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PBPK Modelling of Negative Food Effects upon Oral drug Absorption of the BCS Class III Drug Trospium Chloride: Combination of a Dynamic Viscosity-Disintegration Model and the ADAM (Advanced Dissolution, Absorption and Metabolism) Model

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Background

Orally dosed immediate release (IR) tablets are expected to disintegrate rapidly upon contact with fluid content of the GI tract. However, many studies demonstrate that food, amongst a range of other effects, can alter the viscosity of the GI tract fluids which can delay tablet disintegration and potentially reduce drug absorption rate [1].

The disintegration time of Trospium Chloride (TC) IR tablets in 2% hydroxypropyl methyl cellulose (HPMC) buffer solution (viscosity 1300 cP at 1.29 s^{-1}) is ~17 times longer than that in the same buffer with 0 % HPMC (0.1 M HCl, viscosity 1 cP at 1.29 s^{-1}) [2]. Such delayed disintegration can result in a negative food effect resulting in a lack of efficacy in the clinic depending upon the target therapeutic window [3]. The effects of food upon the disintegration process are complex due to the (time-dependent) physical characteristics of the digesta. Marciani et al. [4] demonstrated that the major determinant of digesta viscosity dynamics *in vivo* is dilution by the luminal fluids and indicated that zero shear rate viscosity should be used in the GI tract dilution process for non-Newtonian fluid.

The aim herein is to model time-dependent dilution effects upon digesta viscosity, link this to the disintegration rate of oral IR TC and thence to predict food effects upon absorption rate. The applicability of a viscosity-matched solution of HPMC polymer as a digesta surrogate is considered.

Methods

Dynamic Dilution Model of the Food in the GI Tract

A nine compartment GI transit model was developed in SimuLink based upon the structure of the Simcyp ADAM (Advanced Dissolution, Absorption and Metabolism) model [5]. The model includes compartmentalised basal (fasted) fluid volumes and adds to this fluid taken with dosage form and/or food via a fluid dynamics model based upon the combined effects of fluid secretion, (re)absorption and transit within each compartment. This model permits the relative dilution of the digesta or HPMC solutions to be tracked for both a representative individual and within trial groups accounting for inter-individual variability of key parameters. Thus estimates can be made of luminal content viscosity as it changes with time/location within the GI tract. The food is assumed to be fully and rapidly mixed with water and is homogeneous. The density difference of the food mixture and GI solution is neglected.

Disintegration process

Tablet disintegration is assumed to follow first order kinetics and the rate constant *k* was fitted to the time disintegration profile [2] (Equation 1).

$$\frac{dx}{dt} = kx \qquad (1)$$

Linking Viscosity to Disintegration

A semi-mechanistic model (Equation 2) was established in the current study to describe the effect of dynamic viscosity change on the disintegration.

$$k = k_f k_0 \left(\frac{w}{\mu} + \frac{1}{\mu_0}\right) \qquad (2)$$

where k_0: disintegration constant in an aqueous environment (0% HPMC); μ: viscosity (linked to HPMC concentration); μ_0: the critical viscosity; k_f is food composition effect 0.158 [6]; *w* is the weight of the dynamic food viscosity change in the GI tract and *k* is the disintegration constant.

Simcyp Simulations

Clinically observed Trospium Chloride (TC) plasma concentration profiles are available in the literature [2]. A minimal PBPK model combined with the ADAM absorption model were used (Simcyp Simulator Version 12 release 2). The required PK input parameters used in the simulations are given below. The regional permeability values were predicted using a Mechanistic Permeability (MechPeff) model (to be made available in Simcyp v14).

Model Input Parameters: MWt., 427.964 dal.; $logP_{o:w}$, -1.44; B/P ratio, 0.64; Fraction unbound in plasma, 0.5; P_{eff} (Regional gut wall permeability), (10^{-4} cm s^{-1}) (Duodenum,3,7;Jejunum I, 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.

Results & Discussion

Apparent viscosity at zero shear rate was obtained by extrapolation from the serial dilution data (as described previously [7]). The zero shear rate viscosity was linked to dilution fraction so enabling prediction of *in vivo* fed state viscosity dynamics (Fig. 1).

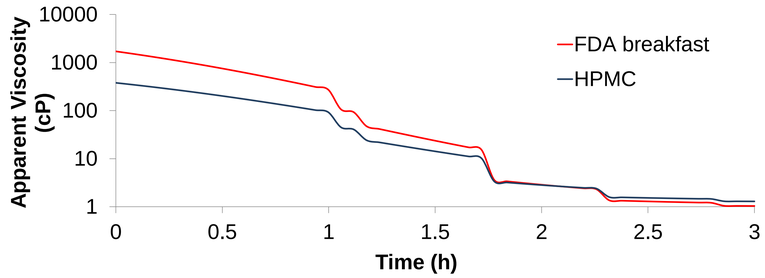

Figure 1: Predicted *in vivo* Food and HPMC viscosity change based upon the ADAM luminal fluid volume dynamics model.

Equation 2 was used to fit the observed data (HPMC) in order to obtain μ_0 (58) and *w* (1) (Fig. 2). Due to the absence of disintegration rate vs. viscosity for digesta these values were also used to estimate the effect of an FDA breakfast on formulation disintegration.

