

Population pharmacokinetics of an antifungal immediate-release formulation of oral flucytosine to characterize absorption and food effects

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Introduction

- Cryptococcal meningitis treatment using an immediate-release (IR) flucytosine (5FC) formulation is sub-optimal due to the short half-life of 5FC, requiring four daily doses¹.
- Absorption of 5FC and the impact of food on PK has not been well characterized despite it having been available for almost 70 years.
- A sustained-release formulation of 5FC is under clinical development to simplify the dosing regimen and enhance access to treatment.

Methods

- Data from two phase I clinical trials^{2,3} with a fasted (n=42) and a fed (n=36) study
- Oral dose of 1500 mg (3x500 mg) administered twice daily at T=0 and T=6
- Below the limit of quantification data (2.36%) handled using the M6 method (lower limit of quantification, 0.4 µg/ml)
- One-, two-, and three-compartment models with different absorption models investigated
- Food and dosing occasion covariates explored on the absorption parameters

Aim: To characterize the PK of IR 5FC, with a focus on the absorption, and investigate any potential food effect using phase 1 clinical data, through non-linear mixed effects modelling

Results

- Food intake led to a slower absorption, with a **60% increase in the MTT**, but did not affect **F**
- A slower absorption, with a **19% increase in MTT**, was observed in the second dosing occasion
- Non-linearity in F1 was identified in the second dosing, with **7% lower F** than in the first dosing occasion

Table 1. IR 5FC parameter estimates, relative standard error (RSE), and confidence interval (CI, 5-95%) derived from sampling importance resampling (SIR). Food = food effect; Time = dosing occasion effect

Parameters	Estimate (RSE%)	5 - 95% CI
CL/F (L/h)	6.24 (2.43)	6.00 - 6.49
V ₁ /F (L)	49 (2.64)	47.0 - 51.1
F	1	-
V ₂ /F (L)	3.00 (21.3)	1.97 - 4.14
Q ₁ /F (L/h)	0.643 (31.4)	0.316 - 1.06
MTT (h)	0.462 (6.41)	0.415 - 0.511
Covariates (%)		
F _{Time, 2nd}	-7.42 (22.8)	-10.2 - -4.31
MTT _{Food, fed}	+60.7 (22.1)	+42.3 - +83.6
MTT _{Time, 2nd}	+18.8 (32.4)	+7.81 - +29.4
Variability (CV%)		
IIV CL/F	26.9 (30.7)	22.9 - 29.9
IIV V ₁ /F	30.8 (29.5)	26.8 - 34.4
IIV F	36.2 (22.0)	33.0 - 39.7
IOV MTT	64.2 (16.1)	60.8 - 69.2
Proportional	35.6 (6.34)	34.6 - 36.5
Additive	0.2	-

