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Comparative Dissolution Enhancement Strategies for BCS Class II Drugs: A Rivaroxaban- Mechanistic and Translational Review

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.ABSTRACT

Poor aqueous solubility remains a primary constraint in the oral development of Biopharmaceutics Classification System (BCS) Class II drugs, where dissolution rather than permeability governs systemic exposure. Although numerous formulation strategies have been proposed to overcome dissolution-limited absorption, comparative mechanistic evaluation and translational assessment remain insufficiently integrated in the literature. This review critically examines major dissolution enhancement platforms—including nanocrystal technology, amorphous solid dispersions, lipid-based self-emulsifying systems, liquisolid compacts, cyclodextrin complexation, and auxiliary excipient-based approaches—from the perspective of mechanistic action, supersaturation behaviour, precipitation control, and pharmacokinetic translation. Rivaroxaban, a direct Factor Xa inhibitor characterized by low aqueous solubility and dissolution-sensitive bioavailability, is employed as a representative model compound to contextualize platform performance. Comparative analysis demonstrates that while surface area reduction accelerates dissolution kinetics, amorphization and lipid-mediated solubilization provide greater thermodynamic driving force for absorption but introduce stability and precipitation challenges. Sustained supersaturation and precipitation inhibition emerge as central determinants of in vivo relevance, underscoring the limitation of dissolution magnitude as a standalone metric. Furthermore, the review evaluates the role of biorelevant dissolution testing and physiologically based pharmacokinetic (PBPK) modelling in strengthening in vitro–in vivo correlation (IVIVC) for solubility-limited compounds. Evidence suggests that predictive formulation development requires integration of dissolution kinetics, supersaturation stability, gastrointestinal physiology, and dose number considerations rather than empirical platform selection. By synthesizing mechanistic insights with rivaroxaban-specific formulation evidence, this review proposes a strategy selection framework aimed at improving translational reliability of dissolution enhancement approaches. Emphasis on precipitation control, stability profiling, and biorelevant evaluation is essential to advance rational oral delivery design for BCS Class II drugs.

Keywords: BCS Class II, dissolution enhancement, rivaroxaban, solid dispersion, SEDDS, nanocrystals, IVIVC, bioavailability

2.INTRODUCTION

Oral delivery remains the most preferred route for small-molecule drugs due to convenience, patient adherence, and cost efficiency. However, a substantial fraction of drug candidates exhibits suboptimal aqueous solubility, which limits their absorption across the gastrointestinal tract. The Biopharmaceutics Classification System (BCS) categorizes drugs into four classes based on solubility and permeability, with BCS Class II compounds characterized by high membrane permeability but low solubility. For these drugs, dissolution in gastrointestinal fluids becomes the primary rate-limiting step for absorption, making formulation design critical for achieving adequate systemic exposure [1,2].

Poor aqueous solubility in BCS Class II compounds creates a pharmacokinetic bottleneck. Although permeability is not inherently limiting, insufficient dissolution leads to incomplete or delayed absorption, variable oral bioavailability, and potential food effects. This links physicochemical constraints directly to clinical performance, particularly for drugs with narrow therapeutic windows or short dosing intervals. From an industrial perspective, the increasing number of lipophilic compounds emerging from modern medicinal chemistry pipelines makes solubility-limited absorption a common development barrier. As a result, improving dissolution has become a central objective in oral formulation research and development [3].

Multiple formulation strategies have been explored to address dissolution limitations. These include reducing particle size to the nanometer scale, converting crystalline drugs into amorphous forms via solid dispersions, incorporating drugs into lipid-based

delivery systems such as self-emulsifying formulations, enhancing wettability through liquisolid systems, and utilizing complexation or solubilizing excipients. Although these approaches share the overarching goal of increasing the effective concentration of drug in the gastrointestinal environment, they differ mechanistically in how they alter surface area, crystallinity, interfacial characteristics, or solubilization behaviour. Selection of an appropriate strategy depends not only on physicochemical properties of the drug but also on manufacturability, stability, and regulatory considerations[4–8].

Despite the availability of multiple dissolution enhancement strategies, the literature is fragmented and often method-centric. Most publications focus on demonstrating performance improvements for a single platform in isolation, with limited effort to compare strategies or rationalize platform selection based on mechanism-fit. As a result, formulation decision-making remains empirical rather than predictive, particularly for BCS Class II drugs where multiple enhancement routes appear feasible. This creates a gap in the ability to evaluate the relative merits, limitations, and application domains of different platforms. Furthermore, few studies examine precipitation behaviour, long-term physical stability, or in vitro–in vivo relationships when enhanced dissolution is achieved, which limits translational relevance[9].

Rivaroxaban provides a suitable model drug for examining dissolution-limited oral absorption. It is a direct Factor Xa inhibitor used for prevention and treatment of thromboembolic events and is classified as a BCS Class II compound due to its poor aqueous solubility and moderate-to-high permeability. Its dissolution rate significantly influences its bioavailability, and its absorption can be sensitive to gastrointestinal conditions. The interest in improving the dissolution of rivaroxaban reflects broader challenges associated with high-potency, lipophilic drugs formulated at relatively low doses, where dissolution kinetics can directly affect systemic exposure and therapeutic consistency[3].

