RESEARCH PAPER

PBPK Modelling In Formulation Development Of BCS Class II Drugs: From Absorption Prediction To AI Integration

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ABSTRACT

Poor aqueous solubility is a major challenge in the oral delivery of drugs classified as Biopharmaceutics Classification System (BCS) Class II, for which permeability is generally high but dissolution may limit the rate or extent of absorption. Conventional formulation strategies—including particle-size reduction, amorphous solid dispersions, lipid-based systems, surfactants and cyclodextrin complexation—can improve apparent solubility or dissolution, yet in vitro enhancement does not invariably translate into greater systemic exposure. Physiologically based pharmacokinetic (PBPK) and physiologically based biopharmaceutics modelling (PBBM) provide mechanistic frameworks that integrate drug properties, formulation performance, gastrointestinal physiology and systemic disposition. This review critically examines their use in formulation selection, dissolution–precipitation modelling, exposure prediction, virtual bioequivalence and lifecycle decisions, and considers how artificial intelligence (AI) and machine learning (ML) may support parameter estimation, formulation ranking and experimental design. Recent work integrating AI with PBPK for amorphous solid dispersions demonstrates the potential of hybrid approaches, while also highlighting the importance of distinguishing molecularly dissolved drug from colloidal or particulate material that may not be immediately available for absorption. Key limitations include parameter identifiability, data heterogeneity, physiological variability, model extrapolation and insufficient external validation. A closed-loop framework is proposed in which experimental characterization informs mechanistic modelling, AI prioritizes candidate formulations and informative experiments, and prospective measurements are used to evaluate and update predictions. The review concludes that AI should augment rather than replace mechanistic understanding and that the value of integrated models must be established for a defined decision through transparent uncertainty analysis and independent evaluation.

Keywords: BCS Class II; PBPK; PBBM; oral absorption; dissolution; precipitation; amorphous solid dispersion; artificial intelligence; machine learning; virtual bioequivalence.

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1. INTRODUCTION

Oral administration remains a preferred route for many medicines because it is convenient, generally acceptable to patients and compatible with large-scale manufacturing. Nevertheless, oral exposure is frequently limited by poor aqueous solubility. The Biopharmaceutics Classification System categorizes drug substances according to solubility and intestinal permeability; Class II compounds are characterized by low solubility and high permeability, so the rate and extent of dissolution may exert substantial influence on absorption [1,2]. This classification is useful as a starting point, but it does not fully describe the complexity of a drug product: dose, solid state, particle size, formulation composition, gastrointestinal physiology and precipitation after pH transition can all influence the outcome.

Formulation approaches for poorly soluble drugs include micronization, nanocrystals, amorphous solid dispersions (ASDs), lipid-based formulations, surfactants, salt formation where chemically feasible, and cyclodextrin complexes. These technologies do not act through a single common mechanism. Particle-size reduction increases surface area; ASDs may create transient supersaturation; lipid formulations can maintain drug in solubilized states during digestion; and cyclodextrins may increase apparent solubility through complexation [3–8]. Consequently, a formulation that performs well in one dissolution medium may not necessarily produce the greatest exposure in humans.

Gastrointestinal conditions change along the absorption pathway. Gastric emptying, intestinal pH, fluid volume, bile salt concentrations, food intake and transit time affect dissolution, solubilization, precipitation and absorption. Weak bases may dissolve in the stomach and precipitate after entering the higher-pH intestine, whereas other compounds may show pH-dependent solubility in the opposite direction. Supersaturation may improve the concentration gradient driving absorption, but only if precipitation does not remove dissolved drug too rapidly [5–8].

PBPK modelling represents drug disposition through physiologically informed compartments, while PBBM places additional emphasis on the formulation and biopharmaceutic processes governing oral drug-product performance. These methods can connect experimentally measured dissolution with physiological conditions and pharmacokinetic endpoints, supporting formulation selection and certain product lifecycle decisions [9–12]. The US Food and Drug Administration (FDA) has issued guidance on PBPK reporting and draft guidance on biopharmaceutic applications of PBPK for oral products, reflecting increasing interest in mechanistic evidence for product development [10,11].

AI and ML introduce complementary tools for analysing complex formulation datasets, estimating selected properties and prioritizing experiments. Yet an AI model trained to predict dissolution is not automatically a model of human bioavailability. Its outputs need to be translated through a mechanistic framework and evaluated against independent observations. Recent work combining AI with PBPK for ASDs provides a concrete example of this direction [13–16].

