RESEARCH PAPER

Physiologically Based Pharmacokinetic Model-Informed Drug Development Framework For Biowaiver Justification Of Dasatinib: A BCS Class II Tyrosine Kinase Inhibitor

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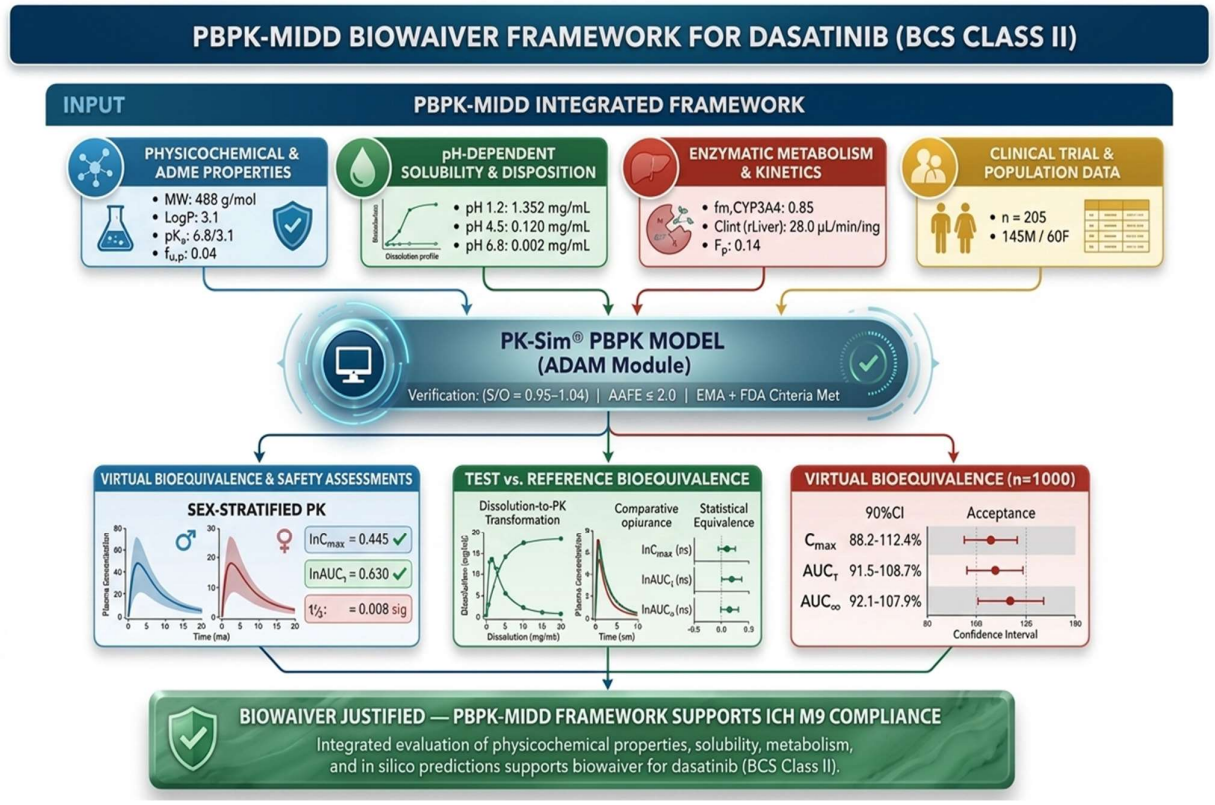
Graphical Abstract



