as well as they can slow gastric emptying and influence the rate of movement of a drug, further causing interpersonal variability of drug absorption and pharmacokinetics[17,18]. Additionally, certain Class II drugs may undergo extensive first-pass metabolism, primarily due to the activity of cytochrome P450 enzymes, especially CYP3A4, present in the wall of intestine and liver, which significantly diminishes the drug's plasma concentration following oral administration[19,20]. Poor solubility, followed by poor bioavailability of BCS Class II drugs, presents several clinical difficulties. Their absorption is inconsistent and unpredictable; therefore, this can cause variation in therapeutic outcomes. Moreover, formulation issues that may compromise the integrity and performance of the dosage form, like drug recrystallization, stability, and in vivo precipitation, may hinder their effectiveness and may require specialized packaging or storage environments (Figure 1)[13,21].

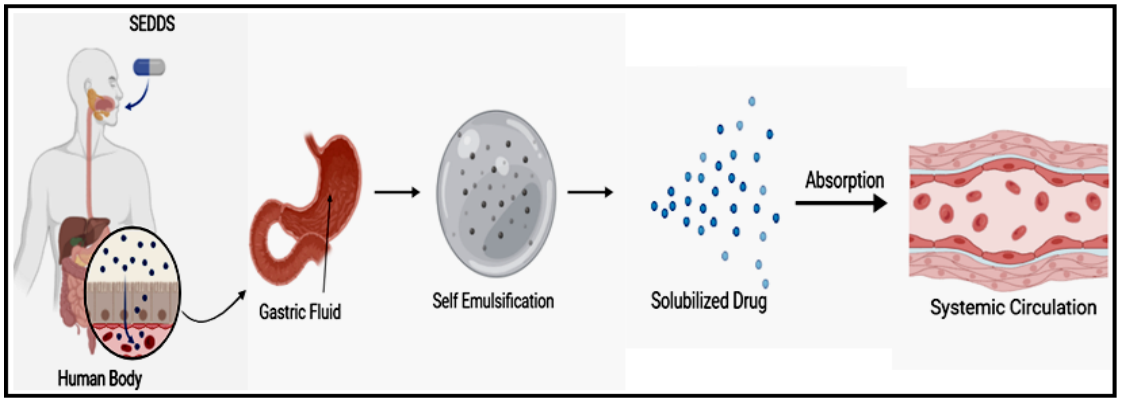

Fig. 1. Absorption barriers if SEDDS

Self-Emulsifying Drug Delivery Systems

SEDDS are isotropic mixtures of oils, surfactants, and sometimes co-surfactants that can spontaneously emulsify in the aqueous medium of the GI tract with gentle agitation. Typically, this motion is provided by the peristaltic movements in the bowels and intestines. When these systems are diluted in GI fluids, oil-in-water emulsions or microemulsions with tiny droplets on the order of nanometers or smaller are formed. The most significant advantage is the remarkable increase in solubility and dissolution rate of low water-soluble pharmaceuticals, particularly BCS Class II compounds[22]. The mechanism of action of SEDDS involves the pre-dissolving of the lipophilic drug in a lipid-based formulation. Upon oral administration, when this formulation encounters aqueous solutions like gastric or intestinal fluids, it rapidly emulsifies, and the minute droplets create a large interfacial area. This increases the absorption surface area of the drug, ensuring solubilization throughout its journey through the GI tract. SEDDS can also induce lymphatic transport, circumventing hepatic first-pass metabolism for certain drugs, resulting in enhanced bioavailability[22,23].

Types of SEDDS (SEDDS, SNEDDS, SMEDDS)

A broad classification based on the size of the emulsion droplets formed after dispersion, their thermodynamic stability, and dispersion media content, SEDDS can be generally divided into three general types: SEDDS, SMEDDS,and SNEDDS.

Table 1: Comparison of SEDDS, SMEDDS, and SNEDDS[24,25]

Parameter	Self-Emulsifying Drug Delivery System	Self-Microemulsifying Drug Delivery System	Self-Nanoemulsifying Drug Delivery System	Bioavailability Outcome/ Real-World Examples
Droplet Size	>250 nm	100–250 nm	<100 nm	A smaller droplet size leads to increased surface area and improved absorption
Appearance	Turbid/emulsion-like	Transparent to slightly opalescent	Transparent/nanoemulsion	—
Composition	Oils, low to moderate surfactant levels	Oils, higher surfactant and co-surfactant content	Oils, high surfactant/co-surfactant, sometimes cosolvents	SNEDDS allows better solubilization of lipophilic APIs
Emulsification Time	Slower	Faster	Very rapid	Rapid emulsification correlates with quicker onset of action
Thermodynamic Stability	Moderate	High	High	SMEDDS/SNEDDS show superior long-term storage stability
Drug Loading	Moderate	Higher than SEDDS	High, with enhanced solubilisation	SNEDDS for Curcumin improved bioavailability >7-fold vs. plain drug
Manufacturing Complexity	Low	Moderate	Moderate to high	SNEDDS requires more precise control of surfactant/co-surfactant ratios

