

Population Pharmacokinetic Modeling and Simulation of Tapentadol Bioequivalence: Assessing the Food Effect

Quintairos L¹, Ortego D¹, Bertoncini C¹, Pérez de la Cruz M¹
¹ CHEMO Research S.L., Insud Pharma, Madrid, Spain

Background

Tapentadol is a μ -opioid receptor agonist that also inhibits norepinephrine reuptake, making it effective for managing various types of pain.

The novel model-integrated evidence (MIE) (1) approach presents a compelling alternative to traditional bioequivalence (BE) methods in specific scenarios.

In this poster, we explore the impact of food on the bioequivalence of a generic tapentadol oral tablets formulation (not yet approved in Spain) compared to Palexia[®] retard, by simulating studies under fed conditions for dose strengths previously evaluated under fasting conditions.

Objectives

- Adapt an existing population pharmacokinetic (PK) model of tapentadol to include the food effect as a covariate, using data from prior studies.
- To simulate the bioequivalence of tapentadol at dose strengths of 100 mg, 150 mg, and 200 mg under fed conditions.

Data & Model

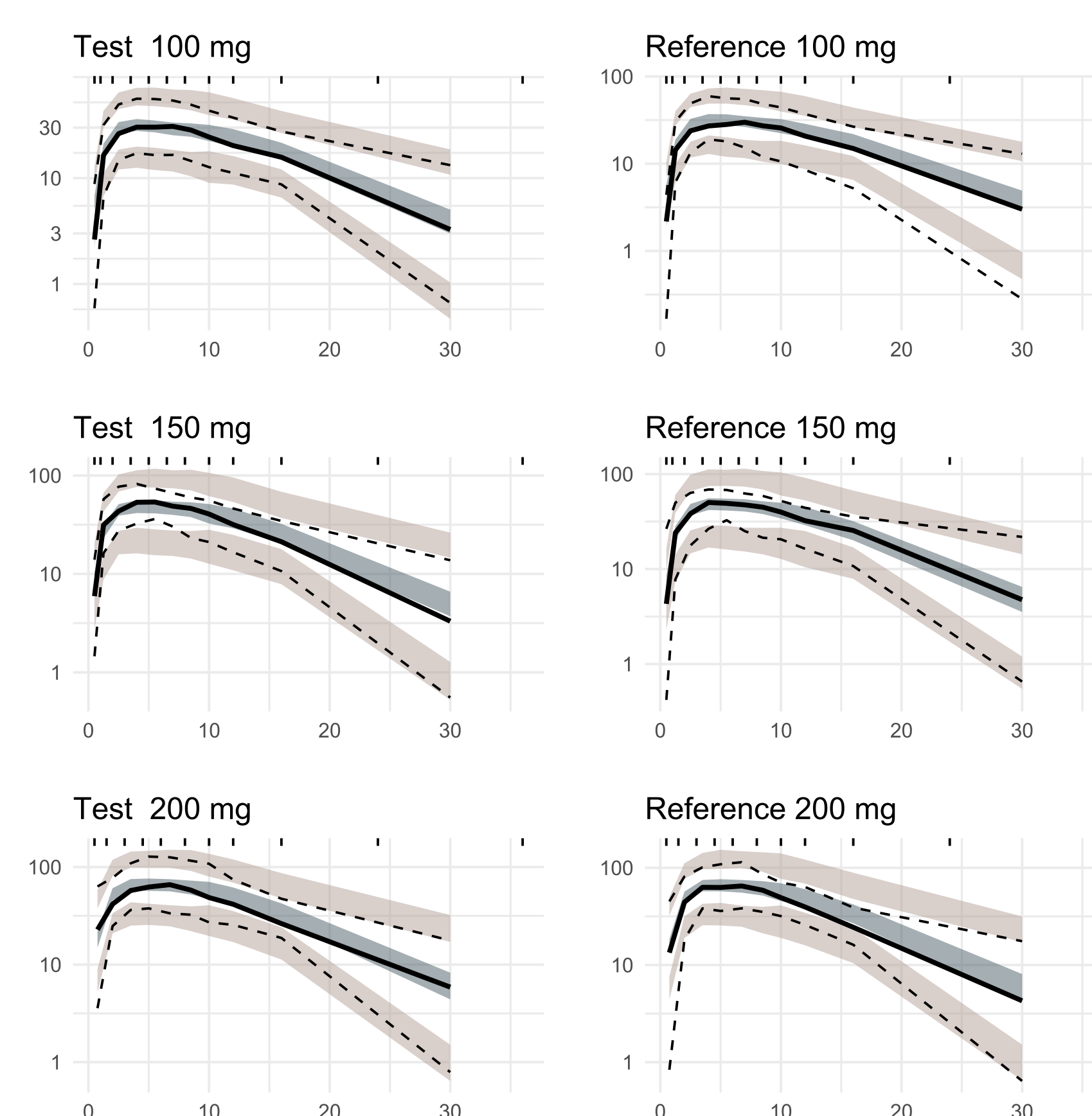
Data from seven bioequivalence single-dose crossover studies were pooled, comprising five conducted under fasting conditions (at strengths of 50, 100, 150, 200, and 250 mg) and two under fed conditions (at strengths of 50 and 250 mg), to adapt a previously published population pharmacokinetic (PK) model for tapentadol (1). A total of 7,136 concentration-time observations from 322 healthy subjects were included in the analysis. This model originally included food effect by increasing the slope of the second input rate constant (K_{a2}). Inter-individual variability was included in clearance (CL/F) and relative bioavailability (F). Age and aspartate aminotransferase (AST) levels were included as covariates in CL/F and body weight in F. The model required an adaptation to fit our data, with AST effect fixed to 1 due to insufficient recorded data. Treatment effects were assessed in absorption parameters, and interoccasion variability (IOV) was included in F to account for period effect.