Given the diversity of available formulation strategies, a structured comparison focused on mechanism and performance is warranted. Understanding how nanocrystal technology, amorphous solid dispersion systems, lipid-based self-emulsifying formulations, and liquisolid compaction differ in their underlying mechanisms and outcomes can help define a more rational formulation pathway for BCS Class II drugs. Such an analysis is particularly relevant for academic formulation research and early-stage industrial development, where platform selection influences both experimental direction and commercial feasibility.

This review aims to provide a comparative evaluation of dissolution enhancement strategies for BCS Class II drugs, with rivaroxaban used as a representative model compound. The scope includes discussion of mechanistic principles, formulation considerations, and reported performance outcomes from the literature. By synthesizing and comparing data across relevant studies, the review highlights strengths and limitations of different approaches and identifies gaps relevant to stability, scale-up, and translational predictability. The intent is to support more informed selection of dissolution enhancement platforms and to frame opportunities for future research focused on rational improvement of solubility-limited oral drug absorption.

3.BCS Class II Drugs: Physicochemical and Biopharmaceutic Considerations

The Biopharmaceutics Classification System (BCS) provides a framework for predicting oral drug absorption based on aqueous solubility and intestinal permeability. BCS Class II drugs are characterized by low solubility and high permeability, indicating that membrane transport across the intestinal epithelium is generally efficient once the drug is in solution. Consequently, for this class of compounds, the rate and extent of dissolution in gastrointestinal fluids become the primary determinants of oral absorption. This shifts formulation focus away from permeability enhancement toward strategies that improve solubilization and maintain sufficient drug concentration in solution during the absorption window.

Low aqueous solubility in BCS Class II drugs is frequently a consequence of physicochemical properties optimized for target binding rather than oral delivery. High lipophilicity, strong crystal lattice energy, and elevated melting points are common features of these compounds. Poor solubility does not necessarily imply poor dissolution kinetics under all conditions; however, for most BCS Class II drugs, the intrinsic dissolution rate is insufficient to maintain concentrations required for complete absorption within gastrointestinal transit time. This distinction between solubility and dissolution is critical, as formulation strategies often target one or both parameters depending on the underlying limitation.

Several physicochemical factors govern solubility and dissolution behaviour. Lipophilicity, commonly expressed as logP or logD, influences both solubility in aqueous media and partitioning into biological membranes. While higher lipophilicity generally enhances permeability, it inversely correlates with aqueous solubility, creating a formulation trade-off. The ionization state of the drug, defined by its pKa and the pH of the surrounding medium, further modulates solubility. Weakly basic or acidic drugs may exhibit pH-dependent solubility profiles, leading to variable dissolution along the gastrointestinal tract. However, for many BCS Class II compounds, ionization alone is insufficient to overcome low intrinsic solubility at physiologically relevant pH values.

Solid-state properties also play a decisive role. Crystalline drugs with strong intermolecular interactions exhibit high lattice energy, which must be overcome during dissolution. A higher melting point often reflects stronger crystal packing and correlates with reduced solubility. Polymorphic form, crystal habit, and particle morphology can further influence wettability and effective surface area exposed to dissolution media. These factors collectively affect the dissolution rate as described by the Noyes–Whitney relationship, where surface area, diffusion coefficient, and concentration gradient drive mass transfer from the solid phase into solution[10].

For BCS Class II drugs, dissolution-limited absorption is a well-recognized phenomenon. Even when permeability is high, insufficient dissolution can result in incomplete absorption, delayed onset of action, and significant inter- and intra-subject variability. This issue is particularly pronounced for compounds administered at higher doses or those with narrow absorption windows. In such cases, rapid gastrointestinal transit may further constrain the time available for dissolution, making formulation intervention essential to achieve consistent therapeutic exposure[2].

Supersaturation plays a dual role in enhancing absorption and introducing formulation challenges. Many dissolution enhancement strategies aim to generate transient supersaturated states to increase the driving force for absorption. However, supersaturation is thermodynamically unstable and often leads to drug precipitation, which can negate absorption gains. The balance between solubilization and precipitation inhibition therefore becomes a key consideration in the formulation of BCS Class II drugs. Failure to control precipitation behaviour can result in misleading in vitro dissolution improvements that do not translate to in vivo performance[6,11].

From a biopharmaceutic perspective, gastrointestinal physiology further complicates dissolution behaviour. Variations in pH, fluid volume, bile salt concentration, and motility can significantly affect solubilization and drug availability. Fed and fasted states may alter the extent of dissolution and absorption, contributing to food effects commonly observed with BCS Class II drugs. These physiological variables highlight the limitations of simple formulation approaches and underscore the need for delivery systems capable of maintaining drug solubility across dynamic gastrointestinal conditions[3].