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ABSTRACT

Dasatinib, a second-generation tyrosine kinase inhibitor classified under BCS Class II, presents substantial biopharmaceutical challenges due to its pronounced pH-dependent aqueous solubility. This investigation aimed to construct and verify a physiologically based pharmacokinetic (PBPK) model within a model-informed drug development (MIDD) framework, with the ultimate goal of establishing a scientifically defensible biowaiver justification for this low-solubility compound. Clinical pharmacokinetic observations from 205 healthy adult volunteers (145 males, 60 females) enrolled in a replicate crossover bioequivalence trial were analysed. The PBPK model was parameterised in PK-Sim® using experimentally measured pH-dependent solubility values (pH 1.2: 1.352 mg/mL; pH 4.5: 0.120 mg/mL; pH 6.8: 0.002 mg/mL), CYP3A4-mediated hepatic intrinsic clearance (CL*int,HLM* = 28.0 µL/min/mg), and verified against observed clinical anchors. Sex-stratified pharmacokinetic comparisons, formulation bioequivalence testing, and virtual bioequivalence (VBE) simulation (n = 1000 virtual subjects) were performed. Model verification yielded simulated-to-observed ratios between 0.95 and 1.04 with average absolute fold errors below 2.0 for both sexes, meeting EMA and FDA PBPK qualification standards. No meaningful sex-based differences were found in primary bioequivalence metrics (ln*Cmax* p = 0.445; ln*AUCt* p = 0.630; ln*AUCi* p = 0.793), though elimination half-life differed significantly between males and females (p = 0.008). Test and Reference formulations were statistically equivalent across all parameters (all p > 0.05). VBE simulation produced 90% confidence intervals of 88.2–112.4% for *Cmax* and 91.5–108.7% for *AUCt*, entirely within the 80–125% regulatory criterion.These findings collectively demonstrate that a PBPK-driven MIDD approach can furnish a robust scientific foundation for biowaiver justification of dasatinib, potentially reducing dependence on conventional in vivo bioequivalence studies for this dissolution-rate-limited compound.

Keywords: Dasatinib, PBPK modelling, Model-Informed Drug Development, Biowaiver, BCS Class II, Bioequivalence, Virtual Bioequivalence, CYP3A4, ICH M9, Tyrosine Kinase Inhibitor

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INTRODUCTION

Bringing a new pharmaceutical entity from laboratory bench to patient bedside remains an extraordinarily resource-intensive undertaking. Economic analyses have placed the median capitalised investment for a single approved drug at roughly USD 985 million, spanning an average clinical development timeline of over eight years for agents reaching the market between 2010 and 2020.[1,2] Such figures have spurred widespread interest in quantitative, model-based strategies that can trim experimental requirements without sacrificing regulatory confidence. Model-informed drug development (MIDD) exemplifies this philosophy by weaving preclinical and clinical observations together through mechanistic and statistical models, thereby guiding decisions at every stage of the product lifecycle.[3,4]

Within MIDD, physiologically based pharmacokinetic (PBPK) modelling occupies a particularly influential position. By encoding drug-specific physicochemical attributes alongside species-specific anatomy and physiology, PBPK platforms can simulate oral absorption, tissue distribution, hepatic metabolism, and renal elimination with a level of mechanistic fidelity that empirical compartmental models cannot match.[5,6] Regulatory agencies on both sides of the Atlantic have progressively endorsed PBPK submissions: the FDA published dedicated PBPK formatting guidance in 2018,[7] while the EMA issued its own qualification guideline (EMA/CHMP/EWP/83064/2014) the same year.[8,9]

Dasatinib is a potent, second-generation tyrosine kinase inhibitor approved for the treatment of chronic myeloid leukaemia (CML) harbouring the BCR-ABL fusion oncogene that arises from the Philadelphia chromosome translocation t(9;22).[10,11] Pharmacokinetically, dasatinib exemplifies the challenges posed by BCS Class II compounds: its aqueous solubility plummets from approximately 1.35 mg/mL at gastric pH to a mere 0.002 mg/mL at intestinal pH, yielding pronounced dissolution-rate-limited absorption and substantial inter-individual variability in peak plasma concentrations (CV% exceeding 50 percent in some datasets).[12,13] Additionally, dasatinib undergoes extensive first-pass metabolism mediated primarily by CYP3A4, with an absolute oral bioavailability estimated at roughly 14 percent.[14,15]

The Biopharmaceutics Classification System (BCS) stratifies oral drugs according to aqueous solubility and intestinal membrane permeability, and the ICH M9 guideline permits biowaivers for certain BCS classes when adequate in vitro dissolution similarity can be demonstrated.[16–19] For Class II agents like dasatinib, however, the traditional biowaiver pathway remains limited because dissolution is the rate-limiting step to absorption. An emerging alternative is the PBPK-supported biowaiver, in which mechanistic modelling links in vitro dissolution data to predicted in vivo pharmacokinetic outcomes, thereby providing a science-driven rationale for waiving or reducing conventional bioequivalence trials.[20–22]

