Application of PBPK Modelling to Explore Complex Food Effects on Trospium Chloride Pharmacokinetics

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PBPK modelling explains formulation-dependent food effect on trospium chloride through *reduced permeability, lower free fraction, and viscosity-delayed disintegration.*

Background and Objective

Trospium chloride (TC) is a quaternary ammonium antimuscarinic agent indicated for overactive bladder. As a BCS Class III compound, TC exhibits very low oral bioavailability (~10%) driven by poor intestinal permeability, with absorption confined to the small intestine. TC displays a pronounced negative food effect: a high-fat meal reduces IR tablet AUC by ~74%. Three mechanisms have been proposed: (1) reduced permeability from disruption of bile salt-drug ion pairing, (2) decreased luminal free fraction due to micellar binding, (3) viscosity-mediated delays in tablet disintegration. The relative contribution of each mechanism remains poorly quantified, particularly across formulations.

The objective of this work was to build a PBPK model to assess the contributions of the three proposed mechanisms for capturing food effects on TC for both IR and XR formulations by integrating permeability changes, micellar partitioning, and viscosity-dependent disintegration.

Methods

A full PBPK model was developed for trospium chloride in Simcyp V24. Distribution was described using Method 2 with an optimized Kp scalar. Hepatic and renal clearance were parameterized using reported IV clearance values, with renal clearance accounting for 70% of total elimination. Absorption was modeled using ADAM with MechPeff for permeability prediction.

Three mechanisms were incorporated for fed-state simulations. First, to capture the ~1.5-fold reduction in permeability from disruption of bile salt–drug ion pairing in the fed state (Heinen et al., 2013), the absorption rate scalar was reduced relative to the fasted state. Second, the ~60% decrease in luminal free fraction observed in FeSSIF and FDA breakfast homogenate (Sumiji et al., 2023) was reproduced by adjusting the $logK_{mw}$ to achieve a jejunal free fraction of ~0.4 (**Figure 1**). Third, for the IR tablet, a disintegration constant–viscosity relationship was derived from *in vitro* dissolution data in HPMC media mimicking FDA breakfast viscosity (Radwan et al., 2012) (**Figure 2**). This was combined with the ADAM fluid volume dynamics model to predict *in vivo* viscosity-dependent disintegration profiles (Liu et al., 2013) (**Figure 3**). For the XR capsule, a monolithic release system with the observed dissolution profile was used as input.

Results

The fasted-state model adequately predicted TC pharmacokinetics across various studies (not shown here). For the XR capsule (**Figure 4**), incorporating mechanisms (1) and (2) (reduced permeability and decreased luminal free fraction) predicted fed and fasted AUC, C_{max} and T_{max} within 2-fold of observed values, with fed/fasted ratios within 1.5–2.5-fold of clinical data (**Table 1**).

However, for the IR tablet, these two mechanisms alone overpredicted fed-state exposure; the negative food effect was not fully recovered (**Table 2**). Adding mechanism (3) (viscosity-mediated delayed disintegration) substantially improved IR tablet predictions (**Figure 5**). With all three mechanisms, fed C_{max}, AUC and T_{max} were predicted within 2-fold across, and fed/fasted ratios showed notable improvement.

Figure 1. Predicted jejunal free fraction of trospium chloride in the fed state after adjusting $logK_{mw}$ to reflect the reduced luminal free fraction under fed conditions.

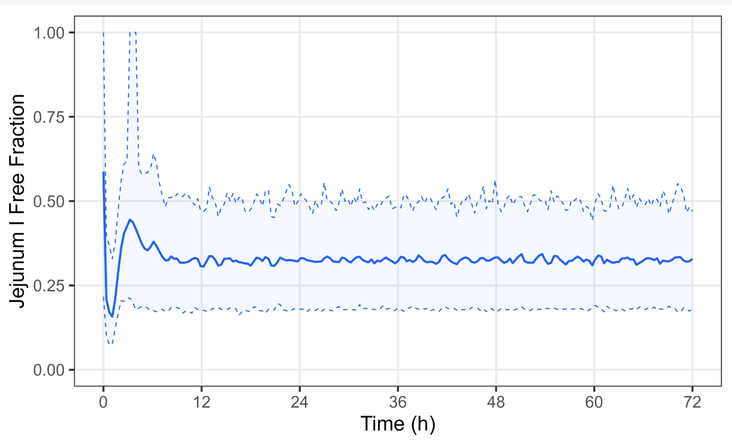


Figure 2. Relationship between the disintegration constant and viscosity, derived from *in vitro* dissolution data in HPMC media (Radwan et al., 2012).