The formulation implications for BCS Class II drugs are therefore substantial. Conventional immediate-release dosage forms relying on simple disintegration and dissolution are often inadequate. The use of excipients such as surfactants or disintegrants alone may improve wettability but rarely produces sufficient and reproducible enhancement in dissolution. As a result, advanced formulation strategies that modify particle size, solid-state form, or microenvironmental solubilization are frequently required. Selection of an appropriate dissolution enhancement platform must consider not only the physicochemical properties of the drug but also stability, scalability, and regulatory acceptability.

4.Rivaroxaban as a Model BCS Class II Drug

Rivaroxaban is an orally administered direct Factor Xa inhibitor widely used for the prevention and treatment of thromboembolic disorders, including deep vein thrombosis, pulmonary embolism, and stroke prevention in atrial fibrillation. Its clinical success and extensive formulation research make it a relevant model compound for examining dissolution-limited oral absorption. From a biopharmaceutic perspective, rivaroxaban is classified as a BCS Class II drug due to its low aqueous solubility and moderate-to-high intestinal permeability, placing formulation-driven dissolution enhancement at the center of its oral delivery strategy.

The physicochemical profile of rivaroxaban presents clear formulation challenges. It is a lipophilic molecule with limited intrinsic solubility in aqueous media and a relatively high solid-state stability. Although rivaroxaban exhibits pH-dependent solubility to some extent, the magnitude of this effect is insufficient to ensure rapid and complete dissolution under typical gastrointestinal conditions. As a result, its absorption is primarily governed by the rate at which the drug dissolves in gastrointestinal fluids rather than by epithelial permeability. This dissolution-limited behaviour has been reflected in variability in bioavailability under different physiological and formulation conditions.

Clinically, rivaroxaban is administered at relatively low doses compared to many small-molecule drugs; however, even at these doses, incomplete dissolution can influence systemic exposure. The drug's absorption profile demonstrates sensitivity to gastrointestinal environment and food intake, indicating that solubilization and maintenance of the drug in solution play an important role in achieving consistent pharmacokinetics. These characteristics mirror challenges commonly encountered with modern lipophilic drug candidates, reinforcing the broader relevance of rivaroxaban as a representative BCS Class II compound[3].

From a formulation standpoint, rivaroxaban has been investigated using multiple dissolution enhancement approaches, including particle size reduction, amorphous systems, lipid-based formulations, and solubilization-based techniques [4,5,7,8,12]. These efforts reflect the absence of a single universally optimal strategy and highlight the need to match formulation platforms with drug-specific properties. Importantly, reported studies vary considerably in their evaluation criteria, with many focusing on in vitro dissolution

improvement without comprehensive assessment of stability, precipitation behaviour, or in vivo relevance[6,9]. This variability makes rivaroxaban a useful case for examining how different strategies perform relative to one another and where current research falls short.

The regulatory and commercial context further strengthens the relevance of rivaroxaban as a model drug. As an established marketed product with well-defined pharmacokinetics and therapeutic outcomes, formulation modifications or alternative delivery strategies must balance performance improvement with regulatory acceptability and manufacturability. This constraint mirrors real-world formulation development scenarios, where enhancement strategies must extend beyond laboratory-scale success to practical implementation.

Overall, rivaroxaban serves as an effective case study for evaluating dissolution enhancement strategies for BCS Class II drugs. Its physicochemical limitations, clinical importance, and extensive formulation literature provide a strong foundation for comparative analysis. Using rivaroxaban as a model allows mechanistic and performance-based assessment of different formulation platforms while maintaining relevance to both academic research and pharmaceutical development.

5.Dissolution Enhancement Strategies for BCS Class II Drugs

Improving the dissolution behaviour of BCS Class II drugs has been a long-standing focus in oral formulation research. Given that permeability is generally adequate, formulation strategies are primarily designed to increase the amount of drug available in solution at the absorption site or to accelerate the dissolution process within the gastrointestinal transit time. Numerous approaches have been reported, each targeting different physicochemical barriers to dissolution. These strategies differ not only in mechanism but also in their implications for stability, scalability, and in vivo predictability. Understanding these distinctions is essential for rational selection of an appropriate formulation platform.

5.1 Particle Size Reduction and Nanocrystal Technology

Particle size reduction is one of the most direct methods for enhancing dissolution. By reducing drug particles to the micrometer or nanometer range, the surface area exposed to dissolution media is significantly increased, leading to faster dissolution rates. Nanocrystal formulations typically consist of pure drug particles stabilized by surfactants or polymers and dispersed in an aqueous medium or converted into solid dosage forms[9].