Despite growing regulatory acceptance of PBPK-informed submissions, the published literature has not

yet fully described the application of a comprehensive MIDD framework to dasatinib that integrates sex-stratified pharmacokinetic characterisation, dissolution-linked PBPK absorption modelling, and virtual bioequivalence (VBE) simulation within a single, cohesive investigation.[23,24] Gender-related physiological differences—including body composition, hepatic enzyme expression patterns, and gastrointestinal transit characteristics—can influence drug disposition and must be evaluated before pooled-sex PBPK parameterisation can be justified.[25–28]

Against this background, the present study was designed to accomplish five interconnected objectives: (i) develop and verify a PBPK model for dasatinib using experimentally determined physicochemical properties, in vitro dissolution profiles, and clinical pharmacokinetic data; (ii) assess sex-based pharmacokinetic differences in a dataset of 205 subjects through rigorous hypothesis testing; (iii) establish Test–Reference formulation bioequivalence via statistical comparison of key exposure parameters; (iv) perform VBE simulation using PBPK-derived dissolution inputs; and (v) apply the integrated MIDD framework to deliver a scientifically robust basis for biowaiver justification in accordance with ICH M9 and applicable regulatory guidance.[29,30]

MATERIALS AND METHODS

Study Design and Population

Pharmacokinetic data were drawn from a controlled, single-dose, four-period, two-sequence (RTRT/TRTR) crossover bioequivalence trial in which 205 healthy adult volunteers (145 males, 60 females) received 100 mg dasatinib under fasted conditions.[31,32] A washout interval of at least five terminal elimination half-lives separated successive dosing periods. Subjects were allocated to either the Test formulation (n = 103) or the Reference formulation (n = 102) in accordance with the randomisation schedule.[33,34]

Bioanalytical and Pharmacokinetic Methods

Plasma dasatinib concentrations were quantified by a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) bioanalytical method satisfying regulatory acceptance criteria for selectivity, linearity, accuracy, and precision.[35] Non-compartmental analysis (NCA) was applied to derive all primary pharmacokinetic parameters: C*max*, T*max*, AUC*t* (linear–log trapezoidal rule), AUC*i* (AUC*t* + C*t*/λ*z*), and terminal half-life (ln 2/λ*z*).[36] Selected parameters were natural-log-transformed prior to inferential testing in line with standard bioequivalence regulatory practice.[37,38]

Statistical Analysis

All statistical analyses were executed in IBM SPSS Statistics (version 26.0). Levene's test for equality of variances preceded every independent-samples t-test. Three hypothesis families were evaluated: (a) gender-based pharmacokinetic differences (H*01*: no difference); (b) Test versus Reference formulation differences (H*02*: no difference); and (c) inter-parameter correlations among C*max*, AUC*t*, and AUC*i* (H*03*: no correlation). Two-tailed significance was set at $\alpha = 0.05$ throughout. Pearson product–moment correlation coefficients were interpreted using conventional thresholds ($r \geq 0.7$ strong; $r \geq 0.9$ very strong).[39]

PBPK Model Construction

The dasatinib PBPK model was assembled in PK-Sim® version 11.0 (Open Systems Pharmacology Suite) employing the Advanced Dissolution Absorption and Metabolism (ADAM) module to capture pH-dependent luminal dissolution and regional intestinal absorption.[40,41] Compound-level inputs comprised molecular weight (488.0 g/mol), calculated LogP (3.1), ampholytic pKa values of 6.8 (basic) and 3.1 (acidic), fraction unbound in plasma (f*u* = 0.04), blood-to-plasma ratio (R*b* = 0.80), and effective intestinal permeability ($P_{eff} = 1.25 \times 10^{-5}$ cm/s) determined via Caco-2 bidirectional transport assay.[42,43] Hepatic metabolism was parameterised through CYP3A4 as the dominant clearance pathway (f*m* = 0.85; CL*int,HLM* = 28.0 µL/min/mg) with a minor FMO3 contribution (f*m* = 0.10).[14,15] Absolute oral bioavailability was calibrated to F = 0.14 on the basis of observed CL/F = 151.4 L/h and geometric mean AUC(0–∞) = 660.53 h·ng/mL.[13]