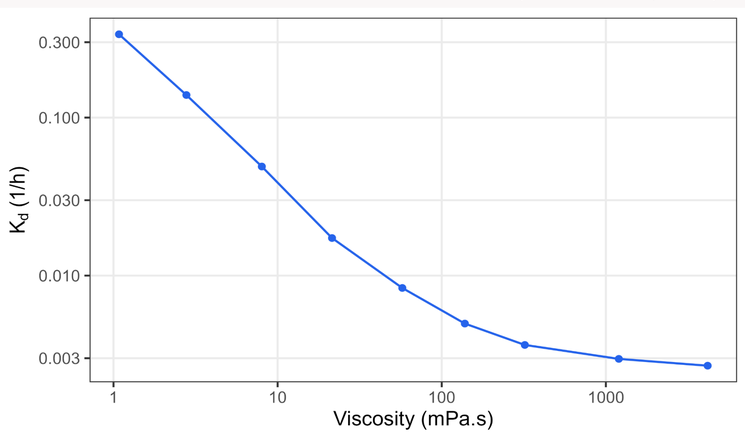
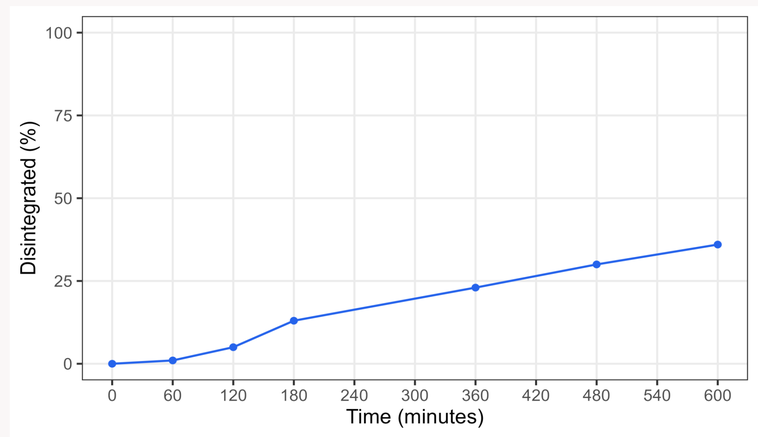


Figure 3. Disintegration profile applied in the fed state to account for the effects of food viscosity on tablet disintegration.



Discussion/Conclusion

The PBPK model demonstrates that negative food effect on TC PK may arise from the interplay of at least three distinct mechanisms, with their relative contributions depending on formulation type. For the XR capsule, reduced permeability and decreased luminal free fraction were sufficient to capture the food effect. For the IR tablet, however, viscosity-mediated delayed disintegration was essential to predict the magnitude of the negative food effect.

Figure 4. Simulated (blue line) and observed (dots) mean plasma concentration after a single oral dose of 60 mg trospium chloride XR capsule following a meal. The blue shaded area represents the 5th and 95th percentiles. Observed mean data were extracted from Hotha et al. 2010.

