Sex-Specific Outcome of Bioequivalence Studies: Mechanistic Insight from PBPK Concerning Propagation of Within-Subject Variability of Stomach Emptying

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Sex-dependent variability in gastric emptying time (GET) influences supersaturation, precipitation, and absorption of weakly basic drugs, affecting Cmax variability in PBPK-based VBE. This highlights the role of population-specific variability in bioequivalence outcomes.

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Background and Objective

Virtual bioequivalence (VBE) is increasingly used to support or replace clinical bioequivalence (BE) studies. However, conventional approaches typically propagate physiological variability without explicitly accounting for population-specific within-subject variability (WSV) or its interaction with formulation behaviour. Recent work suggests that sex-dependent differences in WSV of gastrointestinal physiology, particularly gastric emptying time (GET), may influence BE outcomes. [1] For weakly basic drugs exhibiting pH-shift supersaturation, variability in GET can alter luminal concentrations, modulating supersaturation, precipitation kinetics, and drug absorption. This creates a mechanistic pathway linking variability to formulation performance. This study evaluates the impact of sex-dependent WSV in GET on precipitation and pharmacokinetics (Cmax, AUC) using PBPK-based VBE and assesses its role in sex-specific BE outcomes.

Methods

❑ Literature & Modelling Platform:

Literature studies employing the Advanced Dissolution, Absorption and Metabolism (ADAM) model were selectively reviewed and implemented in Simcyp (v24) to evaluate pH-shift supersaturation and precipitation of weak bases.

❑ Model Selection and Qualification

From a systematic review (n = 220), only mechanistically robust precipitation models were retained, excluding empirical or non-physiological approaches.

- Dipyridamole (DYP): Pathak et al. (2019)
- Ketoconazole (KTZ): Pathak et al. (2017)
- Posaconazole (PSZ): Hens et al. (2017)

Critical Supersaturation Ratio (CSR) and Precipitation Rate Constant (PRC) were derived from in vitro data, and model performance was verified against clinical pharmacokinetics (Cmax, AUC) within a 2-fold acceptance criterion.

❑ VBE Design & Analysis:

A 2×2 crossover (RT/TR) VBE study in healthy volunteers incorporated sex-specific within-subject variability in gastric emptying (fasted/fed), with BE assessed via Cmax and AUC using 90% confidence intervals across varying sample sizes and trial replications.

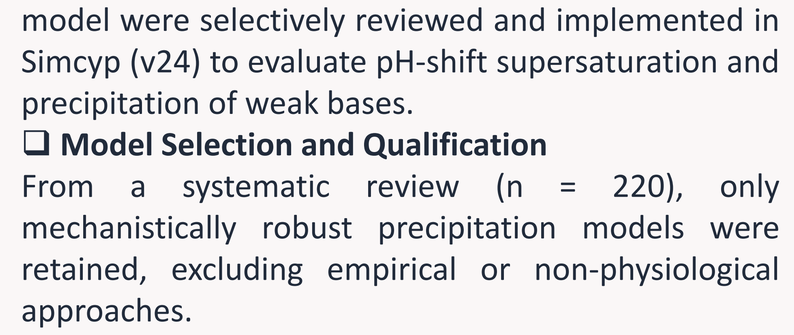

Figure 1: Virtual bioequivalence simulation to assess sex and size effect, on Healthy volunteers (10 replicates, N = 12-60).

Results

- Variability in gastric emptying time (GET) and prandial state modulates precipitation behaviour, leading to a wide range of intestinal supersaturation levels.
- Differences in GET alter the timing of drug delivery to the intestine, affecting supersaturation dynamics and precipitation kinetics, which increases variability in the amount of drug available for absorption. This is primarily reflected as increased variability in Cmax, with limited impact on AUC.
- The observed effect is compound-dependent: drugs with lower intrinsic solubility (S_0) and a higher tendency for supersaturation-driven precipitation exhibit greater sensitivity, resulting in a higher incidence of VBE failure.