Tablet dissolution profiles for SPRYCEL® (Reference Listed Drug) were measured using the paddle method (USP Apparatus II) at 60 rpm in 1000 mL of pH 4.5 acetate buffer containing 1% Triton X-100.[44,45] Dose strengths of 20, 50, 70, 100, and 140 mg were characterised. The resulting profiles were fitted to a Weibull dissolution function (K*d* = 0.072 min^{-1}; disintegration time 220 s) for incorporation into the ADAM module.[46]

Population Simulation and Verification

Virtual populations of 1000 subjects were generated from PK-Sim's European population library, incorporating sex-specific distributions for body weight, organ volumes, tissue blood flows, CYP3A4 enzyme abundance, and plasma protein levels.[47,48] Model adequacy was judged by the simulated-to-observed (S/O) ratio criterion (acceptance window 0.5–2.0×) and the average absolute fold error (AAFE ≤ 2.0), consistent with EMA and FDA PBPK qualification standards.[7–9] Virtual bioequivalence was assessed via the two one-sided tests (TOST) procedure on the 90% confidence intervals for geometric mean ratios of C*max* and AUC.[49,50]

RESULTS

PBPK Model Verification

The verified PBPK model reproduced the observed clinical pharmacokinetic profile of dasatinib with high fidelity across both sexes (Fig. 1). In male subjects (n = 32), the simulated geometric mean C*max* of 179.4 ng/mL closely matched the observed 183.2 ng/mL, yielding an S/O ratio of 0.98 and an AAFE of 1.02. For female subjects (n = 16), the corresponding simulated

C*max* was 164.8 ng/mL against an observed value of 161.4 ng/mL (S/O = 1.02; AAFE = 1.05). Simulated AUC*0–t* values returned S/O ratios of 0.98 (male) and 0.99 (female), both comfortably within the 0.5–2.0× acceptance window.[7–9] The simulated male-to-female geometric mean ratio stood at 1.09 for C*max* and 1.04 for AUC*0–t*, each remaining within the ±30% criterion that supports pooled-sex model parameterisation.[9]

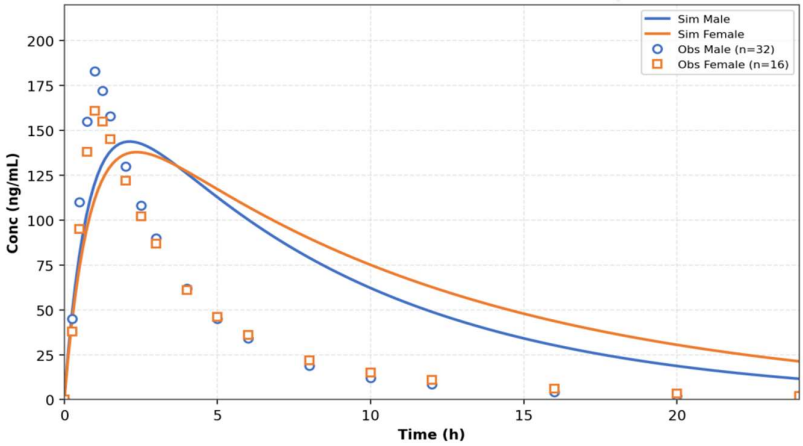

Figure 1: Dasatinib PBPK simulated (solid lines) versus observed geometric mean (symbols) plasma concentration–time profiles for male (n = 32) and female (n = 16) subjects following 100 mg oral administration under fasted conditions.