Advantages of SEDDS over Conventional Systems

Among the prime features is the fact that SEDDS enhance the solubilization of hydrophobic drugs in the GI tract. This will not just enable quick and consistent absorption but also reduce the variability tied to food consumption and the movement of the GI tract[26]. A distinct advantage to SEDDS is that the drug is maintained in a dissolved state, and the dangers of precipitation are negated, and as such a consistent concentration gradient can be established to aid the intestinal absorption process. Also, lymphatic transport may be activated using the lipid-based formulation, where first-pass hepatic metabolism is avoided in relation to some highly lipophilic drugs, thus boosting the systemic availability. This is especially true for peptide/protein drugs and drugs that are susceptible to hydrolysis or oxidation[27]. Furthermore, SEDDS formulations can be customized through a Quality by Design (QbD) strategy to minimize droplet size, time of emulsification and maximize drug load[28,29]. Nevertheless, SEDDS can be an impressive tool that enhances the solubility and bioavailability of those drugs that cannot be well dissolved in water.

Formulation Components of SEDDS

The effectiveness of Self-Emulsifying Drug Delivery System (SEDDS) is greatly determined by the selective choice of its major formulation ingredients like lipid phase (oils), surfactants and co-surfactants. All these components are critical towards drug solubilization, emulsification of the drug, and general stability of the formulation. Also, compatibility of drugs with lipids is very essential to guarantee drug equilibrium, stabilisation and bioavailability[30]. The discussion of each component with appropriate examples is presented below in detail.

Lipid Phase (Oils)

SEDDS A lipid or oil-based phase constitutes the core of an SEDDS formulation and acts as a solvent to the lipophilic drug. The selection of the nature of oil, either long-chain triglycerides or medium-chain triglycerides, influences the size of a droplet, digestion, and the degree of lymphatic absorption[30,31]. Long-chain triglycerides (LCTs) such as corn oil, soybean oil, and oleic acid can enhance lymphatic transport but tend to form larger emulsion droplets. However, medium-chain triglycerides (MCTs) like caprylic/capric triglyceride are preferred for their rapid emulsification and ability to produce smaller droplets. Additionally, modified oils such as Labrafac™ Lipophile WL 1349, composed of glycerides of caprylic and capric acids, provide excellent drug solubilization capacity and high emulsification efficiency. In the formulation of a SEDDS for the poorly soluble drug Itraconazole, LabrafacLipophile was used as the lipid phase, contributing to enhanced dissolution and improved oral bioavailability[32].

Surfactants and Co-surfactants

Surfactants are essential for the spontaneous formation of emulsions in SEDDS by lowering the interfacial tension between the oil and water phases. They also help stabilize the emulsion droplets. The choice of surfactant is critical; it must be non-toxic, possess a high hydrophilic-lipophilic balance (HLB), and be capable of forming nano/microemulsions on mild agitation[30]. High HLB surfactants (HLB>12), such as Tween 80 and Cremophor RH 40, are commonly used to form oil-in-water emulsions. Co-surfactants like Transcutol P and PEG 400 further enhance the interfacial film's fluidity, promote uniform dispersion, and improve drug solubilization. The surfactant-to-co-surfactant ratio (commonly referred to as the Smix ratio) is optimized using pseudo-ternary phase diagrams to identify the self-emulsifying region. The right balance of these components ensures efficient emulsification and stable formulation[33,34].

Quality by Design Approach in SEDDS Development

The systematic, science-based, and risk-based model of pharmaceutical development enables Quality by Design (QbD) to focus more on the significance of identification and management of formulation and manufacturing variables to assure expected product quality. QbD was introduced by the International Conference on Harmonisation (ICH) in its guideline Q8 (R^2) to make sure that quality of the product is not tested after, but incorporated into the product at the beginning. As an example of using QbD concept in Self-Emulsifying Drug Delivery Systems (SEDDS), this application can be used to identify the best possible formulation factors, greater robustness in the process as well as better regulatory compliance[35,36]. QbD ties together the understanding of the drug physicochemical qualities, suitable functioning excipients, and process parameter to identify a design space whereby the product is robustly effective in achieving quality parameters. Such an organized system is more efficient, decreases time on development and allows scaled, repeatable manufacture (Figure 2)[35,37].

Critical Quality Attributes (CQAs)

CQAs refer to physical, chemical, biological or microbiological characteristics that have to be controlled within established limits to guarantee quality, safety and effectiveness of the products. CQAs in the case of SEDDS are usually associated with droplet size characteristics and other functions like zeta potential ratio, emulsification time, the proportion of the drugs, and *in vitro* drug release characteristics. Such changes as decreasing droplet size, which is associated with an increased surface area and an enhanced dissolution, make bioavailability more efficient[38,39]. An important performance indicator is emulsification time, which indicates the formulation's capacity to distribute rapidly in the GI fluids. The content of drugs is the same, guaranteeing the accuracy of dosing and its consistency, and the development of self-emulsifying drugs is vital to an emulsion under physiological conditions.