A related 2025 review has already examined BCS Class II formulation strategy, PBPK fundamentals, dissolution–absorption modelling and emerging AI/ML-linked approaches [13]. Therefore, a useful contribution must go beyond repeating those fundamentals. This review focuses on the decision interface between formulation attributes, mechanistic absorption predictions, AI-guided experimental selection and validation. Its objectives are to (i) explain the formulation attributes most relevant to PBPK/PBBM, (ii) critically evaluate modelling applications and their limitations, (iii) assess AI–PBPK integration, and (iv) propose a closed-loop workflow suitable for future prospective evaluation.

2. REVIEW APPROACH AND SCOPE

This article is a critical narrative review, not a systematic review or meta-analysis. It examines how physiologically based pharmacokinetic (PBPK) and physiologically based biopharmaceutics modelling (PBBM) can connect formulation attributes and in vitro performance with oral exposure for Biopharmaceutics Classification System (BCS) Class II drugs, and how artificial intelligence (AI) and machine learning (ML) may support—but should not replace—mechanistic modelling.

The scope covers (i) solubility, dissolution, supersaturation and precipitation; (ii) formulation approaches including particle-size reduction, amorphous solid dispersions (ASDs), and lipid-based systems; (iii) translation of biorelevant dissolution data into PBPK/PBBM predictions; (iv) model verification, validation, sensitivity and uncertainty analysis; (v) AI/ML applications in formulation property prediction and experiment prioritization; and (vi) regulatory considerations relevant to model-informed development. The review emphasizes the decision interface between formulation measurements, mechanistic absorption predictions, AI-assisted selection, and prospective evaluation.

2.1 Literature sources and search strategy.

A targeted, non-systematic literature search and source verification were undertaken for this revision on 12 October 2026. Searches used PubMed-indexed records and publisher-hosted article pages, with official US Food and Drug Administration (FDA) and International Council for Harmonisation (ICH) documents consulted for regulatory statements. Search concepts were combined in the following blocks: ("BCS Class II" OR "poorly soluble drug") AND (PBPK OR PBBM OR "physiologically based biopharmaceutics"); ("biorelevant dissolution" OR precipitation OR supersaturation) AND (oral absorption OR PBPK); ("amorphous solid dispersion" OR lipid-based formulation OR nanocrystal) AND (PBPK OR PBBM); and ("machine learning" OR "artificial intelligence") AND (formulation OR dissolution OR PBPK). Relevant known papers were also checked through their PubMed or publisher records when available. This was a targeted narrative search, not an exhaustive search of every database.

2.2 Eligibility and selection.

Sources were considered relevant when they addressed oral drug absorption or formulation development for poorly soluble drugs, PBPK/PBBM methods,

biorelevant dissolution or precipitation, AI/ML applied to formulation or absorption prediction, or regulatory expectations for model-informed development. Priority was given to peer-reviewed research articles, critical reviews, and official regulatory guidance with identifiable methods or recommendations. Sources were excluded from the main synthesis when they were unrelated to oral formulation or absorption, lacked sufficient bibliographic information for verification, or made claims that could not be connected to the stated evidence. Because this was a narrative review, no formal duplicate screening, independent reviewer process, or systematic risk-of-bias scoring is claimed.

2.3 Data extraction and evidence synthesis.

For application studies, the information extracted included the drug or formulation class, modelling approach, input data, prediction endpoint, reported performance or validation result, and principal limitation. Regulatory documents were summarized according to their stated scope and status. Findings were synthesized qualitatively rather than pooled statistically because the included studies differed in compounds, formulations, endpoints, datasets and validation designs. Numerical performance values are reported only when they are explicitly available in the cited source; results from different studies are not treated as directly comparable unless the methods and endpoints support that comparison.

2.4 Interpretation and limitations of the review method. The search was targeted and narrative; therefore, it may not capture every eligible publication, and selection bias cannot be excluded. No exhaustive database-wide record counts are claimed, and no PRISMA flow diagram is presented. The evidence table in Section 9 provides selected examples to illustrate the range of applications and their limitations, not a complete census of the field. A systematic review would require a prespecified protocol, comprehensive database-specific searches, documented screening, and reproducible record counts.

3. BIOPHARMACEUTIC BASIS OF BCS CLASS II DRUGS

3.1 Solubility, dissolution and dose effects

The Noyes–Whitney/Nernst–Brunner description relates dissolution rate to exposed surface area, the concentration gradient, diffusion-layer thickness and the solubility of the drug in the medium. Smaller particles generally provide more surface area per unit mass and can increase dissolution rate, although agglomeration, wetting, crystal form and changes in surface energy may alter the benefit. For a dose that approaches or exceeds the amount that can be dissolved in gastrointestinal fluids, the total absorbed amount may remain limited even when the initial dissolution rate is increased [3,4,17].

