

Potential Viscosity-Mediated Food Effect on 'Drug Availability' in the GI tract for a BCS 3 Drug using the Model Drug Product, Immediate Release Trosipium Chloride

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Aim

To study the potential viscosity-mediated food effect on the drug availability investigating food-drug interaction for a Biopharmaceutical Classification Systems (BCS) 3 drug.

Background

Typically, food-drug interactions are focused on a food component effect on inhibition or induction of CYP enzymes or transporters in the gut-wall. There is significantly less research dedicated to understanding the impact of food viscosity on drug absorption. This study explores a potential food effect due to the impact of food viscosity on drug disintegration which reduces bioavailability in the absorptive region of the GI tract. This mechanism is normally neglected. However, it has a potentially significant effect on BCS 3 drugs. Trosipium Chloride (TC) is a low permeability and high solubility drug and is a substrate of OATP1A2 and Pgp. The jejunum is one of the main locations of these transporters. In the fasted state, immediate release (IR) TC dissolved very rapidly due to its high solubility. The drug has high availability from the luminal fluids of the GI tract; there is not a drug 'availability' issue. Although TC has high solubility in the fed state, clinical AUC and C_{max} is much lower in the fasted state (negative food effect). An explanation for this is that food viscosity delays the disintegration of the IR drug product *in vivo*. In this study, a quantitative approach is applied within a PBPK framework to investigate this effect.

Methods

Based upon currently available knowledge, quantitative viscosity-concentration relationships were established for a serially-diluted homogenized standard FDA breakfast (Liu et al. 2014). Similar relationships were established using HPMC solutions as a surrogate for a standard FDA breakfast with the initial viscosity of HPMC matched to the undiluted breakfast homogenate. A relationship between the disintegration rate of IR TC and medium viscosity was established based on *in vitro* dissolution data and combined with *in vivo* viscosity-dilution models to predict disintegration rate in the GI tract. The fluid volume dynamics model as incorporated into the Simcyp ADAM (Advanced Dissolution, Absorption and Metabolism) model was exploited for this purpose. A nine compartment transit model also based on the ADAM model was built using the Simulink® toolkit. Simulated viscosity-dependent disintegration profiles were input into the Simcyp Simulator (Version 15 Release 1) ADAM model to predict plasma profiles in the fasted and fed states for a healthy volunteer Population Representative (PopRep).

Input Parameters: MWt, 427.964 dal.; $\log P_{o:w}$, -1.44; B/P ratio, 0.64; Fraction unbound in plasma, 0.5; P_{eff} (Regional gut wall permeability), ($10^{-4} \text{ cm s}^{-1}$) (Duo, 3.7; Jej, 6.8; Jej. II, 6.3; Ileum I-IV, 2.7, 2.2 1.6, 1.1; Colon, 0.38); Vss (L kg^{-1}), 4.89; IV clearance (L h^{-1}), 55.8; Renal clearance (L h^{-1}), 38.9; Dose (mg), 60. The transporter effect is not quantified in this model.

Some Assumptions: (1) The particles obtained from the disintegration step are fine un-agglomerated particles; (2) In the current model the food-liquid mixture is assumed to be fully mixed with water and forms a homogeneous liquid with elevated viscosity relative to fasted fluids. GI tract fluid secretions are assumed to immediately dilute liquid food without any delay; *i.e.*, the luminal fluid is assumed to be well-stirred at all times.