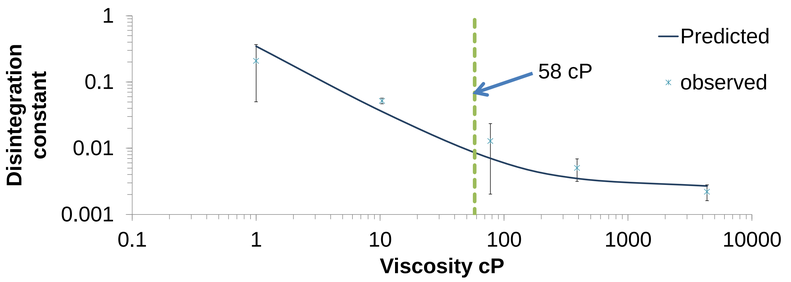

Figure 2: Relationship between viscosity and disintegration constant.

Fig. 3 shows the predicted disintegration profile in the GI tract lumen. While the initial viscosity of the FDA breakfast is higher than that of HPMC (Fig. 1) the rate of reduction of digesta viscosity is more rapid than for HPMC. Thus formulation disintegration in the FDA breakfast becomes more rapid than in HPMC after ~2 hours (Fig. 3). While the apparent viscosity in the GI tract is higher than the critical viscosity (μ_0 = 58 cP) tablet disintegration is minimal; below μ_0 disintegration rate becomes increasingly significant. The FDA breakfast consists of a variety of ingredients with a somewhat different dilution-viscosity relationship to that of HPMC solutions. This may explain why disintegration rate for the FDA breakfast is faster than with HPMC. The predicted *in vivo* disintegration profile (Fig. 3) was supplied as an input release profile to the ADAM model to predict plasma concentration-time profiles. The predictions for the HPMC-based study are slightly under-estimated while those for the FDA breakfast match the observed values well (Fig. 4, Table 1). For the fasted simulations AUC is slightly under-predicted and C_{max} a little more under-predicted.

1. Parojcic et al.2008 *Int J Pharm,* 355**,** 93.
2. Radwan et al.2012 *Biopharm Drug Dispos,* 33**,** 403.
3. Turner et al. 2012 *Biopharm Drug Dispos,* 33**,** 510.
4. Marciani et al. 2000 *J Nutr,* 130**,** 122.
5. Jamei et al. 2009 *AAPS J.* 11:225.
6. Abrahamsson et al. 2004 *Eur J Pharm Sci.* 22,165.
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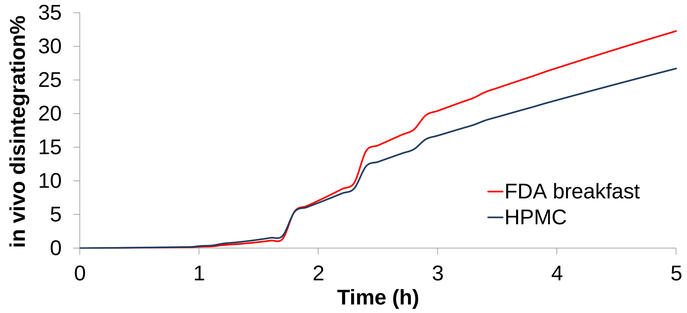

Figure 3: The *in vivo* disintegration profile in different media.

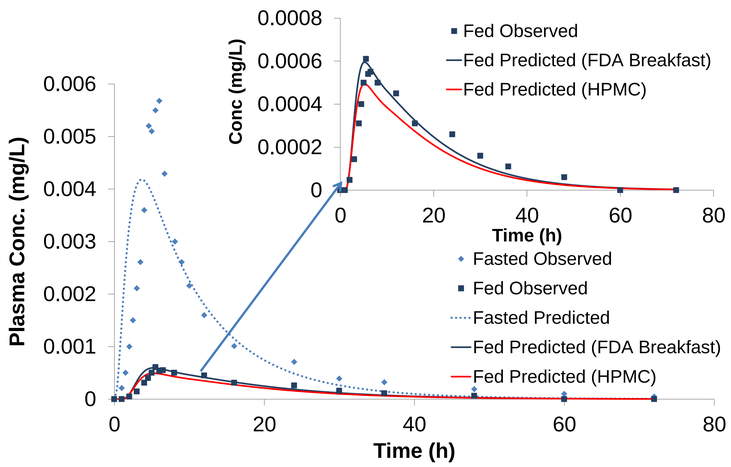

Figure 4: Predicted fed state using FDA breakfast and HPMC as reference and Fasted state prediction.

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

Category		Observed	Predicted FDA breakfast	Predicted HPMC
Fasted	C_{max}	5.68	4.18	4.18
	AUC	55.54	51.09	51.09
Fed	C_{max}	0.61	0.6	0.49
	AUC	11.16	10.62	8.96
Fed / Fasted ratios	C_{max}	0.11	0.14	0.12
	AUC	0.20	0.21	0.18

Conclusion

A model has been developed to anticipate negative food effects upon drug absorption from *in vitro* information. Dynamic changes to the *in vivo* disintegration rate of an IR formulation of a BCS Class III drug have been linked to dilutive, time-dependent viscosity change after food intake.

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