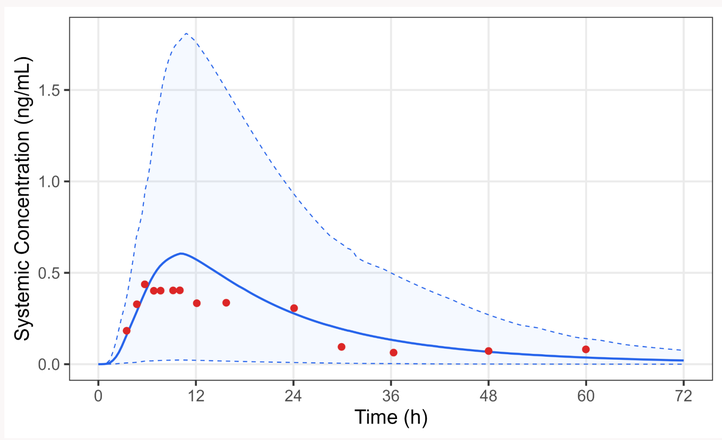


Figure 5. Simulated and observed mean plasma concentration–time profiles of trospium chloride following a single 60 mg oral dose of the IR tablet in the fed state. Simulations accounting for viscosity-dependent tablet disintegration are shown in blue, while simulations without this effect are shown in orange; observed mean concentrations are shown as dots (Liu et al., 2013). Shaded regions represent the 5th and 95th percentile range of the simulations.

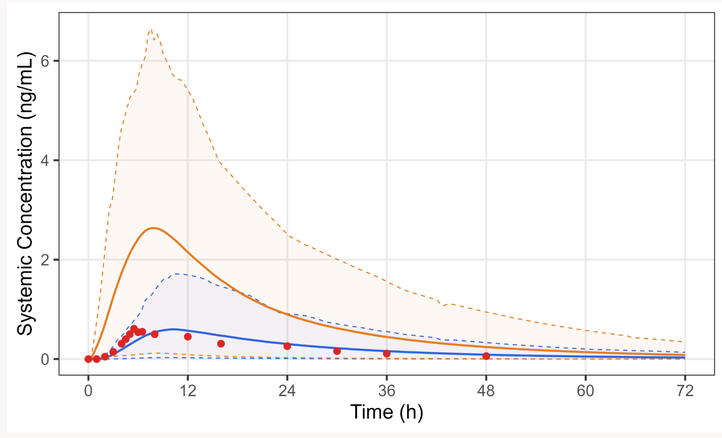


Table 1. Observed and predicted C_{max}, AUC and T_{max} and their fed-fasted ratios for the XR capsule (Hotha et al., 2010).

Category		Observed	Predicted
Fasted	Cmax (ng/mL)	6.04	3.85
	AUC (ng*h/mL)	63.99	57.36
	Tmax (h)	6.48	5.70
Fed	Cmax (ng/mL)	0.44	0.63
	AUC (ng*h/mL)	12.69	13.66
	Tmax (h)	5.71	9.35
Fed/Fasted ratios	Cmax (ng/mL)	0.07	0.16
	AUC (ng*h/mL)	0.20	0.24
	Tmax (h)	0.88	1.64

Table 2. Observed and predicted C_{max}, AUC, and T_{max}, along with their fed-to-fasted ratios, for the IR tablet with and without incorporation of viscosity effects on tablet disintegration (Liu et al., 2013).

Category		Observed	Predicted
Fasted	Cmax (ng/mL)	5.68	8.35
	AUC (ng*h/mL)	55.54	99.70
	Tmax (h)	6.00	3.96
Fed (without viscosity)	Cmax (ng/mL)	0.61	3.44
	AUC (ng*h/mL)	11.16	64.05
	Tmax (h)	6.50	7.92
Fed (with viscosity)	Cmax (ng/mL)	0.61	0.62
	AUC (ng*h/mL)	11.16	14.63
	Tmax (h)	6.50	9.45
Fed/Fasted ratios (without viscosity)	Cmax (ng/mL)	0.11	0.41
	AUC (ng*h/mL)	0.20	0.64
	Tmax (h)	1.08	2.00
Fed/Fasted ratios (with viscosity)	Cmax (ng/mL)	0.11	0.07
	AUC (ng*h/mL)	0.20	0.15
	Tmax (h)	1.08	2.39

1. Heinen, C et al (2013). Mol Pharm. 2013 10(11):3989-96. **2.** Sumiji, T et al. (2023). ADMET DMPK. 11(3):409-17. **3.** Radwan, A et al. (2012). Biopharm Drug Dispos. 33(7):403-16. **4.** Liu, B et al. (2013). AAPS Annual Meeting, San Antonio, Texas. **5.** Hotha, K et al (2010). J Chromatogr B Analyt. 878(13-14):981-6.