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

The properties of the raw materials and the excipients that may affect CQAs and consequently the quality of the finished product are the CMAs. In SEDDS, CMAs are the subsistence and proportion of oils, surfactants, co-surfactants and solubility of the drug in any of these ingredients. As an example, the emulsification potential is determined by the HLB (hydrophilic-lipophilic balance) value of the surfactant, whereas the solubility of the drug in the lipid phase will have a bearing on its stability and the likelihood of precipitation once diluted[40,41]. Critical Process Parameters (CPPs) refer to the operational parameters of the manufacturing process when varied at unacceptable limits, may have adverse effects on CQAs. CPPs that are used in the development of SEDDS can consist of mixing speed and time, temperatures during emulsification, sequence of component addition, and capsule-filling parameters. Such parameters must be well-regulated to prevent issues such as phase separation, uneven drug loading, or uneven droplet distribution[41].

Risk Assessment Tools (Ishikawa, FMEA)

Risk assessment is another fundamental

aspect of QbD and risk assessment helps determine, evaluate and rank the possible risks that may occur and affect product quality. The Ishikawa (fishbone) diagram and Failure Mode and Effects Analysis (FMEA) are two popular tools in development of SEDDS. The Ishikawa diagram assists in picturing the cause-consequence association amongst the possible sources of change, e.g., materials, method, equipment, and atmosphere, with the CQAs. It gives a rational grid on how to do brainstorming and classify factors which might affect the product performance[41]. FMEA is more quantitative and determines possible failure modes of every formulation and every process component and rates their severity (S), occurrence (O) and detectability (D) and computes a Risk Priority Number (RPN = S x O x D). This allows the risks to be prioritized and mitigation to be applied. To give an example, a low value of emulsification efficiency of a chosen surfactant may be allocated the high RPN and requiring reformulation or extra controls. With these tools, the risky factors can be addressed in advance and formulation and process can be optimized as reducing the variability and guaranteeing the robustness[41,42].

Design of Experiments (DoE) in Optimization

DoE is a strategy that is statistic in nature and it is utilized to study the effect of several variables of formulation and process on the CQAs in QbD. DoE is also used in the SEDDS development to determine the most effective mixture of oil, a surfactant and a co-surfactant and their dosage levels which will produce the desired droplets size, drug release profile, and stability. Some examples of popular design are factorial design, central composite design, BoxBehnken design. The fact that DoE enables response surface models that determine how the formulation will respond to diverse conditions is an advantage[41,42].

Recent Research Advancements

The use of SEDDS over the past few years has reached many different therapeutic classes, and there is potential to increase the level of solubility and bioavailability of poorly water-soluble medicines, specifically Class II medicines within BCS category[44]. Some of the most intensively developed ones include antifungal, anticancer, and anti-inflammatory treatments. Voriconazole, Itraconazole and Posaconazole are antifungal drugs that have enjoyed the advantage of the SEDDS formulations by virtue of poor water solubility and an enormous amount of hepatic metabolism. Jahan R *et al.,* developed SNEDDS of bedaquilinefumarate (BDQ-F) using QbD approach. By optimizing critical material attributes with caprylic acid, propylene glycol, and Transcutol-P, the formulation achieved nanosized droplets (~99 nm) with favorable zeta potential and stability. *In vitro* studies demonstrated enhanced drug release and stability under accelerated conditions, while cytotoxicity assays on A549 cells confirmed its safety. The QbD-driven BDQ-F-SNEDDS significantly improved the drug's solubility and bioavailability, offering a cost-effective and efficient alternative for managing drug-resistant tuberculosis, with potential to enhance therapeutic outcomes and reduce treatment burden[45]. Comparative studies between SEDDS and other nano-based drug delivery systems, such as solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and nanosuspensions, are shown in Table 2.

Regulatory and Industrial Perspectives

The Marketed SEDDS Formulations and Their Regulatory Status are shown in Table 3.

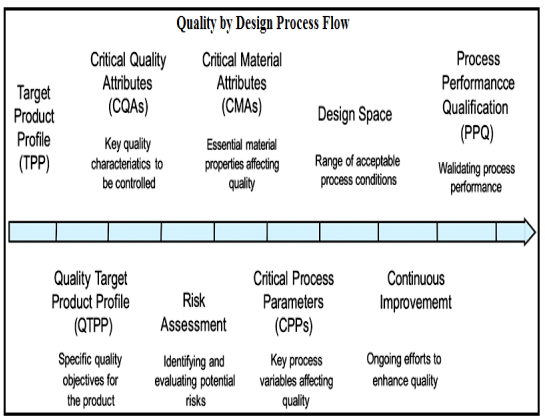

Fig. 2. Quality by Design Elements[43]

Table 2: Comparison of SEDDS with Other Lipid-Based and Nanoformulation Systems[46–48]