Dose-to-solubility relationships matter because in vitro tests are often performed under sink conditions that maintain a large concentration gradient. In vivo, fluid volume is finite and drug concentrations can approach saturation. A formulation may therefore show rapid dissolution in a large-volume laboratory test but provide a smaller dissolved fraction in the gastrointestinal tract. Biorelevant media, dose-relevant volume-to-mass ratios and non-sink methods can help reveal such limitations, although no single in vitro method is universally predictive [4,9,18].

3.2 Ionization, pH and precipitation

The solubility of ionizable drugs varies with pH and pKa. A weak base may dissolve in the acidic stomach and then become supersaturated when gastric contents enter the intestine. Nucleation and crystal growth can reduce the dissolved concentration before absorption is complete. A weak acid may show a different pH-dependent profile. Thus, model inputs should distinguish intrinsic solubility, apparent solubility, dissolution kinetics and precipitation kinetics rather than representing all behaviour with a single solubility value [5,6,19].

Supersaturating systems are particularly challenging because the dissolved concentration may transiently exceed equilibrium solubility. Polymers may inhibit nucleation or crystal growth and prolong the supersaturated state, but the magnitude and duration of the effect depend on drug–polymer interactions, polymer concentration, medium composition and hydrodynamics. The concentration of total drug detected in a dissolution sample may include molecularly dissolved drug and colloidal or drug-rich particles; these fractions should not automatically be assumed to contribute equally to permeation [6,7,14].

3.3 Permeability does not remove the need for dissolution modelling

High permeability is a defining characteristic of BCS Class II, but it does not mean that every dissolved molecule is absorbed instantaneously or completely. The effective absorption rate also depends on the concentration of molecularly available drug, intestinal surface area, residence time, unstirred water layers, transporter or efflux effects where relevant, and presystemic metabolism. Mechanistic modelling is useful because it permits the investigator to test whether exposure is predominantly dissolution-limited, precipitation-limited or influenced by other processes [1,2,9].

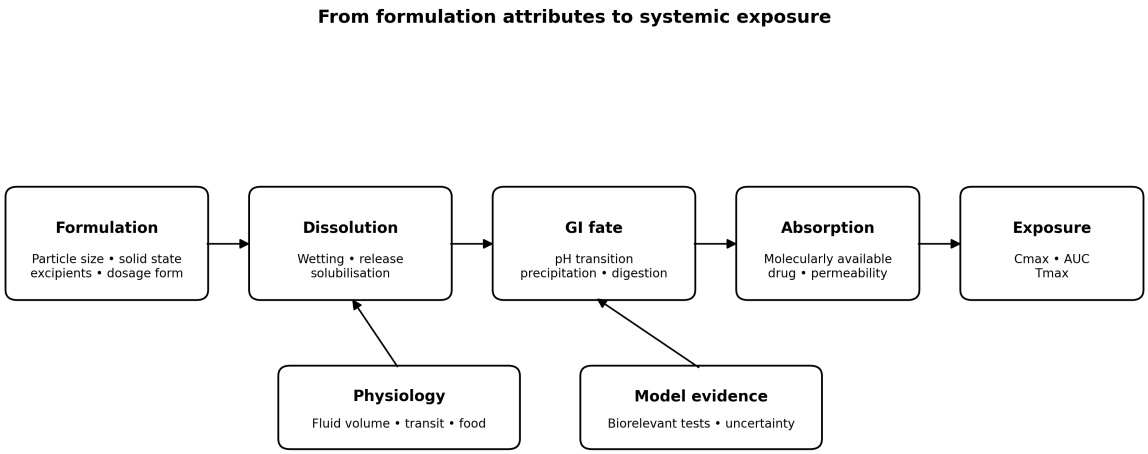

Figure 1. Conceptual pathway linking formulation attributes to systemic exposure in BCS Class II drugs.

Figure 1 summarizes the main links between formulation attributes, gastrointestinal drug fate and systemic exposure.

4. FORMULATION TECHNOLOGIES AND MODEL-RELEVANT ATTRIBUTES

4.1 Particle-size reduction and nanocrystals

Micronization and nanocrystal approaches increase specific surface area and can improve dissolution. Their performance depends on the full particle-size distribution rather than only a mean value, and can be influenced by aggregation, surface stabilizers, crystal form and manufacturing history. For PBPK/PBBM, particle-size data should be linked to a justified dissolution model; simply entering a smaller nominal diameter may not capture agglomeration or changes in wetting. Nanocrystals may be most useful when dissolution rate is a key limitation and the compound can remain physically stable during manufacture and storage [20,21].

