International Journal of Enhanced Research in Educational Development (IJERED)
ISSN: 2320-8708, Vol. 13 Issue 6, November-December, 2025

Advances in Solubility Enhancement Strategies for BCS Class II Drugs: A Comprehensive Review

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ABSTRACT

Biopharmaceutics Classification System (BCS) Class II drugs are characterized by low aqueous solubility and high permeability, making their absorption dissolution-rate limited. Nearly half of newly developed drug molecules fall into this category, resulting in poor oral bioavailability, high dose requirements, and variable therapeutic response. Enhancing solubility and dissolution rate is therefore a critical step in the development of effective oral formulations. This review summarizes the fundamental challenges associated with poorly soluble drugs and provides a comprehensive overview of various solubility enhancement strategies, including physical modification techniques (particle size reduction, solid dispersions, nanocrystals), chemical modification approaches (salt formation, pH adjustment, co-solvency, hydrotropy, complexation), and novel formulation-based technologies (lipid-based systems, SEDDS/SNEDDS, polymeric nanoparticles, amorphous solid forms, co-crystals). Each technique is discussed in terms of its mechanism, advantages, limitations, and applicability to BCS Class II drugs. The review emphasizes the importance of selecting a suitable platform based on drug properties, scalability, regulatory aspects, and intended therapeutic outcomes. Overall, advancements in solubility enhancement continue to play a vital role in improving the bioavailability and clinical performance of BCS Class II drugs.

Keywords: Solubility enhancement · BCS Class II drugs · Solid dispersions · Nanotechnology · Lipid-based formulations

INTRODUCTION

The Biopharmaceutical Classification System (BCS) categorizes drugs into four classes based on their solubility and permeability characteristics. Among these, BCS Class II drugs are defined by their low aqueous solubility and high permeability, which makes their gastrointestinal absorption primarily dissolution-rate limited. A significant proportion of currently marketed drugs—approximately 40–50%—and nearly 60–70% of new chemical entities fall into this category. As a result, improving the solubility of BCS Class II drugs has become a critical focus in contemporary pharmaceutical research and drug development[1-3].

The poor aqueous solubility of these drugs poses multiple challenges in achieving consistent and effective oral delivery. Drugs belonging to this class often show low and variable bioavailability, requiring higher doses to achieve therapeutic plasma levels. Their absorption is also frequently influenced by food intake, contributing to food-dependent variability and unpredictable pharmacokinetic behavior. These limitations can lead to inadequate therapeutic response and significant inter-patient variability, making clinical outcomes less reliable[4,5].

BCS Class II drugs span a wide range of therapeutic categoryies, reflecting the broad diversity of poorly water-soluble molecules in modern medicine. Among nonsteroidal anti-inflammatory drugs (NSAIDs), several widely prescribed agents fall into this class, including Ibuprofen, Diclofenac, Ketoprofen, Naproxen, Indomethacin, Celecoxib, Etodolac, and Mefenamic acid, all of which have high permeability but limited aqueous solubility. In the group of antiepileptics, drugs such as Carbamazepine, Phenytoin, Valproic acid (in its unionized form), and Lamotrigine demonstrate similar solubility challenges. Many lipid-modifying agents, particularly fibrates like Fenofibrate, Gemfibrozil, and Bezafibrate, also belong to BCS Class II due to their pronounced lipophilicity. Several important antihypertensive and cardiovascular drugs, such as Valsartan, Telmisartan, Eplerenone, and Carvedilol, show dissolution-limited absorption and require solubility-enhancing strategies for optimal bioavailability. In the category of antifungal drugs, molecules like Itraconazole, Ketoconazole,

Clotrimazole, Fluconazole (partially), and Voriconazole are well-known for their low solubility. Among antidiabetic agents, drugs such as Glipizide, Repaglinide, Nateglinide, and Pioglitazone also classify under BCS Class II[6-10].

In oncology, many anticancer drugs demonstrate extreme lipophilicity, including Paclitaxel, Docetaxel, Erlotinib, Sorafenib, Tamoxifen, and Letrozole, making solubility enhancement crucial for therapeutic effectiveness. Several antidepressants and CNS-active drugs—including Fluoxetine, Paroxetine, Sertraline, Diazepam, Alprazolam, and Olanzapine—also fall within BCS Class II. Among antimicrobials, drugs like Rifampicin, Ciprofloxacin (in some pH ranges), and Nitrofurantoin exhibit solubility limitations under physiological conditions[11,12].