Parameter	SEDDS	SLNs	NLCs	Liposomes	Nanosuspensions
Main Composition	Oils, surfactants, co-surfactants	Solid lipids + surfactants	Solid+liquid lipids +surfactants	Phospholipids and cholesterol	Pure drug particles stabilized with surfactants
State	Liquid (preconcentrate); forms emulsion *in situ*	Solid particles at room/body temperature	Solid–liquid lipid hybrid particles	Aqueous dispersion of bilayer vesicles	Aqueous dispersion of nano-sized crystals
Size Range	20–300 nm (droplet size after emulsification)	50–1000 nm	50–1000 nm	50–500 nm	100–1000 nm
Stability	High (if optimized); risk of precipitation on dilution	Moderate (gelation, polymorphic transitions)	Higher than SLNs (less crystallization)	Moderate (fusion, leakage)	Physical stability often limited by aggregation
Drug Loading	Moderate to High (lipophilic drugs)	Low to Moderate (limited by crystal structure)	Higher than SLNs	Moderate (depends on drug-lipid interaction)	Very High
Encapsulation Efficiency	Drug is dissolved in lipid mixture	Moderate	High	Moderate to High	Not encapsulated; drug is dispersed
Controlled Release Ability	Limited (depends on droplet size and excipients)	Yes (slow drug release possible)	Yes (sustained release) with improved payload	Yes (with bilayer retention)	Yes (based on particle size and stabilizer)
Manufacturing Complexity	Simple (mixing, filling)	Requires high-pressure homogenization or hot melt extrusion	Moderate (complex lipid blends)	Requires precise control of lipid hydration	Requires high-energy methods (milling, homogenization)
Suitability	Lipophilic BCS Class II drugs	Lipophilic and poorly soluble drugs	Drugs needing a high payload and stability	Hydrophilic/lipophilic; IV and localized delivery	Drugs with poor water solubility across classes

Table 3: Marketed SEDDS Formulations and Their Regulatory Status

Product Name	API	Therapeutic Use	Formulation Type	Regulatory/Approval Status	Reference
Neoral	Cyclosporine A	Immunosuppressant (organ transplant)	SEDDS (Soft gelatin capsule)	Approved by FDA, EMA; widely marketed	49–51
Sandimmune	Cyclosporine A	Immunosuppressant	SEDDS (Oral and IV)	FDA approved; precursor to Neoral	50,52
Norvir	Ritonavir	Antiviral (HIV protease inhibitor)	SEDDS (Soft capsule)	FDA approved; enhanced solubility profile	51,53
Fortovase	Saquinavir	Antiretroviral	SEDDS	FDA approved (withdrawn later for market reasons)	54–56
Targretin	Bexarotene	Anticancer (cutaneous T-cell lymphoma)	SEDDS (Soft capsule)	FDA approved	57,58
Avodart	Dutasteride	Benign prostatic hyperplasia (BPH)	SEDDS (Soft capsule)	FDA and global approvals	59,60
Fenogal	Fenofibrate	Lipid-lowering agent	SMEDDS (Soft capsule)	EMA approved	61

Challenges and Limitations in SEDDS Formulation

Self-Emulsifying Drug Delivery Systems have demonstrated remarkable potential in enhancing the solubility and bioavailability of poorly water-soluble drugs, their development and commercialization are accompanied by several technical and practical challenges. These limitations span across formulation stability, large-scale manufacturing, and in vivo performance, all of which must be carefully addressed to ensure consistent therapeutic outcomes.

Stability Issues

Physical and chemical stability of the SEDDS during the storage and after dilution in the gastrointestinal (GI) tract is one of the main challenges of the formulation. Most SEDDS can be liquids or solid-soft, making them easily degraded relative to solid dosage forms. Surfactants, co-surfactants and other components (oils) are subject to oxidation, hydrolysis, and microbial contamination particularly in moisture- and heat-sensitive formulations. This instability may cause phase separation, color, odor development and result in efficacy loss. Further, the drug excipient combinations can lead to intermolecular interactions (chemical instability), that is, the ability of the drugs to react or degrade the active pharmaceutical substance (API) especially in the event of ester-based oils or PEG surfactants[62,63]. Another critical issue is to ensure that the drug is in a solubilized form and never crystallizes during the shelf life of the product. This dynamic stability problem gives way to absorption and bioavailability even though the product is stable when stored[24,62]. So, both storage stability analysis and *in vivo* dynamic stability should be important in effective development of SEDDS.

Future Prospects and Innovations

SEDDS formulations are attempting to meet this challenge, by interacting drug release and absorption patterns with the individualized physiologic and pharmacogenomic profile of a patient. This can be achieved by employing a 3D printing and digital manufacturing technology in creating personalized SEDDS-based dosage forms. As an example, semi-solid or solidified SEDDS could be printed to a capsule or a tablet with different drug loading or release kinetics depending upon patient-specific dosing necessity, disease progression or weight. These technologies allow the manufacturing of medicines on a prescription basis in a decentralized facility such as a hospital or a pharmacy[64,65]. Also, wearable bio sensors and point-of-care diagnostics can be used to provide real-time data to online health systems used to tailor formulation. As an example, a patient with known polymorphisms in CYP450 enzymes which retards drug metabolism can be treated with a lower dose SEDDS with modified release. In contrast, rapid metabolizers or patients with mal-absorption syndromes may require faster emulsifiers or mucoadhesive SEDDS to increase systemic exposure. The next prospective direction is the creation of the targeted SEDDS with ligands, peptides or antibodies capable of connecting specifically expressed receptors in the diseased tissue. Personalized SEDDS may be created to deliver cytotoxic or immunomodulatory drugs in oncology or inflammatory diseases so that they release their content selectively, minimizing the toxicity in the rest of the body and enhancing therapeutic efficacy[65,66].