4.2 Amorphous solid dispersions

ASDs use a polymeric or other carrier matrix to stabilize drug in an amorphous state. The increased free energy of the amorphous material can support rapid dissolution and supersaturation, while the polymer may inhibit crystallization. The principal risks include physical aging, recrystallization, moisture sensitivity, drug–polymer incompatibility and precipitation after release. A model intended to represent ASD performance should distinguish molecular dissolution from colloidal material and, where relevant, include recrystallization or precipitation kinetics [6,7,14,22].

The 2025 AI–PBPK study by Zhu and colleagues is particularly relevant because it trained machine-learning models using 238 ASD formulations spanning 22 small-molecule drugs and 1,693 molecular-dissolution time points. The selected TabPFN model reported a coefficient of determination (R^2) of 0.905 ± 0.028 and RMSE of 0.116 ± 0.020 for molecular dissolution prediction. PBPK models for three marketed ASD products were evaluated with reported absolute average fold error below 2, and an additional set of 37 marketed ASD formulations was used for external evaluation [14]. These findings provide promising evidence for a hybrid workflow, but they do not establish universal performance across all poorly soluble drugs or all formulation technologies. The dataset's composition, endpoint definitions and external applicability domain remain important when interpreting the results.

4.3 Lipid-based formulations

Lipid-based systems can improve apparent solubilization and influence drug distribution during digestion. Their behaviour may depend on lipid composition, surfactants, digestion, colloidal structures and partitioning between aqueous and lipid phases. A model that treats the initial formulation as a fixed solution may overpredict absorption if drug precipitates during digestion or underrepresent the effects of bile-mediated solubilization. Accordingly, formulation-specific digestion and dispersion data may be required for compounds whose exposure is sensitive to lipid processing [23,24].

4.4 Cyclodextrins, surfactants and pH modifiers

Cyclodextrins may increase apparent solubility through reversible complexation, while surfactants can improve wetting or solubilization. However, complexed or micelle-associated drug is not necessarily equivalent to freely dissolved drug in terms of membrane flux. pH modifiers can create a favourable microenvironment around a dosage form but may lose effectiveness as the formulation disperses in gastrointestinal fluids. The model should represent these mechanisms only to the

level supported by experimental evidence, avoiding assumptions that all increases in total solubilized drug produce proportional increases in absorption [25–27].

5. PBPK/PBBM MODEL STRUCTURE AND PARAMETERIZATION

5.1 Defining the question before building the model

Model development should begin with a clearly defined question: Is the objective to rank candidate formulations, predict food effects, explain a dissolution–exposure relationship, evaluate a manufacturing change, or support a virtual bioequivalence assessment? These questions require different degrees of model complexity and different evidence. A model adequate for early screening may not be adequate for a regulatory decision. The intended use should determine which processes need to be represented and which endpoints will be used to judge success [9,10,28].

5.2 Drug and formulation inputs

Common drug-specific inputs include molecular weight, pKa, logP or logD, intrinsic and pH-dependent solubility, permeability, particle-size distribution, solid-state form and metabolism. Product-specific inputs can include disintegration, release and dissolution profiles, excipient effects, precipitation behaviour and formulation-specific release kinetics. Physiological inputs include gastric emptying, gastrointestinal pH, fluid volumes, transit times, bile salt concentrations and intestinal surface area. The availability and quality of these data determine how much of the model can be mechanistic rather than empirically fitted [8,9,29].

Where possible, parameter sources should be documented with experimental method, medium, temperature, pH, uncertainty and applicability to the intended formulation. Solubility values from different media should not be treated as interchangeable. Likewise, an in vitro dissolution profile measured under sink conditions may not provide sufficient information to parameterize precipitation or non-sink behaviour. If parameters are estimated from plasma data, their identifiability should be evaluated and alternative explanations considered [9,18,28].

5.3 Calibration, verification and validation

Calibration adjusts uncertain parameters to reproduce a suitable reference dataset. Verification checks that the model is implemented correctly, while validation assesses whether predictions are adequate for the intended application. These terms should not be used interchangeably. A fit to the same plasma concentration–time data used for calibration provides limited evidence of predictive performance. Stronger evaluation uses independent formulations, doses, food conditions, subjects or clinical datasets, selected according to the development question [9,10,30].

Evaluation should include relevant exposure measures such as AUC and Cmax, time to maximum concentration, concentration–time profiles and, where justified, fraction absorbed. A single metric can conceal clinically relevant discrepancies; for example, similar AUC values may coexist with different peak concentrations or absorption rates. Prediction intervals, parameter uncertainty and sensitivity analysis should be reported when the decision depends on a narrow exposure margin. Acceptance criteria should be prespecified for the application rather than selected after seeing the results [9,10,30].