Residual error was described by an additive plus different proportional error estimates for each study. The treatment effect (test or reference) was incorporated into the fast absorption constant (K_{a1}) and the relative bioavailability of the absorption compartments (F1/F2).

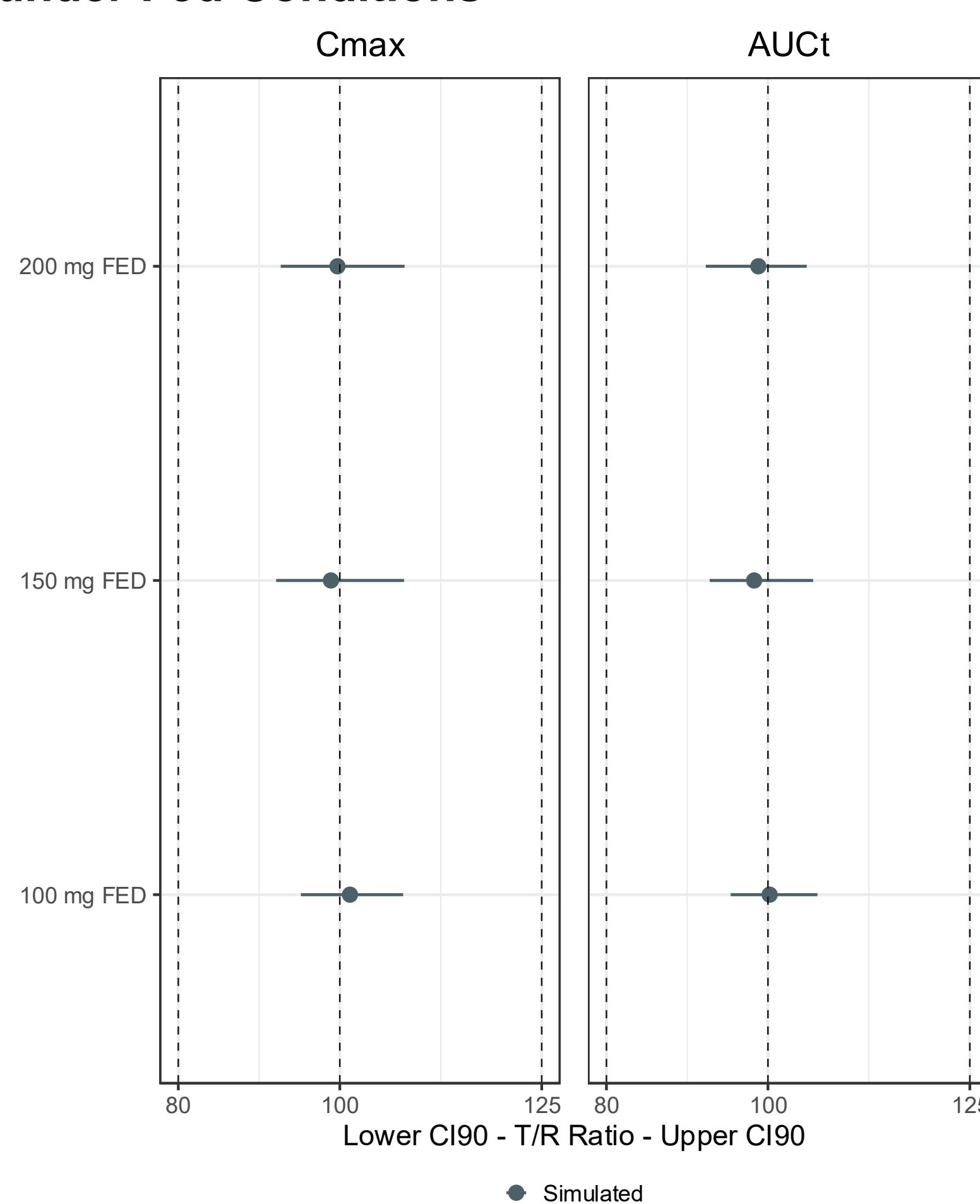
Software