CONCLUSION

Drugs of the BCS Class II that have poor solubility in aqueous media are one of the most difficult pharmaceuticals to be formulated orally, despite the good bamboo permeability values of the drugs. These solubility constraints severely impact drugs dissolution, bioavailability and therapeutic effect and patient outcome. This review presents an in-depth picture of catastrophic importance of SEDDS as the means of overcoming occlusion to oral drug delivery to BCS Class II drug and as well as the usage of QbD concept in systematic development and optimization of SEDDS. SEDDS have acutely utilized the capacity of lipid-based formulations to develop fine oil-in-water emulsions when subjected to GI fluids and in turn amplify the area of absorption of drugs and sustain the drug in a solubilized state during gastrointestinal movement. In such a way, SEDDS eliminate the issue of the poorly soluble drugs absorption that is dissolution rate limited. The incorporation of surfactants and co-surfactants does not only make the emulsification easy but also makes the emulsion more stable and helps in ensuring steady administration of the drug. In

addition, the sub-division of SEDDS, SMEDDS and SNEDS provides flexibility in formulation with regards to target-conditioning needs of the drug and the pharmacokinetic model of the drug. Some of the main improvements implemented with regard to the development of SEDDS include the incorporation of the QbD approach. This science based systematic methodology helps formulators to fingerprint and manage CQAs, CMAs, and CPPs to guarantee the quality and functionality of the goods. The use of risk analysis tools such as Ishikawa diagrams and Failure Mode and Effects Analysis (FMEA) in combination with statistical modeling via Design of Experiments (DoE) allows rational formulation design, process optimization and ensures regulatory compliance. Besides improving product robustness, QbD is also capitalizing on the expectations of regulatory agencies and is therefore an efficient and reliable process to scale-up lab-scale development to commercial production. The discussed case studies of this review revealed the flexibility of SEDDS in terms of the delivery of various therapeutic agents, such as antifungal, anticancer and anti-inflammatory drugs. The findings of these practical applications have found support in the statement that SEDDS can improve therapeutic efficacy, the rate at which they would be dose-taken, and decrease inter-subject variability. Moreover, comparative research using other nanoformulations including SLNs, liposomes, and nanosuspensions, have received evidence that specific SEDDS tend to have some benefits relative to formulation simplicity, stability, and ease of production.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERNECES

1. Samineni R.; Chimakurthy J.; Konidala S. Emerging Role of Biopharmaceutical Classification and Biopharmaceutical Drug Disposition System in Dosage form Development: A Systematic Review. *Turk J Pharm Sci*., **2022**, *19*(6), 706.doi:10.4274/TJPS.GALENOS.2021.73554
2. RJPT-The Biopharmaceutics Classification System: A Review. Accessed June 23, **2025**. https://rjptonline.org/HTMLPaper.aspx?Journal=Research%20Journal%20of%20Pharmacy%20and%20Technology;PID=2009-2-1-60
3. Tsume Y.; Mudie DM.; Langguth P.; Amidon GE.; Amidon GL. The Biopharmaceutics Classification System: Subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC., *Eur J Pharm Sci*., **2014**, *57*(1), 152. doi:10.1016/J.EJPS.2014.01.009
4. Salunke S.; O'Brien F.; Cheng Thiam Tan D., Oral drug delivery strategies for development of poorly water soluble drugs in paediatric patient population., *Adv Drug Deliv Rev*., **2022**, *190*, 114507.doi:10.1016/J.ADDR.2022.114507
5. Dahlgren D.; Sjögren E.; Lennernäs H. Intestinal absorption of BCS class II drugs administered as nanoparticles: A review based on *in vivo* data from intestinal perfusion models., *ADMET DMPK*., **2020**, *8*(4), 375. doi:10.5599/ADMET.881
6. Khadka P.; Ro J.; Kim H., Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability., *Asian J Pharm Sci*., **2014**, *9*(6), 304-316. doi:10.1016/J.AJPS.2014.05.005
7. Salawi A. Self-emulsifying drug delivery systems: a novel approach to deliver drugs., *Drug Deliv*., **2022**, *29*(1), 1811.doi:10.1080/10717544.2022.2083724
8. Zhang X.; Xing H.; Zhao Y.; Ma Z. Pharmaceutical Dispersion Techniques for Dissolution and Bioavailability Enhancement of Poorly Water-Soluble Drugs., *Pharmaceutics*., **2018**, *10*(3), 74.doi: 10.3390/PHARMACEUTICS10030074
9. ŠahinovićM.; Hassan A.; Kristó K.; Regdon G.; VranićE.; Sovány T. Quality by Design-Based Development of Solid Self-Emulsifying Drug Delivery System (SEDDS) as a Potential Carrier for Oral Delivery of Lysozyme., *Pharmaceutics*., **2023**, *15*(3). doi:10.3390/PHARMACEUTICS15030995,