This wide-ranging distribution across multiple pharmacological categories highlights the pervasive challenge of poor aqueous solubility in contemporary drug development. Understanding the classification and behavior of BCS Class II drugs is essential for selecting appropriate formulation strategies to improve their dissolution, absorption, and overall therapeutic performance.

Therefore, enhancing the solubility and dissolution rate of BCS Class II drugs is essential to overcome these challenges. Improved solubility not only increases oral bioavailability but also contributes to better dose consistency, reduced variability, and overall improved therapeutic performance. Developing robust solubility enhancement strategies is thus a key requirement for the successful formulation and clinical development of BCS Class II drug candidates[13-15].

2. Factors Affecting Solubility of BCS Class II Drugs

The solubility of BCS Class II drugs is strongly influenced by their intrinsic physicochemical properties. Parameters such as pKa, lipophilicity (log P), and molecular size determine how effectively the drug interacts with aqueous media and biological membranes. Highly lipophilic drugs, for instance, tend to dissolve poorly in water, while large molecular structures often face steric challenges that limit their solvation. Another important factor is the polymorphic form of the drug. Amorphous forms generally exhibit higher solubility and faster dissolution compared to their crystalline counterparts, which possess stronger lattice energies that resist hydration[16,17].

The drug's ability to form salts also plays a key role in enhancing solubility, particularly for compounds containing ionizable functional groups. Furthermore, the hydration and solvation capacity of the drug molecule influences how easily water molecules or solvent molecules can surround and dissolve the drug. The pH of the surrounding medium is another critical determinant, as weak acids and weak bases show pH-dependent solubility behavior. Finally, the presence of surfactants, co-solvents, or solubilizing excipients can significantly improve solubility by enhancing wetting, reducing interfacial tension, or increasing the solubilization capacity of the medium. Understanding these factors is essential for selecting appropriate strategies to improve solubility and bioavailability of BCS Class II drugs[18,19].

3. Solubility Enhancement Techniques

Solubility enhancement techniques for BCS Class II drugs can be broadly categorized into physical modifications, chemical modifications, and novel formulation-based approaches. Each of these strategies aims to overcome the poor aqueous solubility of lipophilic drugs and improve their dissolution, absorption, and overall therapeutic performance.

3.1 Physical Modification Techniques

One of the simplest and most widely used physical approaches is particle size reduction, which increases the surface area of the drug and thereby improves its dissolution rate according to the Noyes–Whitney equation. Techniques such as micronization, nanomilling, high-pressure homogenization, cryogenic grinding, and supercritical fluid processing have been successfully employed to produce fine particles with enhanced solubility characteristics. Drugs such as fenofibrate, celecoxib, and danazol have demonstrated significantly improved dissolution profiles through particle size reduction[20].

Another important physical strategy is the development of solid dispersions, in which the drug is dispersed in a hydrophilic carrier. This technique improves drug wetting, reduces crystallinity, and enhances the rate of dissolution. Carriers such as PVP, HPMC, PEG, and poloxamers are commonly used, while manufacturing methods include hot-melt extrusion, solvent evaporation, spray drying, and melt granulation. Solid dispersions are highly effective because they often convert the drug from its crystalline form into a more soluble amorphous state[21].

Nanosuspensions offer another promising technique, where the drug is formulated as a stable colloidal dispersion of nanosized particles, usually stabilized with surfactants or polymers. Reducing the particle size to the nanometer range enhances saturation solubility, increases dissolution rate, and often leads to improved oral bioavailability. Nanosuspensions of poorly soluble drugs such as naproxen, itraconazole, and ziprasidone have been widely reported and successfully commercialized[22].

Co-crystals represent a multi-component approach where the drug is crystallized with a pharmaceutically acceptable co-former such as succinic acid, citric acid, or nicotinamide. These co-crystals modify the physicochemical properties of the drug without altering its pharmacological activity, thereby significantly improving solubility and dissolution[22,23].

Another effective strategy is the formation of amorphous solid forms, which lack the long-range crystalline order of traditional solids. Amorphous forms possess higher free energy and therefore dissolve faster than crystalline forms. Techniques such as quench cooling, spray drying, and hot-melt extrusion are commonly used to prepare amorphous drug systems with superior solubility[24].

3.2 Chemical Modification Techniques

Chemical approaches primarily involve altering the drug's chemical environment to improve solubility. Salt formation is a well-established method, especially for ionizable drugs. Drugs such as diclofenac and atorvastatin have more soluble salt forms that dissolve rapidly in aqueous media, thereby improving their bioavailability.