Results

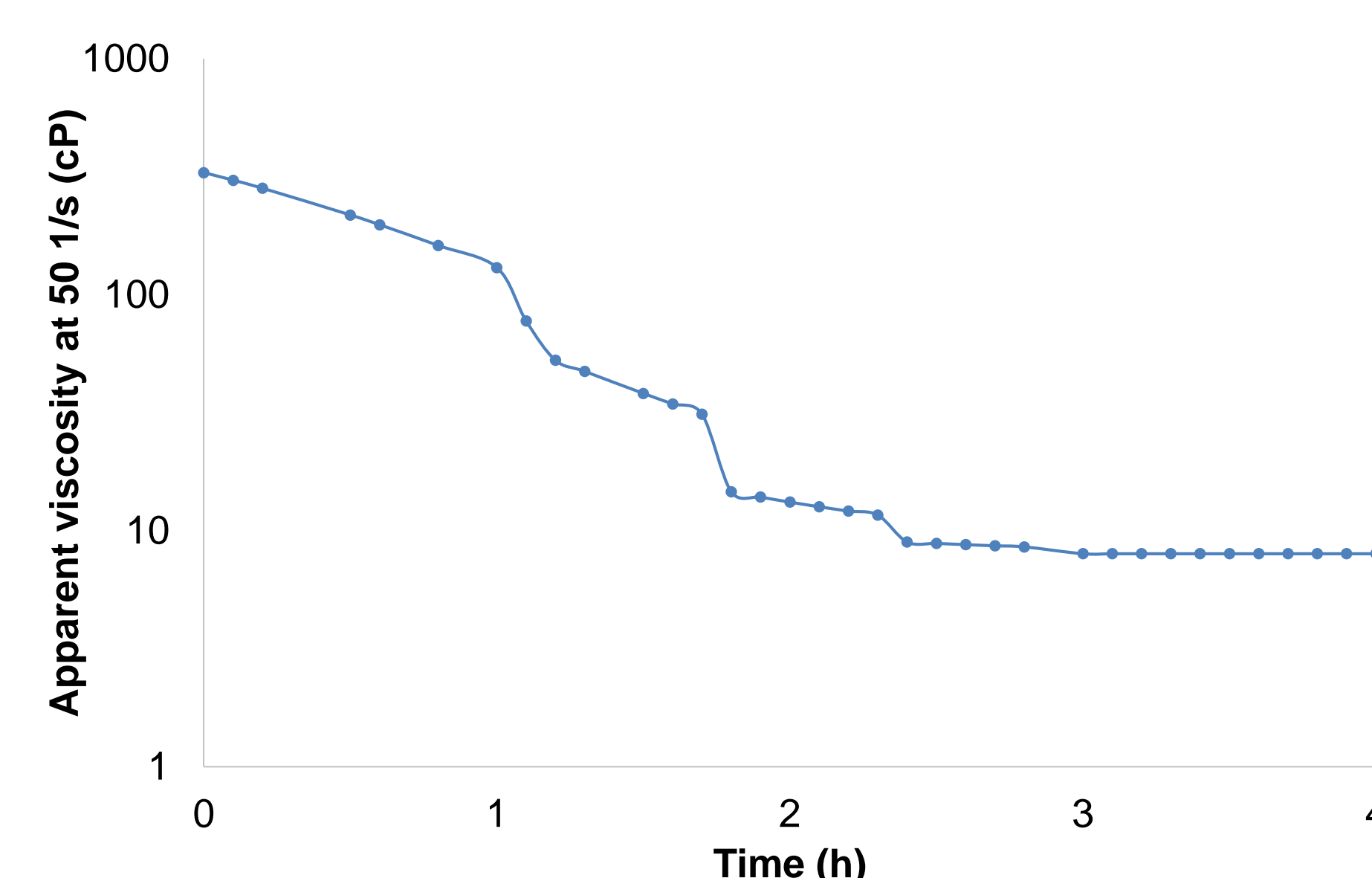


Figure 1: Predicted *in vivo* food viscosity change based upon the ADAM luminal fluid volume dynamics model.