The dissolution enhancement achieved through nanocrystals is primarily governed by increased surface area and, to a lesser extent, by an elevation in apparent saturation solubility due to the curvature effect associated with very small particles. This approach is particularly attractive for BCS Class II drugs because it does not require chemical modification of the drug or extensive use of solubilizing excipients. However, nanocrystal formulations are susceptible to physical instability, including particle growth and aggregation during storage, which can compromise dissolution performance over time. Additionally, nanocrystal systems may exhibit rapid dissolution followed by precipitation in vivo if supersaturation is not adequately controlled[3,4].

5.2 Amorphous Solid Dispersions

Amorphous solid dispersions (ASDs) enhance dissolution by converting the drug from a crystalline to an amorphous state and dispersing it within a polymeric carrier. The amorphous form possesses higher free energy than its crystalline counterpart, resulting in improved apparent solubility and faster dissolution. Polymers used in ASDs also play a critical role in inhibiting drug recrystallization and maintaining supersaturation during dissolution[6,13].

The effectiveness of ASDs depends strongly on drug–polymer compatibility, polymer selection, and processing method. While ASDs can produce substantial dissolution enhancement, they are inherently thermodynamically unstable. Physical instability during storage, particularly under conditions of elevated temperature and humidity, remains a key limitation. Furthermore, the risk of precipitation during gastrointestinal transit necessitates careful polymer selection and evaluation of supersaturation kinetics[11]. Despite these challenges, ASDs remain one of the most widely used strategies for poorly soluble drugs due to their strong dissolution performance and established manufacturing processes.

5.3 Lipid-Based Drug Delivery Systems (SEDDS and SMEDDS)

Lipid-based formulations, including self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS), enhance dissolution by maintaining the drug in a solubilized state within lipid droplets formed upon dilution in gastrointestinal fluids. These systems rely on a combination of oils, surfactants, and co-surfactants to form fine emulsions or microemulsions spontaneously[5,14].

The primary advantage of lipid-based systems lies in their ability to bypass the dissolution step entirely by delivering the drug in a pre-solubilized form. In addition, interactions with bile salts and lipid digestion products can further enhance drug solubilization and absorption. However, lipid-based formulations may face challenges related to formulation complexity, capsule compatibility, and potential precipitation upon dilution. Predicting in vivo performance from in vitro dissolution data can also be difficult due to the dynamic nature of lipid digestion in the gastrointestinal tract[5].

5.4 Liquisolid Compacts

Liquisolid systems involve dissolving or dispersing the drug in a non-volatile solvent and converting the resulting liquid medication into a dry, free-flowing, and compressible powder using suitable carriers and coating materials. This approach improves dissolution by presenting the drug in a molecularly dispersed or solubilized state within the solid dosage form.

Liquisolid compacts offer the advantage of relatively simple processing using conventional tableting equipment. They can significantly enhance dissolution for drugs with adequate solubility in the selected non-volatile solvent. However, their applicability may be limited by the drug's solubility in acceptable solvents and by the maximum liquid load that can be incorporated without compromising flow and compaction properties. As with other solubilization-based approaches, the risk of precipitation following dissolution remains a consideration[12,15].

5.5 Cyclodextrin Complexation

Cyclodextrins enhance drug solubility through the formation of inclusion complexes in which the hydrophobic portion of the drug molecule is encapsulated within the cyclodextrin cavity. This interaction increases apparent aqueous solubility and improves wettability[8,16].

Cyclodextrin complexation is particularly useful for drugs with suitable molecular dimensions and affinity for the cyclodextrin cavity. While effective in increasing solubility, this approach often requires relatively high cyclodextrin concentrations, which may raise concerns related to formulation bulk, cost, and potential gastrointestinal tolerance. Additionally, complex dissociation and dilution effects can influence the extent of dissolution enhancement in vivo[8].

5.6 Use of Surfactants, pH Modifiers, and Precipitation Inhibitors

Surfactants and pH modifiers are frequently employed as auxiliary strategies to improve wettability, reduce interfacial tension, or create a favourable microenvironment for dissolution. These excipients can be used alone or in combination with other formulation platforms. Precipitation inhibitors, typically polymers, are increasingly incorporated to stabilize supersaturated states and prolong drug availability in solution[17].

While these approaches can contribute meaningfully to dissolution enhancement, they rarely provide sufficient improvement when used in isolation for BCS Class II drugs. Their primary value lies in supporting more robust formulation strategies by mitigating precipitation and enhancing dissolution kinetics.

TABLE 1: Comparative Dissolution Enhancement Strategies for BCS Class II Drugs

Strategy	Mechanism	Key Advantages	Key Limitations	Stability Issues	Translational Potential
Nanocrystals	↑ Surface area, ↑ dissolution rate	Simple concept, minimal excipients	Limited solubility gain, precipitation risk	Particle aggregation	Moderate
Solid Dispersions	Amorphization, supersaturation	High dissolution enhancement	Recrystallization risk	Moisture sensitive	High
SEDDS/SMEDDS	Drug pre-solubilization	Bypass dissolution	Complex formulation	Excipient compatibility	High
Liquisolid Systems	Drug in dissolved state	Simple manufacturing	Limited drug loading	Solvent migration	Moderate
Cyclodextrins	Inclusion complexation	Improved wettability	High excipient load	Complex dissociation	Low–Moderate

6. Comparative Performance and Critical Analysis of Dissolution Enhancement Strategies

Although numerous dissolution enhancement strategies have been reported for BCS Class II drugs, direct comparison of their performance is often difficult due to differences in experimental design, formulation composition, and evaluation criteria. Most studies focus on demonstrating improvement relative to an unformulated drug rather than benchmarking multiple approaches under comparable conditions. Consequently, assessment of relative effectiveness requires critical examination of reported dissolution kinetics, stability, and in vivo relevance rather than reliance on absolute performance claims.