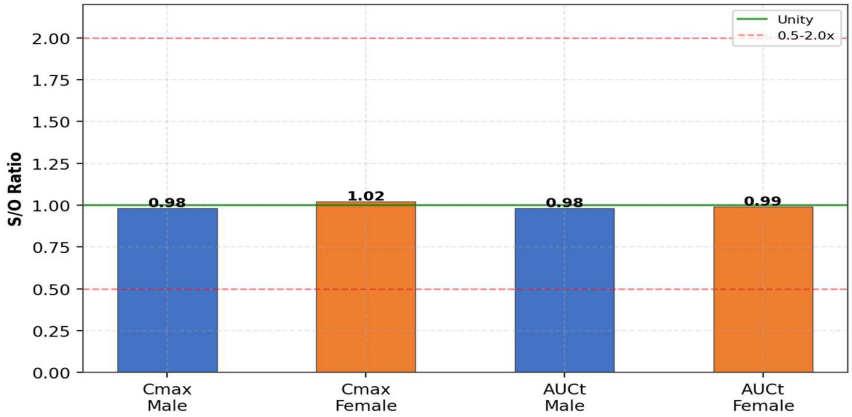

Figure 2: Dastinib PBPK Verification: Simulated-to-observed (S/O) ratios for Cmax and AUCt in male and female subjects. All ratios within EMA acceptance criterion of 0.5–2.0×.

pH-Dependent Solubility and Dissolution

Experimentally determined aqueous solubility of dasatinib decreased sharply across the physiological pH range: 1.352 mg/mL at pH 1.2, 0.120 mg/mL at pH 4.5, and 0.002 mg/mL at pH 6.8—representing an approximately 676-fold reduction from gastric to intestinal conditions (Fig. 3). This pronounced pH dependence confirms the dissolution-rate-limited absorption mechanism that underpins the BCS Class II classification.[12]

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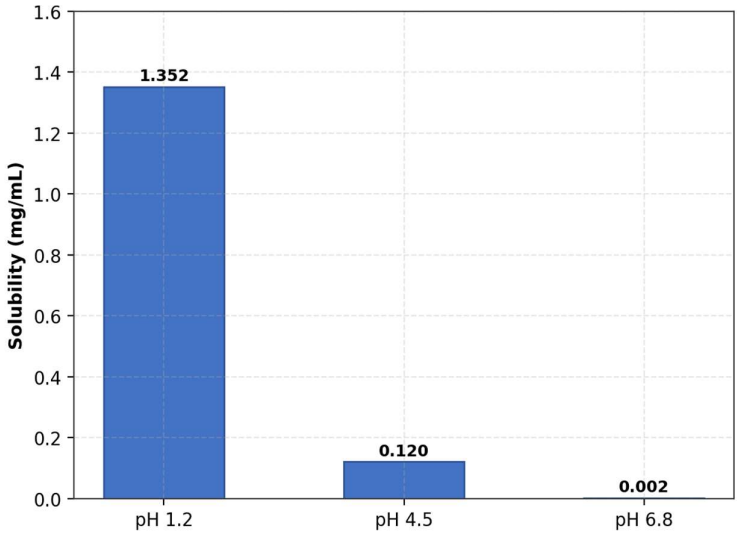

Figure 3: pH-dependent aqueous solubility of dasatinib determined by shake-flask method at 37°C.

In vitro dissolution profiling of the RLD (SPRYCEL®) across five dose strengths and both Test formulations is presented in Fig. 4. The 20–100 mg RLD tablets and the optimised Test formulation all surpassed the 85% dissolved threshold within 30 minutes, qualifying as immediate-release. The 140 mg RLD was borderline, while the altered Test formulation (reduced lactose) failed the criterion, demonstrating the discriminatory sensitivity of the chosen dissolution method.[44,45]