Model development was conducted using NONMEM (3) with Finch Studio (Enhanced Pharmacodynamics LLC) as a supportive tool. R software version 4.3.3 (4) was employed for non-compartmental analysis (NCA) calculations and bioequivalence assessment.

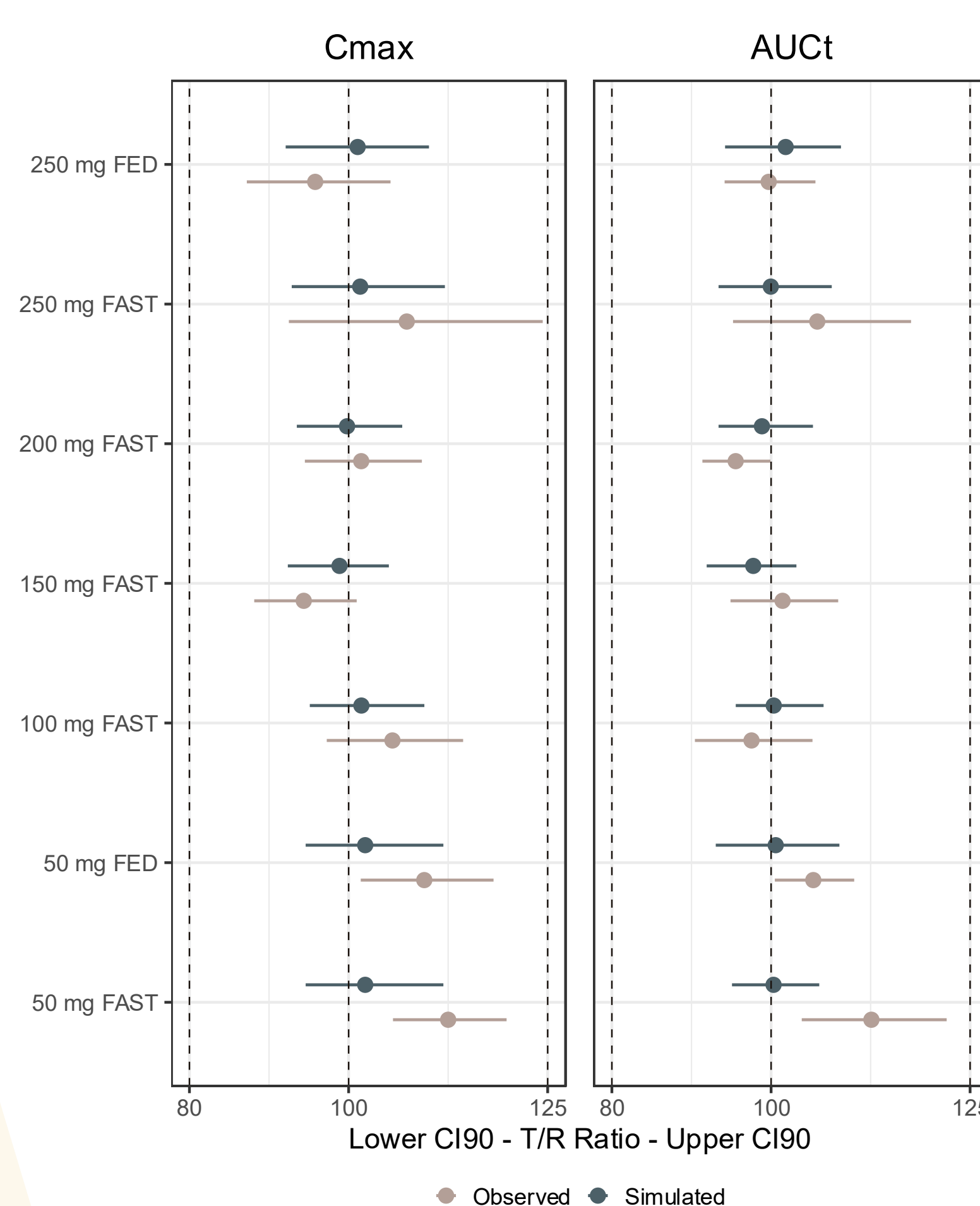
Simulated and Observed T/R Ratios and CI90