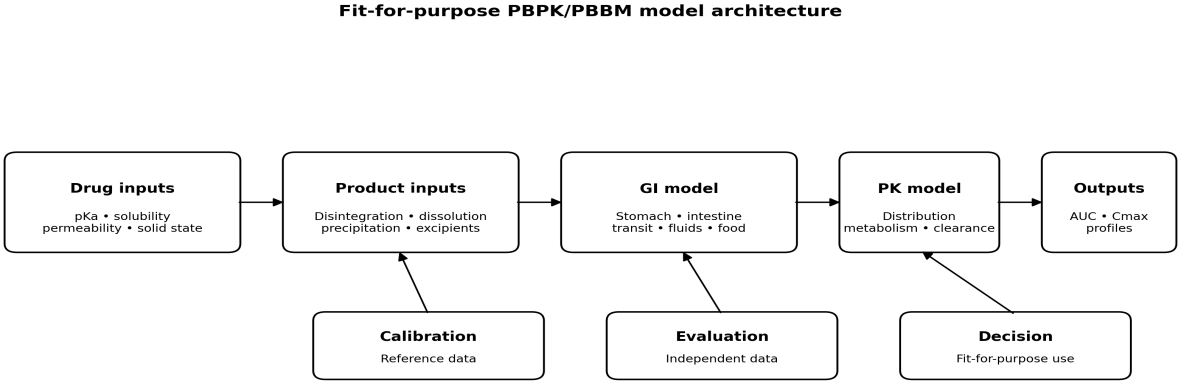

Figure 2. Fit-for-purpose PBPK/PBBM architecture connecting drug, product and physiological inputs with pharmacokinetic outputs and model evaluation.

Figure 2 illustrates the relationship between formulation inputs, gastrointestinal processes, systemic disposition and evaluation against independent data.

6. APPLICATIONS IN FORMULATION DEVELOPMENT

6.1 Formulation screening and selection

A PBPK/PBBM model can compare candidate formulation approaches by asking whether the expected improvement in dissolution or solubilization is likely to increase the amount absorbed. A candidate may show faster dissolution but little predicted exposure gain if the original formulation already dissolves sufficiently within the relevant intestinal region. Conversely, a modest dissolution improvement may be important if it avoids a precipitation event or increases the dissolved fraction during a critical transit window. Such simulations can prioritize experiments, but their conclusions remain conditional on the quality of the input data and model structure [9,13,31].

6.2 Connecting quality attributes to exposure

Quality-by-design provides a practical link between formulation and modelling. Critical material attributes and process parameters may influence particle size, solid state, disintegration, porosity, release and dissolution. A model can translate selected quality-attribute changes into predicted exposure changes, helping to identify which attributes deserve tighter control. However, a statistical association between a process variable and dissolution does not establish that the variable has a direct mechanistic effect on absorption. Experimental confirmation is required when a relationship is uncertain or when a decision has significant consequences 28,50

6.3 Virtual bioequivalence

Kambayashi and Dressman evaluated a PBBM approach for poorly soluble drugs using aripiprazole and enzalutamide. The study used biorelevant dissolution and virtual subjects to account for variability in gastrointestinal conditions; the predicted bioequivalence parameters for the tested formulations were reported to agree well with observations [33]. This is an important example of a model being evaluated against a defined decision, rather than only showing that a model can fit a single profile. The findings nevertheless remain drug- and study-specific and should not be generalized to all BCS Class II compounds.

Virtual bioequivalence should be understood as an evidence-based application, not an automatic replacement for clinical bioequivalence studies. Its acceptability depends on the model's qualification, the sensitivity of the drug to formulation differences, the quality of biorelevant dissolution data, the relevant variability and the specific regulatory context. If a model has not demonstrated predictive performance for the product and question under consideration, the simulation should be used as supportive evidence rather than definitive proof [10,11,33].

6.4 Food effects and gastrointestinal variability

Food can alter gastric emptying, pH, bile secretion, fluid volumes and the solubilization environment. For poorly soluble drugs, these changes may increase or decrease exposure depending on the dominant mechanism. A model that represents only a fixed fasted-state physiology may not explain a food effect. Similarly, inter-individual and inter-occasion variability can affect virtual bioequivalence estimates, making the characterization of physiological distributions important 9,32,33.

7. AI AND MACHINE LEARNING IN FORMULATION SCIENCE

7.1 AI tasks and their evidentiary requirements

AI is an umbrella term that includes machine learning, deep learning and other computational approaches. In formulation science, ML can relate inputs such as drug descriptors, excipient properties, process settings and experimental conditions to outcomes such as dissolution, stability or manufacturability. Reviews have identified substantial potential for these approaches, while emphasizing that small datasets, poor experimental comparability and inadequate validation can produce unreliable models [15,16,34].