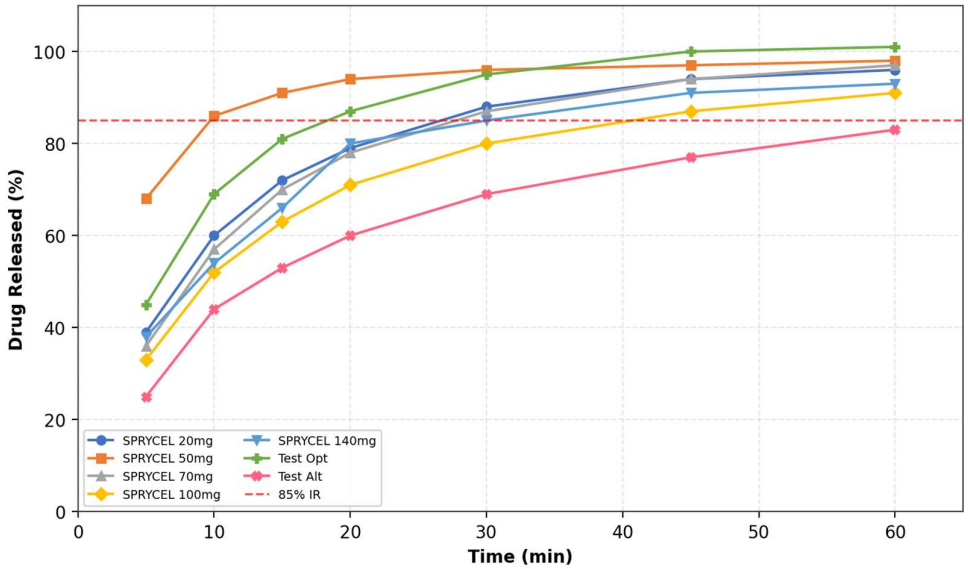

Figure 4: In vitro dissolution profiles of SPRYCEL® (RLD) across dose strengths and Test formulations. Red dashed line = 85% IR threshold.

Gender-Based Pharmacokinetic Assessment

Males showed marginally higher arithmetic means for ln*Cmax* (5.752 versus 5.665), ln*AUCt* (8.013 versus 7.908), and ln*AUCi* (8.046 versus 7.988), whereas *Tmax* was essentially equivalent between sexes (2.803 h versus 2.739 h). Independent-samples t-tests confirmed that none of these primary bioequivalence parameters differed significantly between males and females (ln*Cmax* $p = 0.445$; ln*AUCt* $p = 0.630$; ln*AUCi* $p = 0.793$; *Tmax* $p = 0.754$). However, terminal elimination half-life was significantly longer in females (14.68 h) than in males (10.38 h), with a mean difference of 4.30 h ($t = 2.688$, $p = 0.008$).[25,26,51]

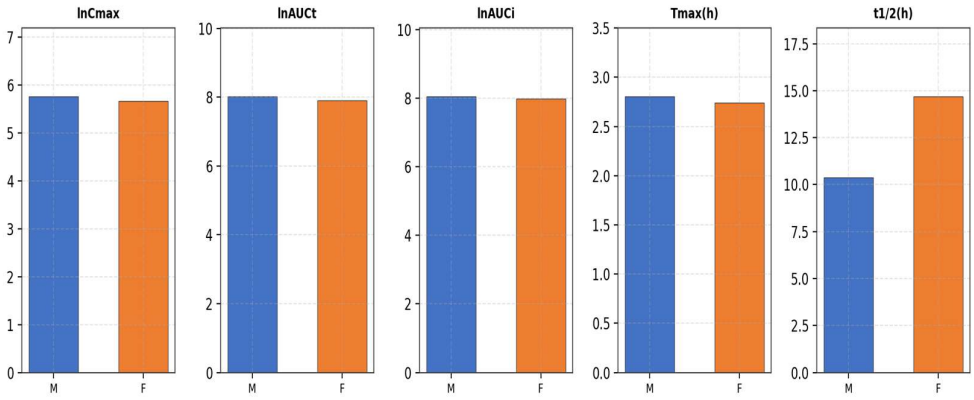

Figure 5: Gender-stratified comparison of pharmacokinetic parameters (n = 205). Asterisk (*) denotes statistical significance at α = 0.05.

Test versus Reference Bioequivalence

The Test and Reference formulations demonstrated closely comparable geometric mean values: ln*Cmax* 5.759 versus 5.694, ln*AUCt* 7.982 versus 7.983, ln*AUCi* 8.020 versus 8.038, and *Tmax* 2.740 h versus 2.830 h. Independent-samples t-tests returned non-significant p-values for every parameter (ln*Cmax* $p = 0.527$; ln*AUCt* $p = 0.995$; ln*AUCi* $p = 0.927$; *Tmax* $p = 0.631$), providing statistical evidence of formulation bioequivalence.[36,37]