Co-solvency is another widely used technique in which water-miscible solvents—such as ethanol, propylene glycol, or PEG 400—are added to enhance drug solubility. These solvents reduce the polarity of the aqueous environment, allowing greater solubilization of lipophilic compounds.

pH adjustment involves modifying the pH of the formulation or the microenvironment around the drug to enhance solubility. Weak acids show increased solubility at higher pH, while weak bases dissolve better at lower pH. This approach is commonly used in liquid formulations and immediate-release tablet technologies.

Hydrotropy employs large quantities of hydrotropic agents such as sodium benzoate, urea, or sodium salicylate to dramatically increase solubility through improved solvation and structural interactions. It is considered a safe, simple, and effective method for many poorly soluble compounds.

Among chemical techniques, complexation—especially with cyclodextrins—is one of the most effective. Cyclodextrins such as β-CD, γ-CD, HPβCD, and methyl-β-CD form inclusion complexes that improve drug solubility by entrapping hydrophobic molecules within their hydrophobic cavity. These complexes enhance wettability, reduce crystallinity, and protect the drug from degradation. Cyclodextrin-based solubility enhancement has been extensively applied to drugs like celecoxib, acyclovir, and carbamazepine[25-28].

3.3 Novel Formulation-Based Techniques

Advanced formulation technologies have gained prominence as highly effective solubility enhancement tools. Lipid-based drug delivery systems are particularly suitable for highly lipophilic drugs (log P > 3). These include SEDDS, liposomes, niosomes, and phytosomes, which not only improve solubilization but also facilitate lymphatic transport and reduce first-pass metabolism. Such properties result in enhanced bioavailability and improved therapeutic outcomes.

Self-emulsifying drug delivery systems (SEDDS and SNEDDS) are mixtures of oils, surfactants, and co-surfactants that spontaneously form fine emulsions upon contact with gastrointestinal fluids. These systems maintain the drug in a solubilized state, preventing precipitation and ensuring consistent absorption. Drugs such as itraconazole, ritonavir, and fenofibrate have been effectively formulated using SEDDS[29-31].

Nanocrystal formulations consist of pure drug nanoparticles stabilized by polymers or surfactants. These systems improve solubility by increasing the dissolution pressure and surface area of the drug. Nanocrystals exhibit excellent bioavailability enhancement and have gained significant industrial importance.

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) provide additional benefits such as improved stability, controlled release, and enhanced solubility. These lipid-based nanocarriers protect the drug from degradation while facilitating improved gastrointestinal absorption.

Polymeric nanoparticles made from biodegradable polymers such as PLGA and chitosan are also extensively used to enhance solubility and provide sustained release. These formulations encapsulate the drug within a polymer matrix, improving its solubility, stability, and bioavailability.

Finally, microencapsulation and spray drying involve the entrapment of drug particles within hydrophilic matrices. This not only enhances solubility but also protects the drug from environmental degradation and improves flow characteristics, making these techniques suitable for large-scale manufacturing[32].

4. Evaluation Parameters for Solubility-Enhanced Formulations

Evaluating solubility-enhanced formulations requires a systematic assessment of several critical parameters that collectively determine the efficiency and performance of the developed system. Aqueous solubility is the fundamental parameter, measured to determine the extent to which a drug dissolves in water or physiological fluids. This provides an initial indication of how effectively a solubility enhancement technique has improved drug dissolution. Closely related to this is saturation solubility, which reflects the maximum concentration of the drug that can dissolve under equilibrium conditions. This parameter is particularly important for supersaturating formulations such as solid dispersions and nanocrystals, where maintaining a high solubility state is essential for improved absorption.

The dissolution rate is another key parameter, as the rate at which a drug dissolves in gastrointestinal fluids directly influences its bioavailability, especially for BCS Class II drugs where dissolution is the primary absorption-limiting step. Dissolution studies, typically performed using USP apparatus, help compare the performance of different solubility-enhanced systems and establish in vitro–in vivo correlations[33].

CONCLUSION

BCS Class II drugs pose significant challenges due to their poor aqueous solubility and dissolution rate–limited absorption. A variety of solubility enhancement strategies—including physical modifications such as particle size reduction, nanocrystals, and solid dispersions; chemical modifications such as salt formation and complexation; and advanced formulation approaches like SEDDS, nanosuspensions, and lipid-based carriers—play a crucial role in improving their oral bioavailability.

Selection of an appropriate technique depends on the drug's physicochemical properties, stability profile, scalability, and regulatory acceptability. With continued advancements in nanotechnology and formulation science, solubility enhancement.

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