6.1 Comparison of Dissolution Enhancement Efficiency

Across reported studies, particle size reduction and nanocrystal formulations consistently demonstrate rapid initial dissolution due to increased surface area. These systems often achieve high percentages of drug release within short timeframes under sink conditions. However, the enhancement is predominantly kinetic rather than thermodynamic, and dissolution performance may decline under non-sink conditions where saturation limits are quickly reached. In contrast, amorphous solid dispersions typically produce higher apparent solubility and sustained supersaturation, resulting in greater overall drug availability over time. This distinction highlights the importance of evaluating dissolution profiles beyond early time points[4,7].

Lipid-based formulations such as SEDDS and SMEDDS often show near-complete drug release when assessed using appropriate dispersion and digestion models. Unlike solid-state approaches, these systems avoid the dissolution step by maintaining the drug in a solubilized form. However, reported dissolution results are highly dependent on the choice of in vitro method, and conventional USP dissolution apparatus may not accurately capture their in vivo behaviour. Liquisolid compacts and cyclodextrin complexes generally show moderate dissolution enhancement, with performance strongly influenced by solvent selection, carrier capacity, and complex stability[5,12].

6.2 Supersaturation and Precipitation Behaviour

Generation of supersaturated drug concentrations is a common feature of several dissolution enhancement strategies, particularly amorphous solid dispersions and lipid-based systems. While supersaturation increases the driving force for absorption, it also introduces the risk of precipitation, which can negate dissolution gains. Many studies report improved dissolution without evaluating the duration or stability of supersaturation, limiting the translational value of the findings.

Nanocrystal systems may also induce transient supersaturation due to rapid dissolution of small particles, but lack inherent precipitation inhibition mechanisms. In contrast, polymer-based systems often incorporate precipitation inhibitors that delay nucleation and crystal growth. Comparative analysis indicates that strategies capable of sustaining supersaturation for longer durations are more likely to translate dissolution improvement into enhanced bioavailability. Nevertheless, systematic evaluation of precipitation kinetics remains underrepresented in the literature[6,11].

6.3 In Vitro–In Vivo Relevance

One of the major limitations across dissolution enhancement studies is the weak correlation between in vitro dissolution performance and in vivo outcomes. Improvements in dissolution profiles do not consistently translate into proportional increases in bioavailability. This disconnect is partly attributable to the use of non-physiological dissolution conditions and the absence of biorelevant media that account for gastrointestinal variability.

Lipid-based formulations tend to show better alignment between in vitro solubilization and in vivo absorption due to their interaction with bile salts and digestive processes. However, these systems require specialized in vitro models to generate meaningful data. Solid dispersions and nanocrystals often demonstrate improved bioavailability in preclinical or clinical studies, but reported increases vary widely, reflecting differences in formulation composition, dosing conditions, and evaluation methods. The lack of standardized assessment frameworks complicates cross-study comparison and platform selection[3].

6.4 Stability and Manufacturability Considerations

Beyond dissolution performance, formulation stability and manufacturability are critical factors influencing the viability of enhancement strategies. Nanocrystal formulations may suffer from physical instability, including aggregation and particle growth, during storage or processing. Amorphous solid dispersions face challenges related to recrystallization and moisture sensitivity, necessitating careful polymer selection and packaging.

Lipid-based systems, while effective in maintaining solubilization, may encounter issues related to excipient compatibility, leakage, and capsule stability. Liquisolid systems offer simpler manufacturing pathways but are constrained by formulation capacity and excipient load. Cyclodextrin-based formulations may be limited by high excipient requirements and cost considerations. Comparative evaluation suggests that no single strategy universally satisfies dissolution performance, stability, and manufacturability requirements, reinforcing the need for drug-specific platform selection.

6.5 Critical Evaluation of Existing Studies

A recurring limitation in the literature is the tendency to prioritize dissolution enhancement magnitude over mechanistic understanding and long-term performance. Many studies lack comprehensive stability testing, precipitation assessment, or in vivo validation. Head-to-head comparisons between multiple strategies for the same drug are rare, making it difficult to establish relative superiority. Furthermore, variability in reporting dissolution conditions and performance metrics hinders reproducibility and cross-study interpretation.