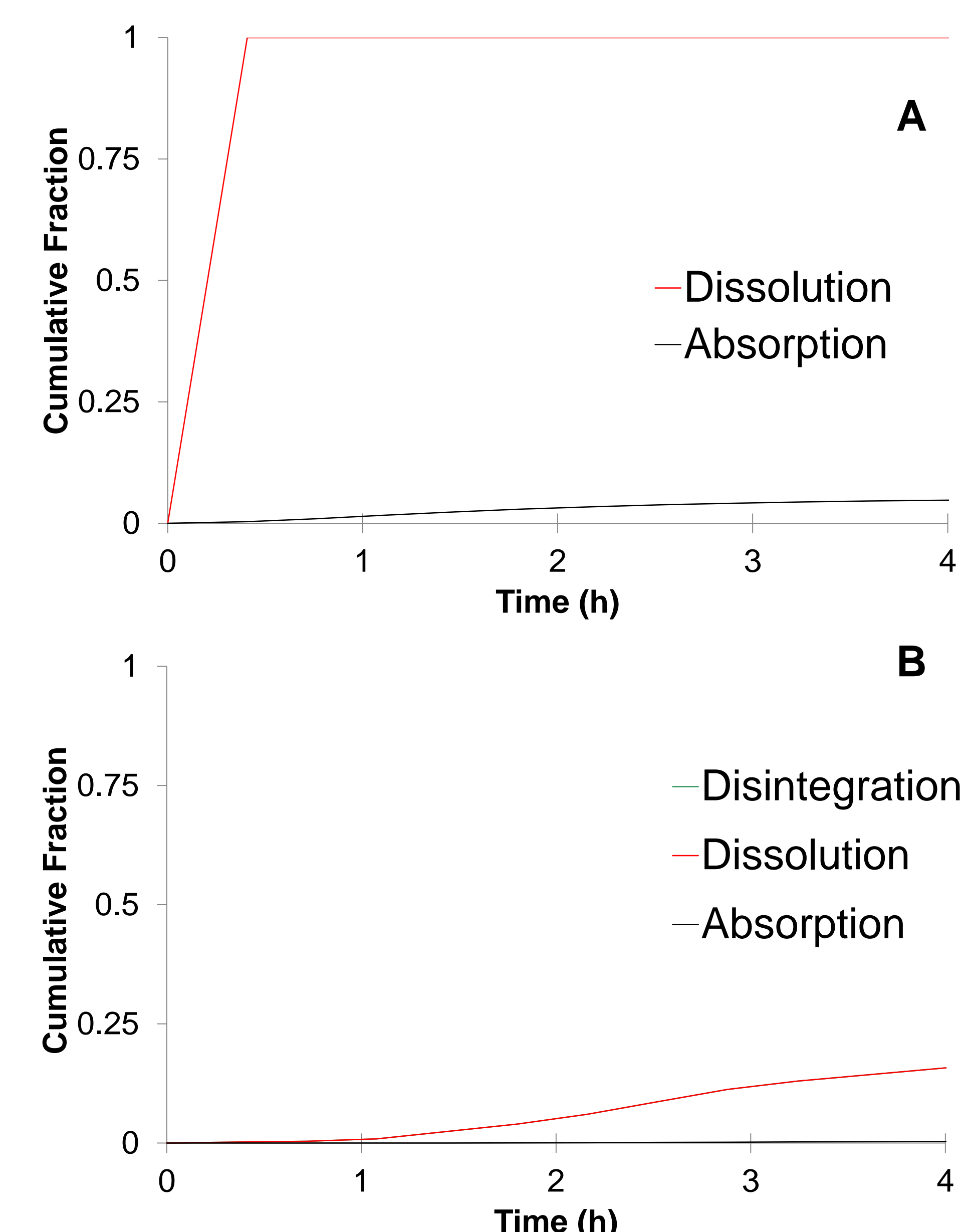


Figure 2: A) The predicted dissolution profile and absorption profile in the GI tract in the fasted state. B) The predicted disintegration, dissolution and absorption profile in the GI tract in the fed state.

Reference:

Liu, B. Jamei, M. Rostami-Hodjegan, A. Turner, D. B.; 2014, PBPK Modelling of Negative Food Effects upon Oral drug Absorption of the BCS Class III Drug Trosipium Chloride: Combination of a Dynamic Viscosity-Disintegration Model and the ADAM (Advanced Dissolution, Absorption and Metabolism) Mode; AAPS Annual Meeting.