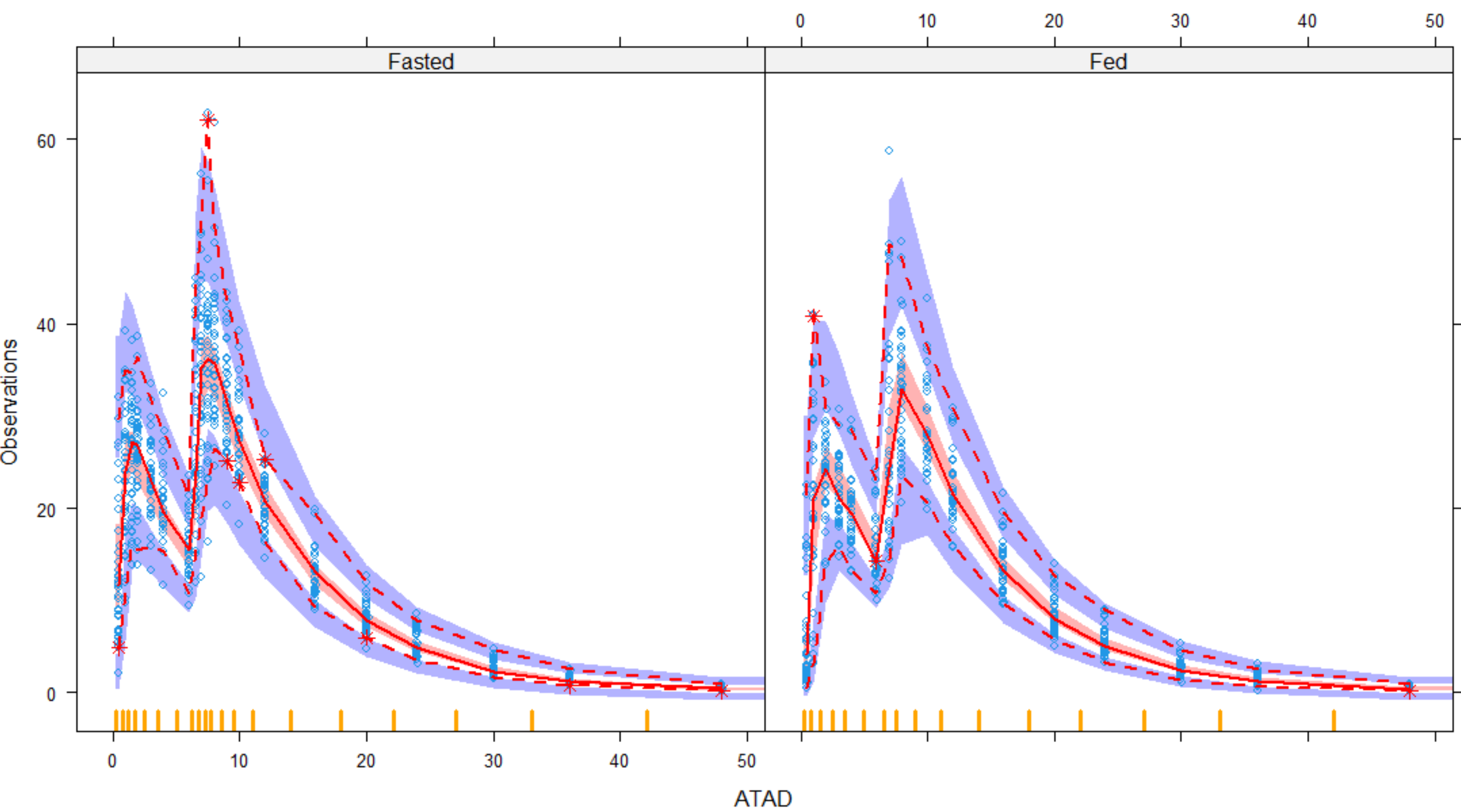
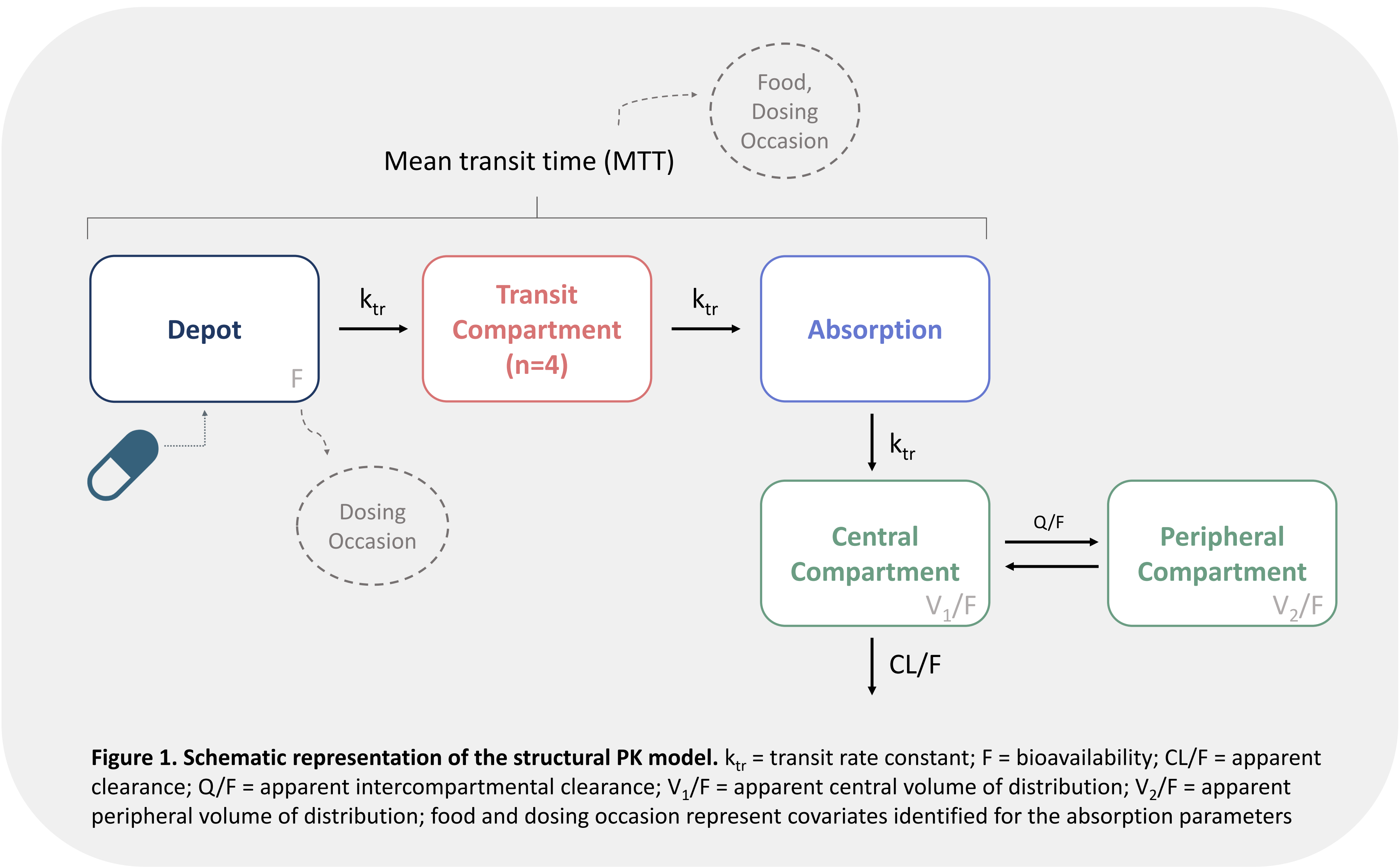


Figure 1. Visual predictive check (VPC) of the final IR 5FC PK model stratified by food intake. The solid and dashed lines represent the 5th, 50th, and 95th percentiles of the observed data, and the shaded areas represent the model-predicted 95% CI of the same percentiles

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Conclusion

- Our study identified a delay in IR 5FC absorption that was significantly influenced by food intake – a finding not previously reported in other 5FC popPK models^{4,5}
- Food intake led to an increase in mean transit time, but did not affect bioavailability
- A small decrease in bioavailability was identified for the second dosing occasion

References

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