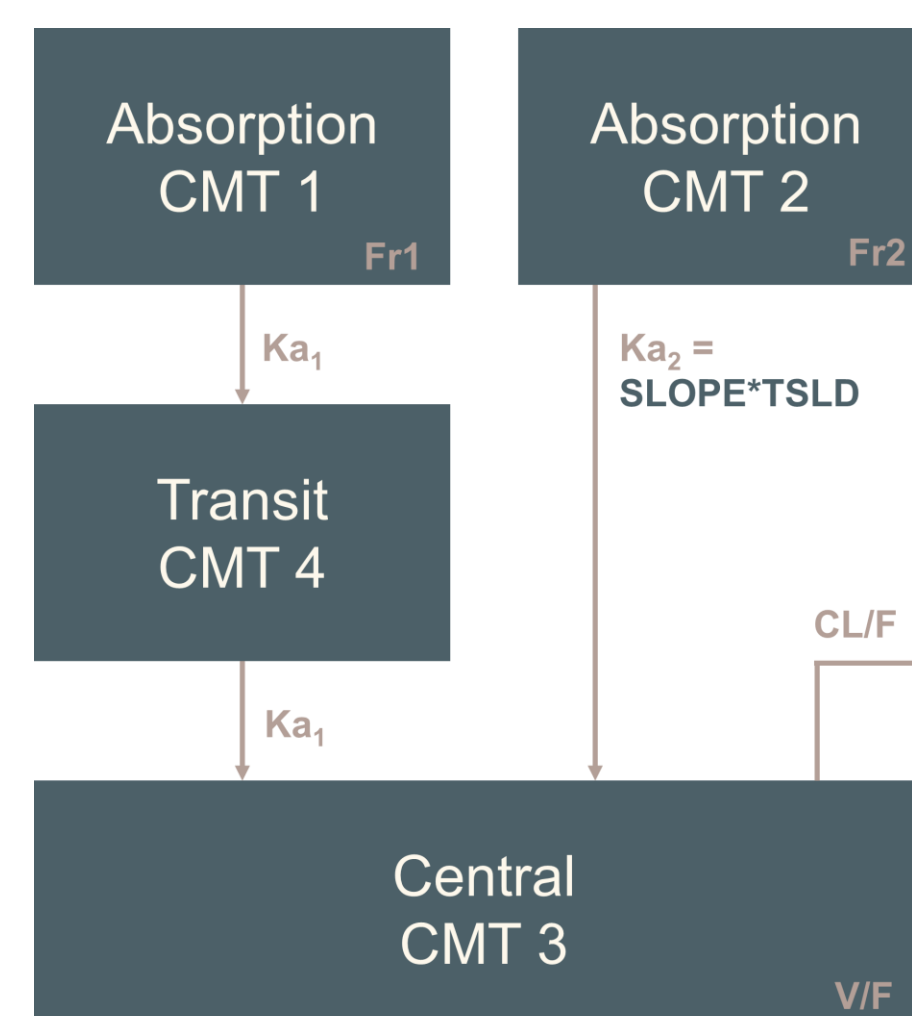
Simulated T/R Ratios and CI90 under Fed Conditions