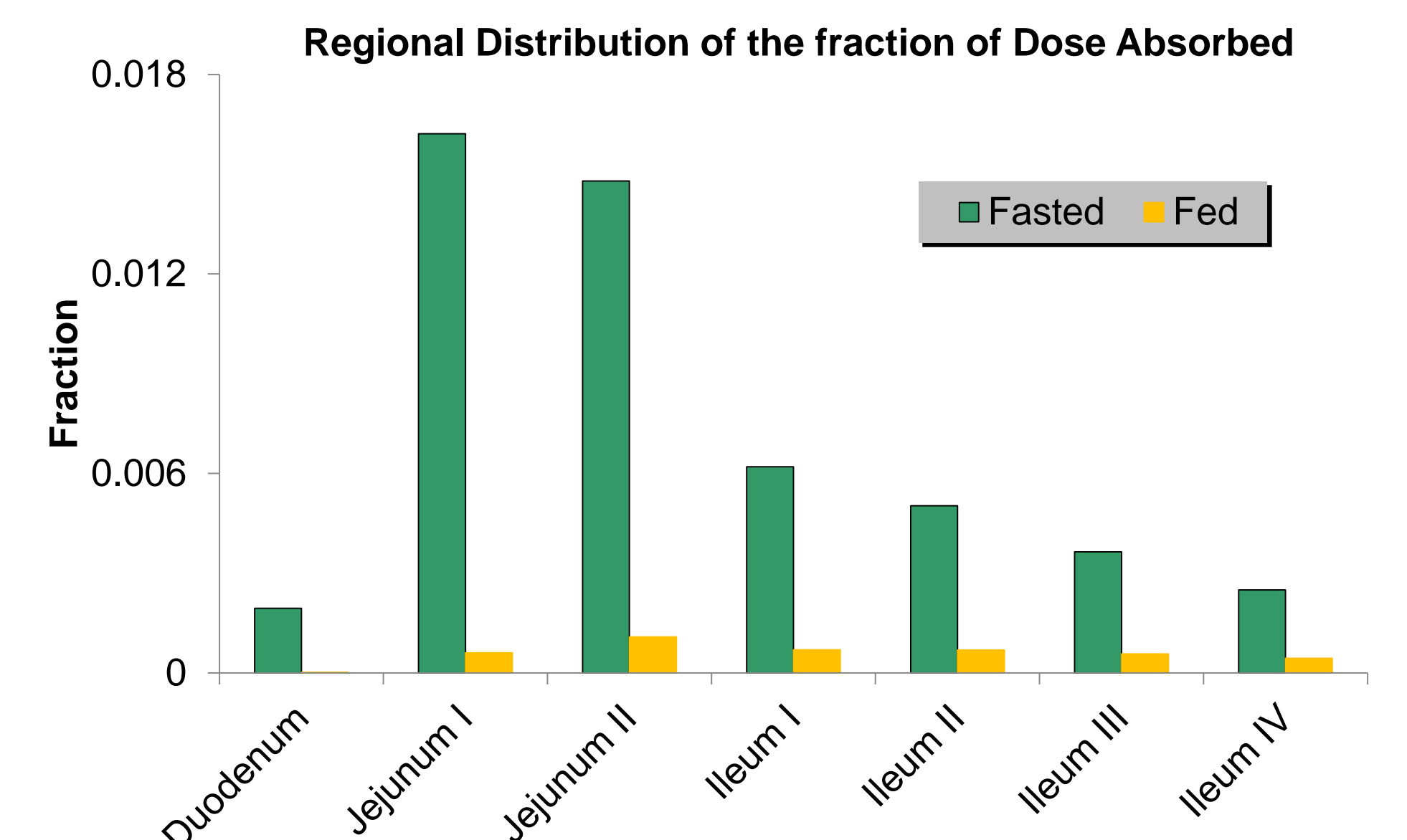


Figure 3: Predicted Fasted and Fed state drug fraction absorbed in each segment of the small intestine.