10. ŠahinovićM.; Hassan A.; Kristó K.; Regdon G.; VranićE.; Sovány T. Quality by Design-Based Development of Solid Self-Emulsifying Drug Delivery System (SEDDS) as a Potential Carrier for Oral Delivery of Lysozyme., *Pharmaceutics*., **2023**, *15*(3), 995.doi:10.3390/PHARMACEUTICS15030995/S1
11. Shriya VA.; Nayak UY.; Sathyanarayana MB.; Chaudhari BB, Bhat K. Formulation Strategy of BCS-II Drugs by Coupling Mechanistic *In-vitro* and Nonclinical *In-vivo* Data with PBPK: Fundamentals of Absorption-Dissolution to Parameterization of Modelling and Simulation., *AAPS PharmSciTech*., **2025**, *26*(5), **2025**, *26*(5), 1-44.doi:10.1208/S12249-025-03093-9
12. Poovi G.; Damodharan N. Lipid nanoparticles: A challenging approach for oral delivery of BCS Class-II drugs., *Futur J Pharm Sci*., **2018**, *4*(2), 191-205.doi:10.1016/J.FJPS. 2018.04.001
13. Bhalani D V.; Nutan B.; Kumar A.; Singh Chandel AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics., *Biomedicines*., **2022**, *10*(9), 2055.doi:10.3390/BIOMEDICINES10092055
14. Zhang J.; Guo M.; Luo M.; Cai T. Advances in the development of amorphous solid dispersions: The role of polymeric carriers., *Asian J Pharm Sci*., **2023**, *18*(4), 100834.doi:10.1016/J.AJPS.2023.100834
15. Bhujbal S V.; Mitra B.; Jain U., Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies., *Acta Pharm Sin B*., **2021**, *11*(8), 2505-2536.doi:10.1016/J.APSB.2021.05.014
16. Pandi P.; Bulusu R.; Kommineni N.; Khan W.; Singh M. Amorphous solid dispersions: An update for preparation, characterization, mechanism on bioavailability, stability, regulatory considerations and marketed products., *Int J Pharm*., **2020**, *586*, 119560.doi:10.1016/J.IJPHARM.2020.119560
17. Liu Y.; Liang Y.; Yuhong J., Advances in Nanotechnology for Enhancing the Solubility and Bioavailability of Poorly Soluble Drugs., *Drug Des DevelTher*., **2024**, *18*, 1469.doi: 10.2147/DDDT.S447496
18. Ghadi R.; Dand N. BCS class IV drugs: Highly notorious candidates for formulation development., *Journal of Controlled Release*., **2017**, *248*, 71-95.doi:10.1016/J.JCONREL.2017.01.014
19. Nguyen TTL.; Duong VA.; Maeng HJ. Pharmaceutical Formulations with P-Glycoprotein Inhibitory Effect as Promising Approaches for Enhancing Oral Drug Absorption and Bioavailability., *Pharmaceutics*., **2021**, *13*(7), 1103.doi:10.3390/PHARMACEUTICS13071103
20. Takano M.; Yumoto R.; Murakami T. Expression and function of efflux drug transporters in the intestine., *Pharmacol Ther*., **2006**, *109*(1-2), 137-161.doi:10.1016/J.PHARMTHERA.2005.06.005
21. Zhuo Y.; Zhao YG.; Zhang Y. Enhancing Drug Solubility, Bioavailability, and Targeted Therapeutic Applications through Magnetic Nanoparticles., *Molecules*., **2024**, *29*(20), 4854.doi:10.3390/MOLECULES29204854
22. Gursoy RN.; Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs., *Biomedicine and Pharmacotherapy*., **2004**, *58*(3), 173-182.doi:10.1016/j.biopha.2004.02.001
23. Maji I.; Mahajan S.; Sriram A., Solid self emulsifying drug delivery system: Superior mode for oral delivery of hydrophobic cargos., *Journal of Controlled Release*., **2021**, *337*, 646-660.doi:10.1016/J.JCONREL.2021.08.013
24. Divate MP.; Bawkar SU.; Chakole RD.; Charde MS. Self Nano-Emulsifying Drug Delivery System: A Review. *J Adv Sci Res.,* **2021**, *12*(03 Suppl 2), 1-12.doi:10.55218/JASR.S2202112301
25. Rani ER.; Radha G V. Insights into novel excipients of self-emulsifying drug delivery systems and their significance: an updated review., *Crit Rev Ther Drug Carrier Syst*., **2021**, *38*(2), 27-74.doi:10.1615/EVTHERDRUGCARRIERSYST.2020034975
26. Laffleur F.; Millotti G.; Lagast J. An overview of oral bioavailability enhancement through self-emulsifying drug delivery systems., *Expert Opin Drug Deliv*., **2025**, *22*(5).doi:10.1080/17425247.2025.2479759,
27. Park H.; Ha ES.; Kim MS. Current Status of Supersaturable Self-Emulsifying Drug Delivery Systems., *Pharmaceutics*., **2020**, *12*(4), 365.doi:10.3390/PHARMACEUTICS12040365

