

Toward Mechanistic Modeling of Negative Food Effects upon Oral Drug Absorption: Linking *In Vivo* Dynamic Dilution of Digesta to Viscosity, Disintegration and Dissolution Rate

Objectives

The presence of food and its digestion products *can* have a significant impact upon the rate and extent of absorption of orally dosed drugs. A contributory factor (amongst many) is the elevation of the viscosity of the GI lumen contents which, particularly for BCS Class I and III drugs, can have a negative impact upon disintegration / dissolution times of formulations and dissolution rate of the API itself^{1,2}. *A priori* the *in vivo* viscosity might be expected to change with time and/or GI tract (GIT) location due to the combined effects of fluid secretion, (re)absorption and transit, the breakdown / absorption of food itself and changes in the secretion of bile salts and enzymes *etc* into the gut lumen. Marciani et al.³ suggest that the major determinant of the dynamics of digesta viscosity change is dilution by the luminal fluids. Thus, the aim herein is to build a model linking dynamic dilution effects to viscosity and thence to diffusion coefficient (D) and diffusion layer thickness (h_{eff}) two key parameters impacting upon the modelling of disintegration and/or dissolution rate of oral dosage forms. Assessment is made of the suitability of HPMC solutions as a surrogate for food.

Method

Based upon published data¹ links were established between viscosity and (relative) concentrations of a serially diluted homogenized standard FDA breakfast. Data are also available for the viscosity of a range of concentrations of hydroxypropyl methyl cellulose (HPMC) polymer¹. As these solutions exhibit pseudo-plastic flow, they are non-Newtonian and a power law (Equation 1) was used to describe the rheology of these viscous fluids.

$$\tau = K\gamma^n \quad (1)$$

K : Flow-consistency-index ($mPa \cdot s^n$)
 n : Flow-behaviour-index (no-units)
 τ : Shear-stress (mPa)
 γ : Shear-rate (s^{-1})

A nine compartment GI transit model was developed in SimuLink based upon the structure of the Simcyp ADAM (Advanced Dissolution, Absorption and Metabolism) model.⁴ 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 meal/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 food mixture and GI solution is neglected.

The Levich approach (Equations 2 and 3) was used to calculate diffusion coefficient (D) and thickness of diffusion layer (h_{eff})⁵ according to the solution viscosity. Tropicium chloride (TC)¹ and p-aminobenzoate (PA)⁶ were chosen as model drugs.

$$\text{Rotation system: } R = 0.62D^{2/3}C_0\omega^{1/2}v^{-1/6} \quad (2)$$

$$\text{Flow-through system: } R = 2.16D^{2/3}C_0\alpha^{1/3}r^{5/3} \quad (3)$$

$$\text{Effective thickness of diffusion layer: } h_{eff} = DC_0/R \quad (4)$$

R : Dissolution rate
 D : Diffusion coefficient
 C_0 : Solubility
 r : Radius
 v : Kinematic viscosity
 α : Shear rate
 ω : Angular velocity

Results & Discussion

During the dilution process both K and n (Eqtn. 1) change (Figure 1). Based on the K and n values, an extrapolation of apparent viscosity to zero shear rate was generated during the dilution process (Table 1). This apparent viscosity at zero shear rate was linked to dilution fraction and thereby enabled prediction of *in vivo* viscosity change in the fed state (Figure 2). The calculated diffusion coefficients and h_{eff} of TC and PA are shown in Figs. 3 and 4 respectively.