These gaps suggest that current research often emphasizes proof-of-concept rather than translational applicability. Future studies would benefit from standardized evaluation criteria, inclusion of biorelevant dissolution testing, and integration of in vitro and in vivo data. Comparative studies examining multiple enhancement strategies under consistent conditions are particularly needed to support rational formulation decision-making.

7. Rivaroxaban-Specific Formulation Evidence

Rivaroxaban has been investigated using multiple formulation strategies aimed at overcoming its dissolution-limited oral absorption. These studies provide valuable insight into how different dissolution enhancement platforms perform when applied to a single BCS Class II drug. However, the available literature also illustrates recurring limitations in evaluation depth, consistency, and translational relevance.

7.1 Particle Size Reduction Approaches

Nanocrystal and micronization-based formulations of rivaroxaban have demonstrated accelerated dissolution rates compared to conventional crystalline drug forms. Reduction of particle size increases effective surface area, leading to rapid initial drug release under in vitro conditions. Several studies report near-complete dissolution within short timeframes, particularly under sink conditions.

Despite these improvements, many reports do not address physical stability during storage or processing, which is a critical concern for nanocrystal systems. In addition, dissolution enhancement is often assessed using non-physiological media, limiting predictive value. Few studies evaluate precipitation behaviour following rapid dissolution, leaving uncertainty regarding sustained drug availability in vivo[4,6].

7.2 Amorphous Solid Dispersions

Amorphous solid dispersion formulations of rivaroxaban have been explored using various polymeric carriers to enhance apparent solubility and dissolution. These systems generally show superior dissolution performance compared to crystalline formulations, often achieving higher drug concentrations over extended periods. Polymer selection plays a key role in maintaining supersaturation and inhibiting recrystallization during dissolution.

However, the majority of published studies emphasize short-term dissolution improvement without comprehensive evaluation of physical stability. Moisture sensitivity and recrystallization risk during storage are rarely examined in depth. Furthermore, while dissolution enhancement is evident, in vivo bioavailability data are limited, making it difficult to assess the extent to which improved dissolution translates into clinical benefit[6,13].

7.3 Lipid-Based Formulations

Lipid-based delivery systems, including self-emulsifying formulations, have been investigated for rivaroxaban to improve solubilization and absorption. These systems typically demonstrate efficient drug dispersion upon dilution, maintaining rivaroxaban in a solubilized state. In some cases, improved pharmacokinetic profiles have been reported, suggesting that bypassing the dissolution step can enhance absorption.

Nevertheless, formulation complexity and variability in in vitro evaluation methods complicate comparison across studies. Standard dissolution testing often fails to capture the dynamic behaviour of lipid digestion and drug precipitation. As a result, reported dissolution performance may not accurately reflect in vivo outcomes unless biorelevant testing approaches are employed[5,14].

7.4 Liquisolid and Solubilization-Based Systems

Liquisolid compacts and solvent-based systems have been explored to improve the dissolution of rivaroxaban by presenting the drug in a pre-dissolved or molecularly dispersed state. These formulations generally show moderate improvement in dissolution compared to conventional tablets. Their advantages include relatively simple processing and compatibility with standard solid dosage form manufacturing.

However, the extent of dissolution enhancement achievable with liquisolid systems is constrained by rivaroxaban's solubility in acceptable non-volatile solvents and by formulation load limitations. Additionally, precipitation following dissolution remains a concern, particularly in the absence of effective precipitation inhibitors[12,15].

7.5 Critical Appraisal of Rivaroxaban Formulation Studies

Across formulation strategies, several common limitations emerge. Most studies assess dissolution improvement using a single formulation approach without benchmarking against alternatives. Stability testing is often insufficient, particularly for amorphous and nanoscale systems. Evaluation of precipitation kinetics and supersaturation maintenance is rarely performed, despite its relevance to in vivo absorption. Moreover, in vivo pharmacokinetic data are limited and inconsistently reported.

These gaps highlight the need for systematic, comparative evaluation of multiple dissolution enhancement strategies for rivaroxaban under consistent experimental conditions. Such an approach would enable more rational selection of formulation platforms and improve translational relevance. The diversity of reported strategies and outcomes makes rivaroxaban an appropriate model for exploring comparative dissolution enhancement, rather than promoting a single "best" formulation solution.

8. Discussion: Strategy Selection Framework for BCS Class II Drugs

The diversity of dissolution enhancement strategies available for BCS Class II drugs reflects the absence of a universally optimal formulation solution. Each platform addresses specific physicochemical limitations while introducing distinct challenges related to stability, manufacturability, and in vivo predictability. Therefore, rational selection of a dissolution enhancement strategy should be guided by a systematic evaluation of drug properties, formulation objectives, and development constraints rather than by empirical trial-and-error.

For drugs with high intrinsic lipophilicity and moderate dose requirements, particle size reduction through nanocrystal technology offers a straightforward approach to accelerating dissolution without altering chemical structure. However, its effectiveness is primarily kinetic and may be insufficient when solubility limits are rapidly reached. In contrast, amorphous solid dispersions provide both kinetic and thermodynamic advantages by increasing apparent solubility and sustaining supersaturation. Their application is best suited to drugs with favourable polymer compatibility and manageable stability risks.