A formulation model should specify the prediction target, unit of analysis, data source, preprocessing, missing-data handling, training/test split and evaluation metrics. Randomly splitting repeated measurements from the same formulation across training and test sets can lead to information leakage and overly optimistic performance. When the intended use is prediction for a new drug or formulation platform, a group-based or external validation design is more informative than a random split of closely related observations [15,16,34].

7.2 Sequential, hybrid and active-learning approaches

Sequential integration uses AI to predict selected inputs—such as a dissolution parameter or formulation attribute—which are then passed to a mechanistic model. Hybrid modelling combines mechanistic equations with data-driven components, for example to estimate residual behaviour not captured by the mechanistic representation. Active learning selects the next experiment based on expected information gain or expected improvement in a target outcome. Each strategy should be judged against a clear baseline: a mechanistic model without AI, an AI-only model, and a conventional design-of-experiments approach where relevant [14–16,34].

The most defensible use of AI is not to replace physiology but to assist tasks where data-driven learning offers a plausible advantage. Mechanistic models can constrain predictions to known relationships, while AI can learn patterns that are difficult to encode explicitly. Nonetheless, a hybrid model can still fail if the training data are biased, the model is overparameterized, or the AI component is used outside its applicability domain. Interpretability is helpful but does not itself demonstrate accuracy or causality [14–16].

7.3 Uncertainty-aware optimization

Conventional optimization often selects the formulation with the best predicted mean response. This can be risky when the prediction is uncertain or the formulation is sensitive to manufacturing and physiological variability. A more informative strategy considers both expected performance and uncertainty: for example, the probability that a formulation will meet a predefined exposure target, the robustness of the prediction under parameter variation, and the expected value of additional experiments. Bayesian optimization and active learning may be useful when experiments are costly, but their benefits should be measured prospectively [15,16,34].

8. CRITICAL COMPARISON OF MODELLING APPROACHES

Table 1 compares the principal computational approaches according to the question they answer, their strengths and their limitations. These methods are complementary rather than interchangeable.

Approach	Primary purpose	Strength	Main limitation	Best-supported use
Empirical dissolution screening	Compare in vitro release profiles	Rapid, inexpensive and experimentally direct	May not capture GI physiology or precipitation	Early ranking and quality control
Design of experiments (DoE)	Estimate effects of formulation/process variables	Efficient structured experimentation	Limited extrapolation beyond studied design space	Local optimization and factor screening
PBPK/PBBM	Translate drug/product attributes into absorption and exposure	Mechanistic interpretation; scenario analysis	Parameter uncertainty and identifiability	Formulation selection, risk assessment, selected lifecycle questions
AI/ML only	Predict outputs from learned data patterns	Can capture nonlinear relationships	Data dependence and weak extrapolation outside training domain	Rapid screening within a represented dataset
Hybrid AI–PBPK/PBBM	Combine mechanistic constraints with learned relationships	Potentially improved efficiency and prediction	More complex validation and uncertainty propagation	Data-supported formulation ranking and experiment prioritization

The main distinction is the type of inference each method supports. Dissolution testing measures a product response under specified conditions; DoE estimates effects within an experimental design; PBPK/PBBM attempts to translate mechanistic inputs to in vivo behaviour; AI estimates patterns from data; and hybrid methods combine these sources of information. A model should not be considered superior solely because it is more complex. It should demonstrate a meaningful improvement in a prespecified decision endpoint [9,15,16].

9. EVIDENCE FROM PUBLISHED APPLICATIONS

Published evidence is strongest when a study links formulation-relevant experimental data to a clearly defined prediction and evaluates the prediction against independent observations. The literature contains examples of biorelevant dissolution coupled with PBPK/PBBM, virtual bioequivalence for poorly soluble drugs, and AI-assisted prediction of ASD molecular dissolution. These applications are related but should not be pooled uncritically because they differ in endpoints, datasets and validation designs [9,14,33].