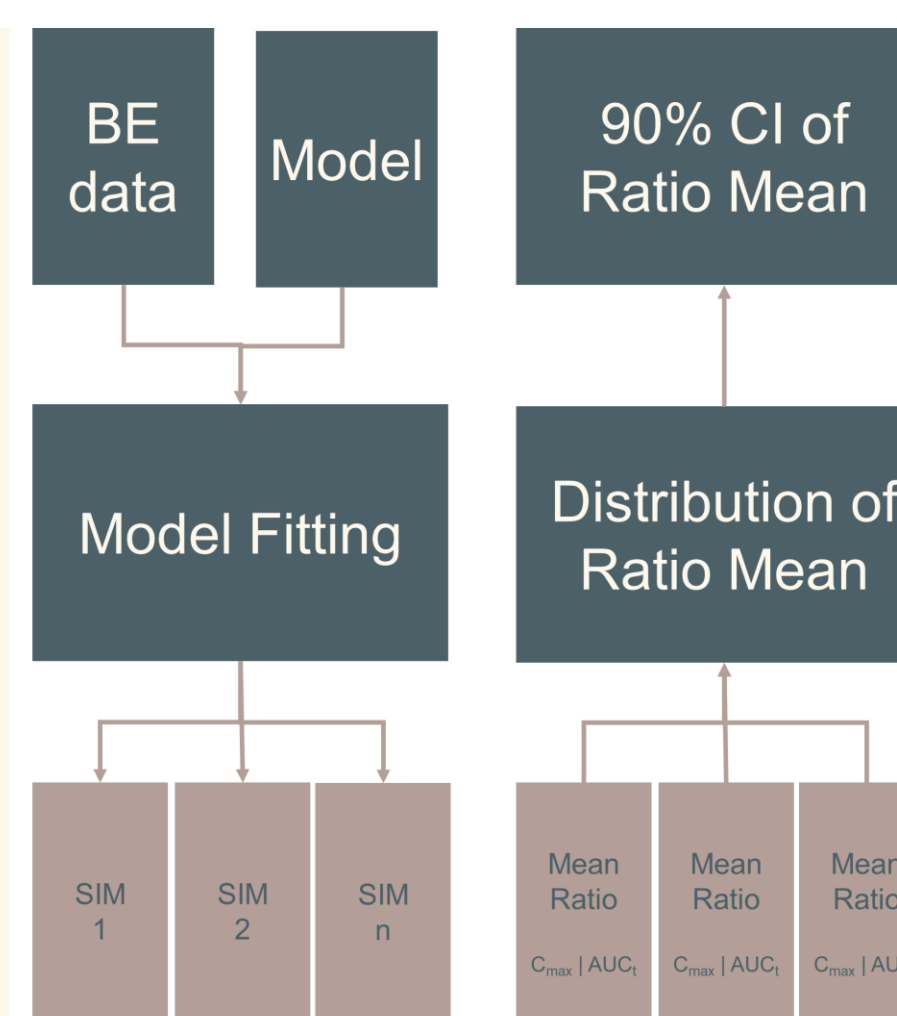
Simulated and Observed T/R Ratios and CI90



Model Structure



MIE Approach



CMT 2 Free Tapentadol Fraction

$$\frac{A_{abs2} \cdot B_{max} \cdot K_D \cdot \sqrt{A_{abs2} \cdot B_{max} \cdot K_D^2 \cdot 4 \cdot A_{abs2}}}{2 \cdot A_{abs2}}$$

Simulation & BE

To confirm the validity of the model for assessing BE, the studies used to build the model were simulated, and the ratio and 90% confidence intervals (CI90) were compared with the observed data. The BE results of the simulated studies compared to observed ones confirmed the prediction ability of the model. The model was then used to simulate dose strengths of 100, 150 and 200 mg under fed conditions to assess the BE following previously published MIE method (2). The ratio and CI90 calculated from these simulations indicated that the tested formulations would be bioequivalent under fed conditions.

Conclusion

MIE method was successfully applied to simulate and determine the BE of tapentadol at dose strengths of 100 mg, 150 mg, and 200 mg under fed conditions, using data collected from previous studies conducted under both fasting and fed conditions.

MIE method for BE assessment represents a highly valuable tool in the development of generic drugs and could serve as a waiver method to reduce the number of studies required.

References

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