28. Holm R.; Kuentz M.; Ilie-Spiridon AR.; Griffin BT. Lipid based formulations as supersaturating oral delivery systems: From current to future industrial applications., *European Journal of Pharmaceutical Sciences*., **2023**, *189*, 106556.doi:10.1016/J.EJPS.2023.106556
29. Seo E Bin.; du Plessis LH.; Viljoen JM. Solidification of Self-Emulsifying Drug Delivery Systems as a Novel Approach to the Management of Uncomplicated Malaria., *Pharmaceuticals*., **2022**, *15*, 120. **2022**, *15*(2), 120.doi:10.3390/PH15020120
30. Uttreja P.; Karnik I.; Adel Ali Youssef A., Self-Emulsifying Drug Delivery Systems (SEDDS): Transition from Liquid to Solid-A Comprehensive Review of Formulation, Characterization, Applications, and Future Trends., *Pharmaceutics*., **2025**, *17*(63), **2025**, *17*(1), 63.doi:10.3390/PHARMACEUTICS17010063
31. Salawi A. Self-emulsifying drug delivery systems: a novel approach to deliver drugs., *Drug Deliv*., **2022**, *29*(1), 1811.doi:10.1080/10717544.2022.2083724
32. Hong JY.; Kim JK.; Song YK.; Park JS.; Kim CK., A new self-emulsifying formulation of itraconazole with improved dissolution and oral absorption., *Journal of Controlled Release*., **20060**, *110*(2), 332-338.doi:10.1016/J.JCONREL.2005.10.002,
33. Silberstein S.; Spierings ELH.; Kunkel T. Celecoxib Oral Solution and the Benefits of Self-Microemulsifying Drug Delivery Systems (SMEDDS) Technology: A Narrative Review. *Pain Ther*., **2023**, *12*(5), 1109.doi:10.1007/S40122-023-00529-7
34. Kaur G.; Chandel P.; Harikumar SL. Formulation development of self nanoemulsifying drug delivery system (snedds) of celecoxib for improvement of oral bioavailability., *Pharmacophore*., **2013**, *4*(4-2013), 120-133. doi:10.51847/030YO7Y
35. Khan A.; Naquvi KJ.; Haider MF.; Khan MA. Quality by design-newer technique for pharmaceutical product development., *Intelligent Pharmacy*., **2024**, *2*(1), 122-129. doi:10.1016/J.IPHA.2023.10.004
36. Yang S.; Hu X.; Zhu J., Aspects and Implementation of Pharmaceutical Quality by Design from Conceptual Frameworks to Industrial Applications., *Pharmaceutics*., **2025**, *17*(5), 623doi:10.3390/PHARMACEUTICS17050623
37. Simão J.; Chaudhary SA.; Ribeiro AJ. Implementation of Quality by Design (QbD) for development of bilayer tablets., *European Journal of Pharmaceutical Sciences*., **2023**, *184*, 106412. doi:10.1016/J.EJPS.2023.106412
38. Nasr A.; Gardouh A.; Ghorab M. Novel Solid Self-Nanoemulsifying Drug Delivery System (S-SNEDDS) for Oral Delivery of OlmesartanMedoxomil: Design, Formulation, Pharmacokinetic and Bioavailability Evaluation., *Pharmaceutics*., **2016**, *8*(3), 20. doi:10.3390/PHARMACEUTICS8030020
39. Gonçalves A.; Nikmaram N.; Roohinejad S., Production, properties, and applications of solid self-emulsifying delivery systems (S-SEDS) in the food and pharmaceutical industries., *Colloids Surf A Physicochem Eng Asp*., **2018**, *538*, 108-126.doi:10.1016/J.COLSURFA.2017.10.076
40. Zupančić O.; Dočan A.; Martins Fraga R., On the influence of raw material attributes on process behaviour and product quality in a continuous WET granulation tableting line., *Int J Pharm*., **2023**, *642*, 123097.doi:10.1016/J.IJPHARM.2023.123097
41. Kavitha AN.; Janakiraman K.; Dang R. A Structural Framework for Developing Self-emulsifying Drug Delivery System through Quality by Design Approach., *Asian Journal of Pharmaceutics.,* **2020**, *14*(03), 308.doi:10.22377/AJP.V14I03.3679
42. Priani SE.; Fakih TM.; Wilar G.; Chaerunisaa AY.; Sopyan I. Quality by Design and In Silico Approach in SNEDDS Development: A Comprehensive Formulation Framework., *Pharmaceutics.,* **2025**, *17*(701), **2025**, *17*(6), 701.doi:10.3390/PHARMACEUTICS17060701
43. Namjoshi S.; Dabbaghi M.; Roberts MS.; Grice JE.; Mohammed Y. pharmaceutics Quality by Design: Development of the Quality Target Product Profile (QTPP) for Semisolid Topical Products.doi:10.3390/pharmaceutics12030287