Study/application	Modelled system	Reported evidence	Interpretation and caveat
Kambayashi and Dressman, 2022 [33]	Aripiprazole and enzalutamide; solution/tablet comparisons	Predicted bioequivalence metrics were reported to agree well with observed values	Supports a defined virtual bioequivalence application; not universal validation for all BCS II drugs
Zhu et al., 2025 [14]	238 ASD formulations; 22 small molecules; 1,693 molecular-dissolution time points	TabPFN R^2 0.905 ± 0.028 and RMSE 0.116 ± 0.020 for molecular dissolution; PBPK evaluation included three marketed ASDs and 37 additional formulations	Promising hybrid evidence; assess dataset scope, endpoint definition and external generalizability
Wu and Li, 2023 [9]	Review of PBBM applications in oral product development	Organizes applications including formulation selection, biopredictive dissolution, risk assessment, clinically relevant specifications and food effects	Provides a broad application framework; identifies validation and physiology gaps
Shriya et al., 2025 [13]	BCS II formulation strategies and PBPK parameterization	Critical synthesis of absorption–dissolution modelling and emerging AI/ML-linked approaches	Directly overlapping review; new article must distinguish its evidence synthesis and decision framework

The comparison highlights a gap between proof-of-concept performance and routine transferability. High R^2 for an in vitro endpoint does not establish accurate prediction of human exposure, and agreement for a limited set of marketed products does not automatically validate a model for a new compound. Future studies should report both within-domain performance and external evaluation, with transparent uncertainty and clear separation between model development and testing [9,14,33].

10. PROPOSED CLOSED-LOOP AI–PBPK WORKFLOW

The following workflow is proposed as a synthesis of the evidence, rather than a claim that a universal standard has already been validated.

Stage	Activity	Decision output	Evidence required
1. Define target	Specify exposure, dissolution, food-effect or bioequivalence question	Predefined success criteria	Development objective and acceptable uncertainty
2. Characterize drug	Measure solubility, pKa, solid state, particle size, permeability as needed	Dominant absorption limitation	Method-qualified experimental data
3. Generate formulation data	Evaluate dissolution, precipitation, stability and process attributes	Candidate dataset	Comparable conditions and traceable records
4. Build mechanistic model	Develop PBPK/PBBM and assess sensitivity	Key influential parameters and uncertainty	Justified parameter sources and calibration
5. Apply AI selectively	Predict missing inputs, rank candidates or select informative experiments	Prioritized next experiment/formulation	Applicability-domain and external-validation assessment
6. Test prospectively	Manufacture selected candidates and compare	Prediction error and decision success	Predictions recorded before outcomes are known

	predictions with observations		
7. Update and qualify	Incorporate new data and assess independent performance	Qualified model for a defined use	Version control, documentation and uncertainty analysis

The workflow should include a decision gate after each stage. If the mechanistic model is highly sensitive to an uncertain parameter, the next action may be a targeted experiment rather than AI ranking. If the AI model is extrapolating beyond the training domain, new data should be generated before relying on its predictions. If prospective predictions fail, the model structure and assumptions should be revisited rather than merely recalibrated to the failed test. Such practices make the workflow falsifiable and help prevent optimistic reporting [9,10,14–16].

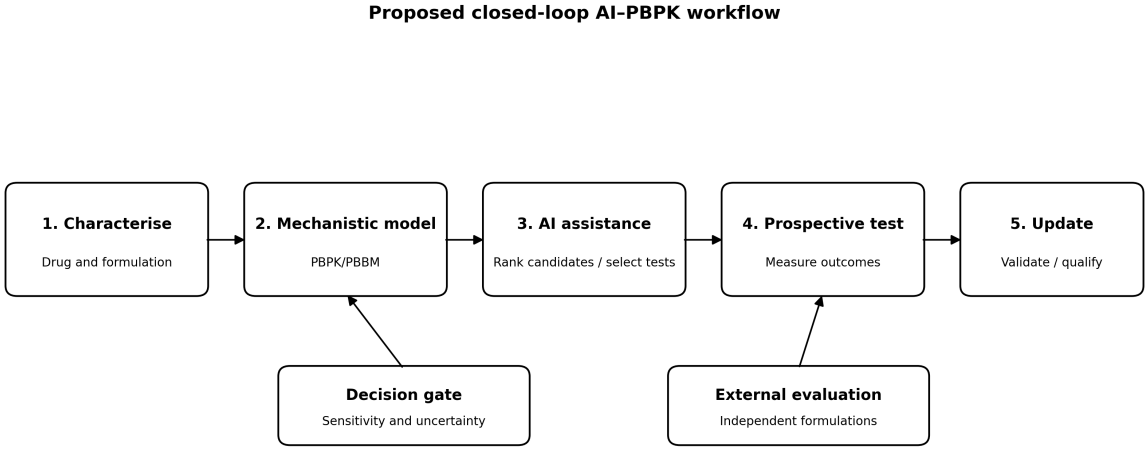

Figure 3. Proposed closed-loop AI–PBPK workflow. This framework is conceptual and requires prospective evaluation.