Lipid-based delivery systems are particularly advantageous for compounds that exhibit adequate solubility in lipid excipients and benefit from solubilization within gastrointestinal fluids. These systems can effectively bypass dissolution constraints but require careful formulation design and specialized evaluation methods. Liquisolid systems and cyclodextrin complexes may serve as intermediate solutions, offering moderate enhancement with simpler manufacturing pathways, albeit with limitations in formulation capacity and excipient load.

Importantly, formulation selection should also consider downstream development factors. Strategies that demonstrate strong in vitro dissolution enhancement but lack physical stability or scalability may have limited translational value. Regulatory familiarity, excipient safety, and manufacturability play a decisive role in determining the feasibility of advanced delivery platforms. Consequently, comparative evaluation across multiple strategies under standardized conditions is essential to identify the most appropriate approach for a given BCS Class II drug.

Rivaroxaban exemplifies the need for such a framework. The range of reported formulation strategies and variable outcomes highlight that dissolution enhancement must be tailored to drug-specific properties. Comparative analysis enables identification of platforms that not only enhance dissolution but also maintain stability and translational relevance. This approach aligns with current formulation development paradigms that prioritize mechanism-based design and predictive evaluation.

9. Research Gaps and Future Directions

Despite extensive research on dissolution enhancement for BCS Class II drugs, several critical gaps remain. Head-to-head comparisons of multiple formulation strategies for the same drug are rare, limiting the ability to draw definitive conclusions regarding relative performance. Most studies focus on isolated improvements in dissolution without comprehensive assessment of stability, precipitation behaviour, or in vivo correlation.

Standardization of in vitro evaluation methods represents a major unmet need. Dissolution testing often employs non-physiological conditions that overestimate formulation performance. Incorporation of biorelevant media and precipitation assessment could improve the predictive value of in vitro studies. Furthermore, integration of in vitro dissolution data with in vivo pharmacokinetic outcomes remains limited, restricting development of meaningful in vitro–in vivo correlations.

Stability considerations are frequently underreported, particularly for amorphous and nanoscale systems. Long-term physical stability, moisture sensitivity, and recrystallization risk should be systematically evaluated to ensure translational viability. In addition, scalability and manufacturing feasibility are seldom addressed in academic studies, despite their importance for real-world application.

Future research should emphasize comparative, mechanism-driven studies that evaluate multiple dissolution enhancement strategies under consistent experimental conditions. Such studies would enable rational platform selection and facilitate translation from laboratory-scale formulations to clinically relevant dosage forms. Using model drugs such as rivaroxaban, systematic comparison of nanocrystals, amorphous solid dispersions, lipid-based systems, and liquisolid formulations could provide valuable insights into the relationship between formulation design, dissolution behaviour, and bioavailability.

10. Pharmacokinetic Implications of Dissolution Enhancement

For BCS Class II drugs, oral absorption is primarily governed by the rate and extent of drug dissolution within the gastrointestinal tract. While permeability across the intestinal epithelium is generally sufficient, inadequate dissolution can limit the concentration gradient required for passive diffusion, thereby constraining systemic exposure. Consequently, formulation strategies that enhance dissolution may directly influence pharmacokinetic parameters such as maximum plasma concentration (Cmax), time to peak concentration (Tmax), and area under the plasma concentration–time curve (AUC).

One of the key determinants linking dissolution to pharmacokinetics is the temporal overlap between drug supersaturation and the intestinal absorption window. Rapid dissolution leading to transient supersaturation can increase the driving force for absorption; however, if precipitation occurs before absorption is complete, the pharmacokinetic advantage may be diminished. This interplay highlights the importance of not only generating supersaturation but also maintaining it through precipitation inhibition strategies.

Dose dependency further complicates pharmacokinetic translation. For low-dose, highly potent drugs such as rivaroxaban, modest improvements in dissolution can produce measurable increases in systemic exposure. Conversely, for higher-dose BCS Class II drugs, solubility limitations may persist even after formulation intervention, restricting bioavailability gains. This relationship underscores the need to consider dose number and solubility–dose ratio during platform selection[3].

Gastrointestinal residence time also plays a critical role. Drugs absorbed primarily in the upper intestine require rapid dissolution to maximize absorption before transit to distal regions with reduced permeability. In such scenarios, particle size reduction or lipid-based solubilization strategies may provide pharmacokinetic advantages by accelerating drug availability at the absorption site[6,14].

Food effects provide additional insight into dissolution–pharmacokinetic relationships. Enhanced solubilization in fed-state conditions, driven by bile salts and lipid digestion products, often results in increased bioavailability for BCS Class II drugs. Formulation approaches that mimic fed-state solubilization, such as lipid-based delivery systems, can therefore reduce food-dependent variability in pharmacokinetic profiles[3].