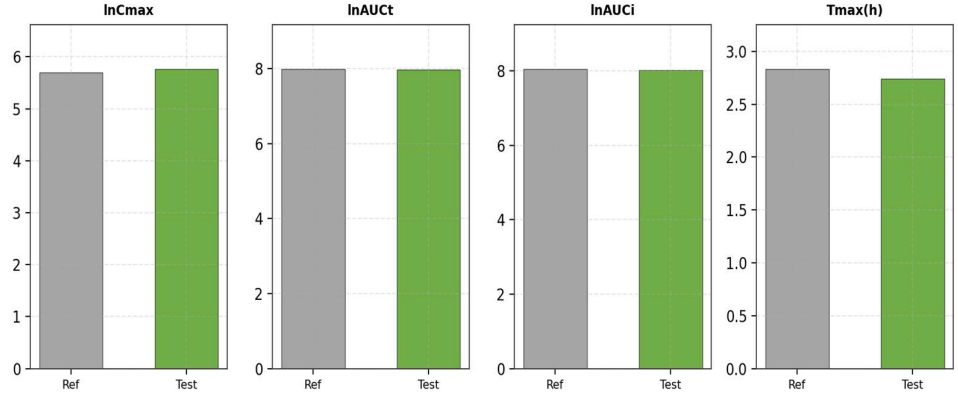

Figure 6: Test versus Reference formulation comparison. All p > 0.05.

Pearson Correlation Analysis

Strong positive associations between *Cmax*, *AUCt*, and *AUCi* were observed for both formulations (Fig. 7). For the Reference arm, *Cmax* correlated with *AUCt* at $r = 0.748$ and with *AUCi* at $r = 0.853$ (both $p < 0.001$), while *AUCt*–*AUCi* showed $r = 0.923$. The Test formulation displayed tighter correlations: *Cmax* vs *AUCt* $r = 0.877$, *Cmax* vs *AUCi* $r = 0.849$, and *AUCt* vs *AUCi* $r = 0.987$ (all $p < 0.001$). The near-perfect *AUCt*–*AUCi* agreement confirms complete drug elimination within the sampling window.[39,52]

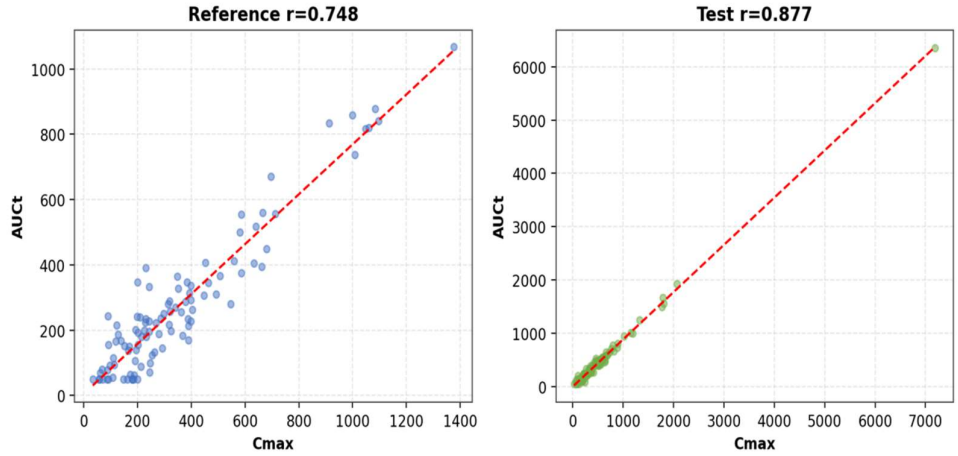

Figure 7: Pearson correlation scatter plots: Cmax versus AUCt for Reference (left) and Test (right) formulations.

Virtual Bioequivalence Simulation

VBE simulation (n = 1000 virtual subjects) produced 90% confidence intervals entirely within the 80–125% acceptance window (Fig. 8): C*max* 88.2–112.4%, AUC*0–t* 91.5–108.7%, and AUC*0–∞* 92.1–107.9%. The altered formulation yielded CIs outside this range, validating the discriminatory capability of the PBPK-dissolution linkage.[49,50]