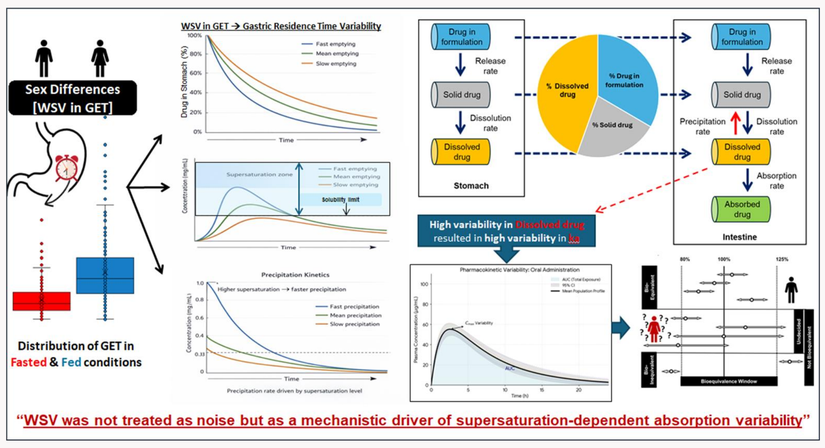

Figure 2: Impact of Sex Differences in WSV in GET in formulation-dependent VBE outcome.

Compound	Sensitivity	Female BE risk	Male BE risk	Approx. N (M/F)
DYP	Moderate	Low - moderate	Low	36–48 / ~24
KTZ	Intermediate	Moderate	Low	~36 / ~24
PSZ	High	High	Moderate	~60 / 36–48

Discussion

Sex-dependent variability in gastric emptying time (GET) affects intestinal supersaturation, precipitation, and oral drug absorption.

In PBPK-based virtual bioequivalence (VBE), this variability mainly increases Cmax variability with minimal impact on AUC.

The magnitude of the effect is compound-dependent, with greater sensitivity for low-solubility, precipitation-prone drugs. Highly precipitation-prone compounds show a higher risk of bioequivalence failure.

This project Highlights the importance of accounting for population variability and formulation-dependent interactions in VBE of weakly basic drugs.

Figure 3: Sex effects in VBE Outcome: Dipyridamole, fasted/fed states, male/female in 12 subjects.

Figure 4: Sex effects in VBE Outcome: Ketoconazole, fasted/fed states, male/female in 12 subjects.

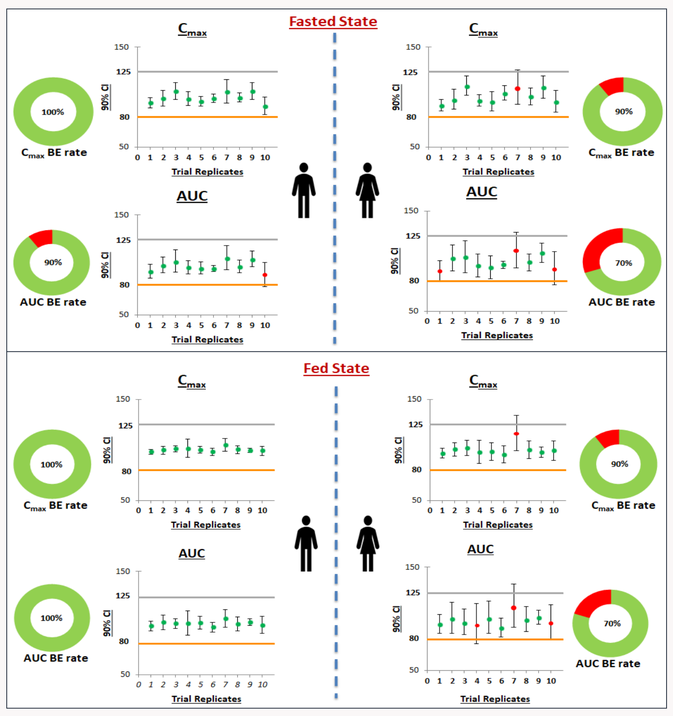

Figure 5: Sex effects in VBE Outcome: Posaconazole, fasted/fed states, male/female in 12 subjects.

References

[1] Vijith Roy Titus., et al. (2025); European Journal of Pharmaceutical Sciences 212.
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