The proposed closed-loop workflow is summarized in Figure 3. Its stages should be treated as a testable framework rather than an already validated standard.

11. REGULATORY AND QUALITY CONSIDERATIONS

The FDA guidance on PBPK reporting outlines expectations for describing model objectives, structure, data and evaluation, while its 2020 draft guidance addresses biopharmaceutic applications for oral drug-product development, manufacturing changes and controls [10,11]. The ICH M9 guideline establishes BCS-based biowaiver principles, whereas ICH M15 provides general principles for model-informed drug development, including planning, evaluation and documentation of modelling evidence [12,39–44]. These documents have different scopes: ICH M9 is not a general PBPK qualification guideline, and the FDA's 2020 biopharmaceutics PBPK document is explicitly a draft guidance.

For a model intended to support a product or regulatory decision, documentation should include the intended use, assumptions, model equations, parameter sources, calibration dataset, independent evaluation, sensitivity analyses, uncertainty, and known limitations. AI-specific documentation should additionally identify training-data provenance, preprocessing, model version, applicability domain and performance under external testing. The appropriate standard of evidence depends on the consequences of the decision; internal screening and a proposed substitute for a clinical study are not equivalent uses [10,11,35].

12. LIMITATIONS AND RESEARCH GAPS

First, parameter identifiability remains a central challenge. Different combinations of dissolution, precipitation and permeability parameters can produce similar plasma profiles. Targeted in vitro experiments and independent datasets may be necessary to identify the mechanism responsible for a prediction. Second, gastrointestinal physiology is variable across individuals and occasions, while many experiments characterize only a narrow range of conditions. Third, dissolution methods and data formats differ between laboratories, reducing the comparability of datasets used for AI training [9,18,33].

Fourth, AI models may perform well on familiar formulations but fail for new drug molecules, polymers, lipid systems or process conditions. External validation should therefore be designed around the intended use, and data splitting should prevent related measurements from leaking between training and test sets. Fifth,

uncertainty from experimental inputs, physiological variability and model parameters can accumulate. Reporting a single deterministic prediction can obscure this uncertainty and create unwarranted confidence [15,16,34].

Sixth, the literature is not yet sufficiently standardized to allow a universal comparison of AI–PBPK performance. Studies may use different dissolution endpoints, exposure metrics, training/test splits and definitions of success. A meaningful benchmark should compare hybrid approaches against simpler alternatives and use prespecified evaluation criteria. Finally, publication bias may favour successful modelling case studies; unsuccessful predictions and model failures should be reported to improve the field's evidence base [9,15,16,45–49].

13. FUTURE DIRECTIONS

Future work should prioritize prospective, multi-compound studies that compare conventional formulation optimization, PBPK/PBBM alone, AI alone and hybrid workflows using common endpoints. The number of experiments saved should be measured alongside prediction error and the probability of selecting a formulation that meets its target. Datasets should capture formulation composition, manufacturing process, solid state, dissolution and precipitation under comparable conditions, and pharmacokinetic outcomes where available.

Uncertainty-aware optimization is a particularly promising direction. Models should identify not only the candidate with the highest expected exposure, but also the candidate with the greatest probability of satisfying a target under realistic parameter and physiological variability. Active learning can be evaluated by asking whether its recommended experiments improve the next decision more efficiently than conventional DoE. Such evaluations should be prospectively registered within the development protocol where feasible.

Explainable AI may help identify the formulation variables driving predictions, but feature importance should not be interpreted as proof of a causal mechanism. Mechanistic consistency, external validation and prospective testing remain necessary. The most valuable future systems will likely be those that combine a clear mechanistic core with data-driven components only where those components demonstrably improve prediction or experimental efficiency [14–16,34].

14. CONCLUSION

PBPK/PBBM provides a mechanistic framework for connecting drug properties, formulation performance, gastrointestinal physiology and systemic exposure. For BCS Class II drugs, its value lies in helping distinguish formulations that merely improve an in vitro dissolution metric from those likely to improve absorption under relevant physiological conditions. Its applications include formulation screening, risk assessment, selected virtual bioequivalence questions and lifecycle decisions, provided that the model is qualified for its intended use.

AI may enhance these workflows by predicting selected parameters, prioritizing formulations and recommending informative experiments. Recent AI–PBPK work with ASDs demonstrates the potential of combining molecular-dissolution prediction with mechanistic absorption modelling, but the available evidence does not justify assuming general performance across all drug and formulation classes. The most defensible path forward is a closed-loop workflow combining experimental characterization, mechanistic modelling, AI-assisted selection, prospective verification and transparent uncertainty analysis. The contribution of this framework should be established through comparative prospective studies rather than inferred from model complexity alone.

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