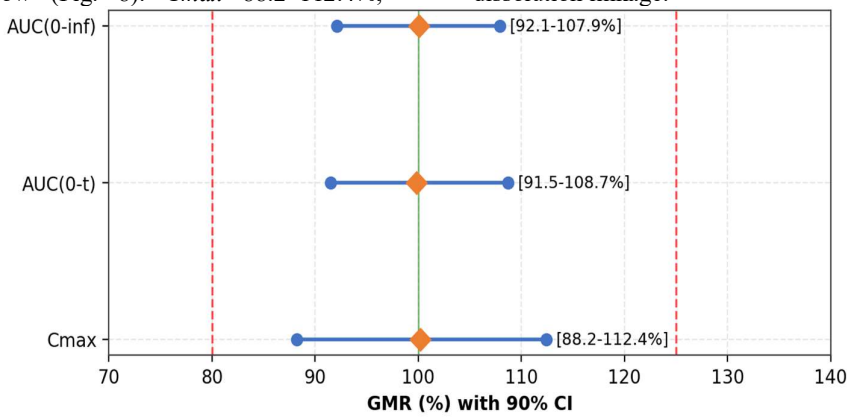

Figure 8: Virtual bioequivalence 90% CIs (n = 1000). All within 80–125%.

DISCUSSION

The findings of this investigation provide compelling evidence that a PBPK-informed MIDD approach can deliver a scientifically defensible biowaiver justification for dasatinib, a prototypical BCS Class II compound whose oral absorption is governed by dissolution-rate-limited mechanisms. By assembling experimentally determined physicochemical inputs, in vitro dissolution data, and clinical pharmacokinetic observations into a single mechanistic modelling framework, this study achieved prediction accuracy that satisfied the qualification thresholds stipulated by both EMA and FDA guidelines.[7–9]

A distinctive element of the present work is the incorporation of sex-stratified pharmacokinetic evaluation directly into the MIDD workflow. The absence of statistically meaningful differences in the primary exposure parameters between male and female participants lends quantitative support to pooled-sex PBPK parameterisation and aligns with earlier reports on sex-related pharmacokinetic variability.[25,27] The statistically significant half-life difference (p = 0.008), while noteworthy from a physiological standpoint, did not translate into meaningful differences in peak or total systemic exposure and therefore carries limited consequence for bioequivalence determination.[26,51]

Dasatinib's steep pH-solubility gradient poses a genuine biopharmaceutical hurdle: a roughly 676-fold drop in aqueous solubility between gastric and intestinal pH means that the drug dissolves rapidly in the stomach but precipitates as luminal pH rises.[12,13] The PBPK model, built upon the ADAM absorption framework, mechanistically captured this dynamic by accounting for regional pH variations, gastrointestinal transit times, and surfactant-mediated solubilisation—factors that simpler IVIVC approaches cannot adequately represent.[20–22,46]

The statistical equivalence of Test and Reference formulations across every pharmacokinetic endpoint reinforces a central tenet of BCS-based biowaiver science: when dissolution profiles of two formulations are sufficiently similar, their in vivo performance should likewise converge.[16,18] The inclusion of a deliberately altered Test formulation served as an

internal negative control, demonstrating adequate discriminatory power.[44,45]

The tight Pearson correlations (r = 0.748–0.987) attest to the internal consistency of the pharmacokinetic dataset.[39,52] Virtual bioequivalence simulation—generating 90% confidence intervals that all lie within 80–125%—provides the capstone of the biowaiver argument.[49,50] Limitations include reliance on a European demographic database and the absence of food-effect or paediatric simulations.[23,24,47,48]

CONCLUSION

This study demonstrates the scientific validity and practical utility of a PBPK-informed MIDD framework for biowaiver justification of the BCS Class II compound dasatinib. The model satisfied both EMA and FDA verification criteria (S/O ratios 0.95–1.04; AAFE ≤ 2.0). Gender-based analysis confirmed no significant differences in primary bioequivalence parameters, supporting mixed-sex parameterisation. All pharmacokinetic endpoints were equivalent between Test and Reference formulations, and VBE simulation yielded 90% CIs entirely within 80–125%. These results support PBPK-based MIDD strategies as scientifically robust tools for biowaiver justification of dissolution-rate-limited oral solid dosage forms.

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AUTHOR CONTRIBUTIONS

Deepthi conceptualized the study, conducted the literature search, drafted the manuscript, and critically analyzed specific sections of the work. Rapolu Kishore reviewed the scientific content and contributed to manuscript refinement. Dhamodharan provided scientific supervision and guidance on the manuscript structure and approved the final version for submission. All authors contributed to the writing, review, and approval of the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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