44. AboulFotouh K.; Allam AA.; El-Badry M.; El-Sayed AM. Role of self-emulsifying drug delivery systems in optimizing the oral delivery of hydrophilic macromolecules and reducing interindividual variability., *Colloids Surf B Biointerfaces*., **2018**, *167*, 82-92.doi: 10.1016/J.COLSURFB.2018.03.034
45. Jahan RN.; Khan Z.; Akhtar MS., Development of Bedaquiline-Loaded SNEDDS Using Quality by Design (QbD) Approach to Improve Biopharmaceutical Attributes for the Management of Multidrug-Resistant Tuberculosis (MDR-TB)., *Antibiotics*., **2023**, *12*(10). doi:10.3390/ANTIBIOTICS12101510,
46. Rehman M.; Tahir N.; Sohail MF., Lipid-Based Nanoformulations for Drug Delivery: An Ongoing Perspective., *Pharmaceutics*., **2024**, *16*(11),1376.doi:10.3390/PHARMACEUTICS 16111376
47. Viegas C.; Patrício AB.; Prata JM.; Nadhman A.; Chintamaneni PK.; Fonte P. Solid Lipid Nanoparticles vs. Nanostructured Lipid Carriers: A Comparative Review. *Pharmaceutics*., **2023**, *15*, 1593. **2023**, *15*(6), 1593.doi:10.3390/ PHARMACEUTICS 15061593
48. Subroto E.; Andoyo R.; Indiarto R. Solid Lipid Nanoparticles: Review of the Current Research on Encapsulation and Delivery Systems for Active and Antioxidant Compounds., *Antioxidants*, **2023**, *12*(3), 633. doi:10.3390/ANTIOX12030633
49. Fda. NEORAL®Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED NEORAL®Oral Solution (cyclosporine oral solution, USP) MODIFIED. Accessed June 23, **2025**. https://www.fda.gov/drugsatfda
50. Laffleur F.; Millotti G.; Lagast J. An overview of oral bioavailability enhancement through self-emulsifying drug delivery systems., *Expert Opin Drug Deliv*., **2025**, *22*(5), 659-671.doi: 10.1080/17425247.2025.2479759;WGROUP:STRING:PUBLICATION
51. Norvir | European Medicines Agency (EMA). Accessed July 27, **2025**. https://www.ema.europa.eu/en/medicines/human/EPAR/norvir
52. fda. Sandimmune®Soft Gelatin Capsules Sandimmune®Oral Solution Sandimmune®Injection.Accessed June 23, **2025**. https://www.fda.gov/drugsatfda
53. fda. label. Accessed June 23, **2025**. https://www.fda.gov/drugsatfda
54. fda. INVIRASE®.Accessed June 23, **2025**. https://www.fda.gov/drugsatfda
55. Fortovase | European Medicines Agency (EMA). Accessed July 27, **2025**. https://www.ema.europa.eu/en/medicines/human/EPAR/fortovase
56. Tam CW. New formulation of saquinavir (Fortovase) is more effective. Fac Notes (New Orleans La). **1998**;10(2):11.
57. PACKAGE INSERT Targretin ® (bexarotene) capsules, 75 mg. Accessed June 23, **2025**. https://www.fda.gov/drugsatfda
58. Drug Approval Package: Targretin (Bexarotene) NDA #21-056. Accessed July 27, **2025**. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-056_Targretin.cfm
59. FDA, CDER. Highlights of prescribing information. Accessed June 23, **2025**. www.fda.gov/medwatch.
60. FDA Denies Approval for Avodart for Prostate Cancer Prevention. Accessed July 27, **2025**. https://www.cancernetwork.com/view/fda-denies-approval-avodart-prostate-cancer-prevention
61. Cbg-meb. Public Assessment Report Scientific discussion.Published online **2010**.
62. Pratik Korade HJAK. Advances InSedds: Overcoming Challenges in Drug Delivery., *International Journal of Pharmaceutical Sciences*., **2025**, *03*(01), 1-13.doi:10.5281/ ZENODO.14784958
63. Lee YZ.; Seow EK.; Lim SC.; Yuen KH.; Khan NAK.Formulation and in vivo evaluation of a solid self-emulsifying drug delivery system using oily liquid tocotrienols as model active substance., *Pharmaceutics*., **2021**, *13*(11), 1777. doi:10.3390/PHARMACEUTICS 13111777/S1
64. Su J.; Yang L.; Sun Z.; Zhan X. Personalized Drug Therapy: Innovative Concept Guided With Proteoformics., *Mol Cell Proteomics*., **2024**, *23*(3), 100737.doi:10.1016/J. MCPRO.2024.100737
65. Goetz LH.; Schork NJ. Personalized Medicine: Motivation, Challenges and Progress., *Fertil Steril*., **2018**, *109*(6), 952.doi:10.1016/J. FERTNSTERT.2018.05.006
66. Shipp L.; Liu F.; Kerai-Varsani L.; Okwuosa TC. Buccal films: A review of therapeutic opportunities, formulations & relevant evaluation approaches., *Journal of Controlled Release*., **2022**, *352*, 1071-1092. doi:10.1016/J.JCONREL.2022.10.058