From a translational perspective, it is critical to recognize that dissolution enhancement does not uniformly translate into proportional pharmacokinetic improvement. Strategies that generate rapid but short-lived supersaturation may produce strong in vitro dissolution profiles yet yield limited in vivo benefit. In contrast, systems capable of sustaining supersaturation and preventing precipitation are more likely to demonstrate consistent bioavailability enhancement.

Overall, pharmacokinetic optimization of BCS Class II drugs requires an integrated approach that considers dissolution rate, supersaturation kinetics, precipitation behaviour, dose dependency, and gastrointestinal physiology. Understanding these

interrelationships is essential for selecting formulation platforms that deliver clinically meaningful absorption improvements rather than isolated in vitro performance gains.

11. In Vitro–In Vivo Correlation (IVIVC) and Predictive Dissolution Modelling

Establishing a reliable in vitro–in vivo correlation (IVIVC) is a critical objective in the development of dissolution enhancement strategies for BCS Class II drugs. IVIVC describes the predictive relationship between in vitro dissolution behaviour and in vivo pharmacokinetic performance, enabling formulation optimization without extensive clinical evaluation. However, for poorly soluble drugs, achieving robust IVIVC remains challenging due to the complex interplay of solubilization, supersaturation, precipitation, and gastrointestinal variability.

Traditional dissolution testing methods, including USP Apparatus I and II, often employ simple buffer systems that fail to replicate physiological solubilization conditions. As a result, these methods may overestimate or underestimate formulation performance. For instance, lipid-based delivery systems may demonstrate limited dissolution in aqueous buffers despite exhibiting strong in vivo absorption due to bile-mediated solubilization. Conversely, amorphous solid dispersions may show high in vitro release but experience precipitation in vivo, weakening correlation with pharmacokinetic outcomes.

Biorelevant dissolution media have emerged as essential tools for improving IVIVC predictability. Simulated intestinal fluids such as FaSSIF and FeSSIF incorporate bile salts and phospholipids that better mimic gastrointestinal solubilization capacity. These media enable more accurate assessment of drug solubilization, supersaturation maintenance, and precipitation kinetics under physiologically relevant conditions. Incorporation of digestion models, particularly for lipid-based systems, further enhances predictive value by simulating lipolysis-driven drug release and absorption[14].

The level of IVIVC achievable varies depending on formulation platform and drug properties. Level A IVIVC, representing point-to-point correlation between dissolution and plasma concentration profiles, is rarely achieved for BCS Class II drugs due to precipitation dynamics and regional absorption variability. More commonly, Level B or Level C correlations are established, providing rank-order or single-point predictive relationships.

Advanced modelling approaches are increasingly being applied to bridge dissolution and pharmacokinetics. Physiologically based pharmacokinetic (PBPK) modelling integrates dissolution data with physiological parameters such as intestinal transit, bile salt concentration, and absorption permeability. These models enable simulation of formulation performance across fed and fasted states and support rational design of dissolution enhancement strategies[3].

Deconvolution techniques also play a role in IVIVC development by extracting in vivo absorption profiles from plasma concentration data. Comparison of these profiles with in vitro dissolution curves facilitates evaluation of predictive accuracy and identification of formulation limitations.

Despite methodological advances, IVIVC development for dissolution-enhanced systems remains constrained by variability in gastrointestinal physiology, precipitation kinetics, and formulation-dependent solubilization mechanisms. Future research should emphasize integration of biorelevant dissolution testing, precipitation assessment, and PBPK modelling to strengthen predictive capability and reduce reliance on empirical formulation selection.

12. Conclusion

Dissolution-limited absorption remains a defining challenge in the oral delivery of BCS Class II drugs, where permeability is generally sufficient but solubilization constraints restrict systemic exposure. This review has comparatively evaluated major dissolution enhancement platforms through a mechanistic and translational lens, highlighting the distinct advantages and limitations of nanocrystal technology, amorphous solid dispersions, lipid-based delivery systems, liquisolid compacts, cyclodextrin complexation, and auxiliary excipient strategies.

Comparative analysis demonstrates that dissolution enhancement alone does not guarantee bioavailability improvement. Sustained supersaturation, precipitation inhibition, and physical stability emerge as critical determinants of pharmacokinetic translation. Rivaroxaban, employed as a model compound, illustrates how formulation-driven dissolution control can influence systemic exposure while also revealing limitations in stability, scalability, and predictive evaluation.

Current literature remains fragmented, with insufficient integration of biorelevant dissolution testing, precipitation kinetics, and physiologically based pharmacokinetic modelling. Future formulation development should therefore adopt comparative,

mechanism-driven approaches that integrate in vitro and in vivo evaluation frameworks. Such strategies will improve translational predictability and support rational platform selection for solubility-limited drug candidates.

Advancing dissolution enhancement from empirical formulation optimization toward predictive, mechanistically informed design is essential for developing robust oral delivery systems capable of delivering consistent therapeutic outcomes.

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