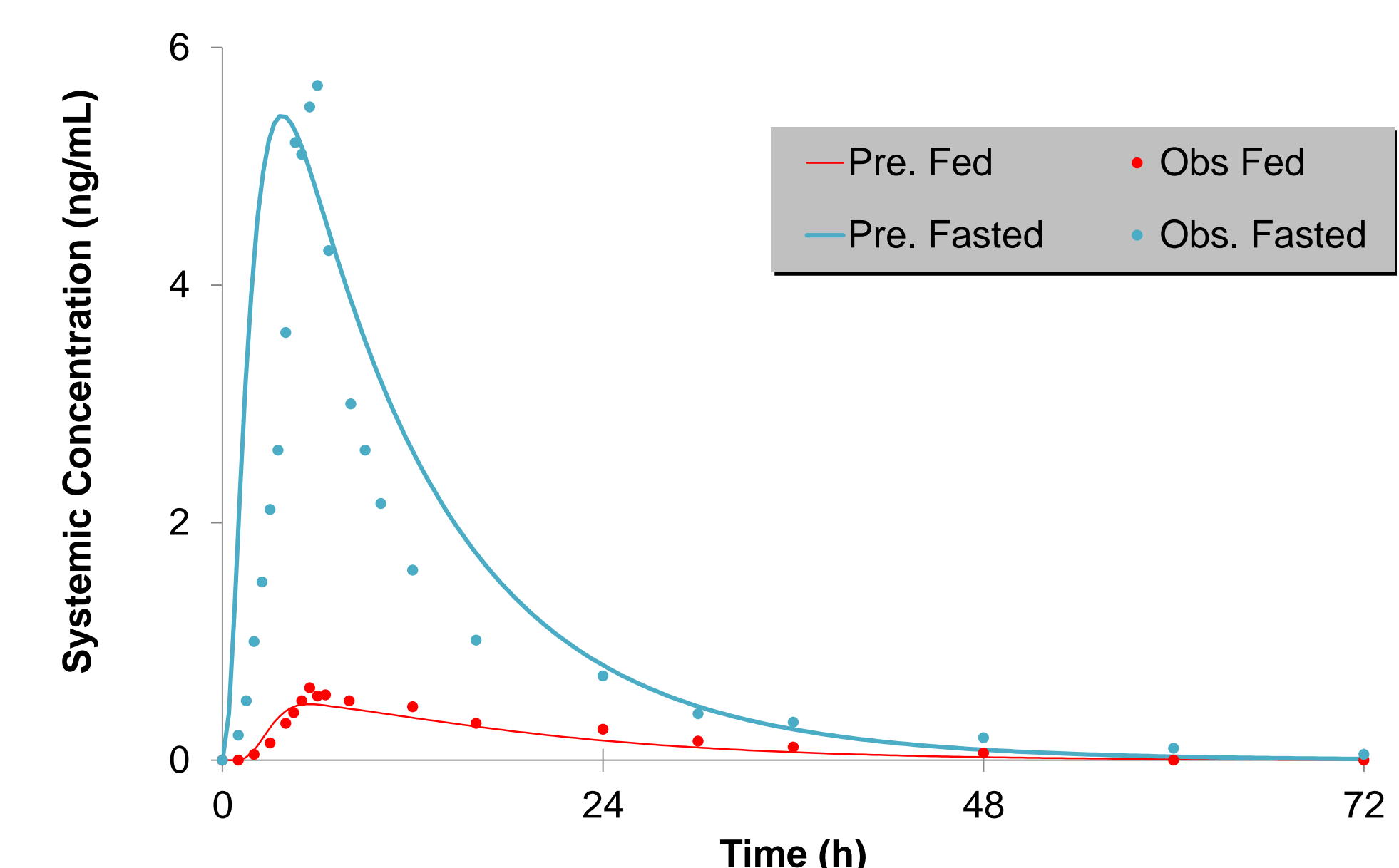


Figure 4: Predicted fasted and fed state plasma profiles using FDA breakfast and HPMC as reference.

Table 1: Observed and predicted C_{max} and AUC and their Fed-Fasted Ratios
Units: C_{max} – ng/mL; AUC – ng/mL.h

| | | Predicted FDA | |
|---------------------|-----------|---------------|-------|
| Category | Observed | breakfast | |
| Fasted | C_{max} | 5.68 | 5.43 |
| | AUC | 55.54 | 72.72 |
| Fed | C_{max} | 0.61 | 0.47 |
| | AUC | 11.16 | 9.15 |
| Fed / Fasted ratios | C_{max} | 0.11 | 0.09 |
| | AUC | 0.20 | 0.13 |

The model predicted both fasted and, using the homogenized meal viscosity model, fed PK parameters C_{max} , T_{max} and AUC, and the corresponding Fasted-Fed ratios, within 1.6 fold of observed values. The predicted *in vivo* fed state drug product disintegration was less than 10% of total dose in the first 2 hours, while the *in vivo* disintegration in the fasted state was completed within 10 minutes in the stomach. This suggests that availability of TC was reduced in duodenum and part of jejunum under fed state leading to negative food effect.

Conclusion

Mechanistic modelling of the impact of food viscosity on disintegration and dissolution of drug product is shown to be important for BCS class III drugs such as TC. More research is required to understand the impact of such mechanisms *in vivo* for drugs with different physicochemical properties and BCS class to improve our understanding and prediction of negative food effects. It's possible that the relative food effect may be different if transporters were to be accounted for.

Acknowledgment

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