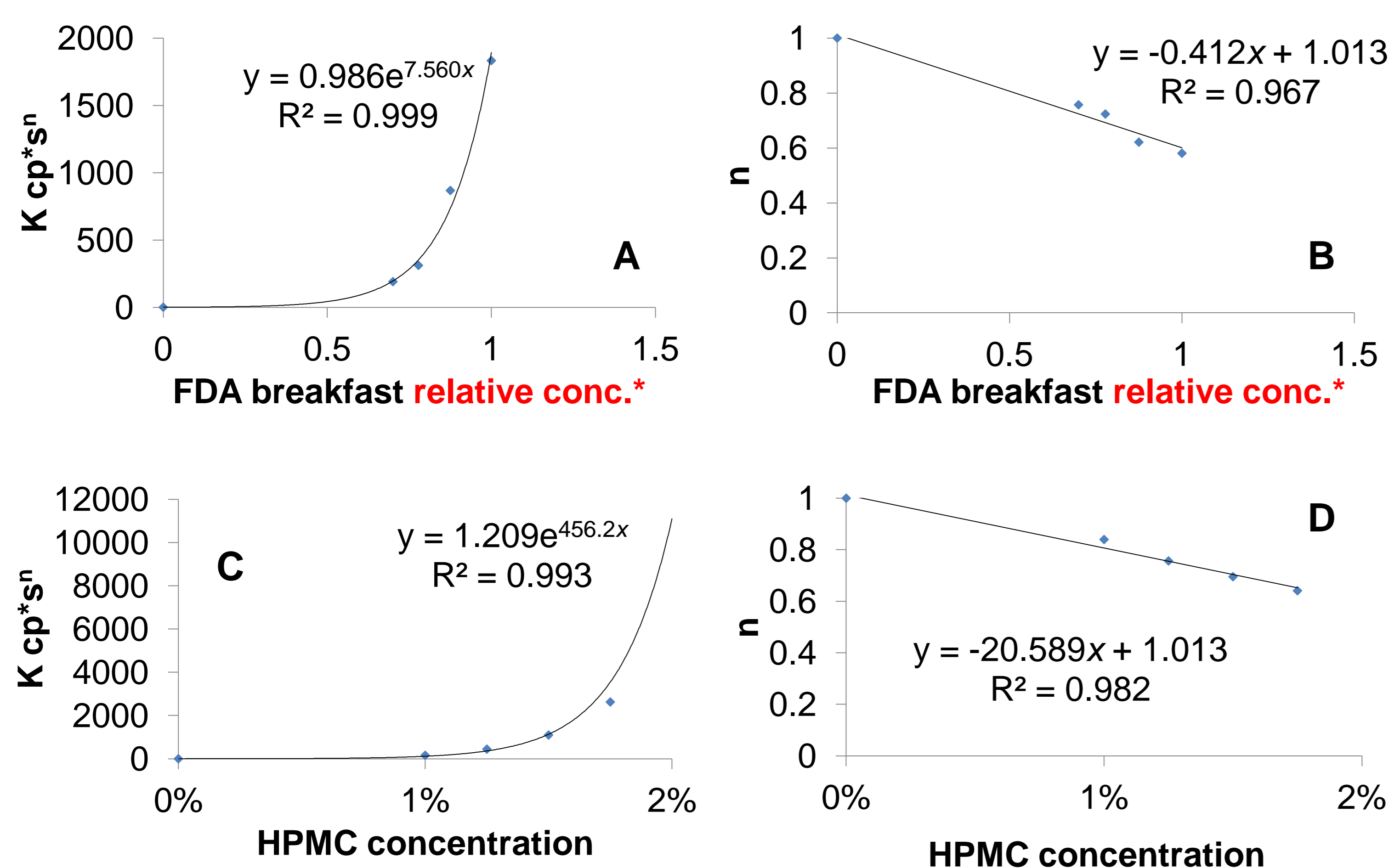


Figure 1. A: K vs. dilution of FDA breakfast; B: n vs. dilution of FDA breakfast; C: K vs. [HPMC]; D: n vs. [HPMC]s. * Relative conc. of 1 refers to undiluted homogenised meal.

Table 1: Representative viscosity at zero shear rate extrapolated from K and n (Eqtn. 1).

HPMC concentration fraction	1%	1.25%	1.50%	1.75%	0.50%	1.40%	2%
Apparent Viscosity (cps)	110.1	257.0	546.1	1130.8	9.6	377.8	632.8
FDA Breakfast dilution ratio	1	0.88	0.78	0.70	N/A	N/A	N/A
Apparent Viscosity (cps)	1644.4	789.8	288.7	178.7	N/A	N/A	N/A

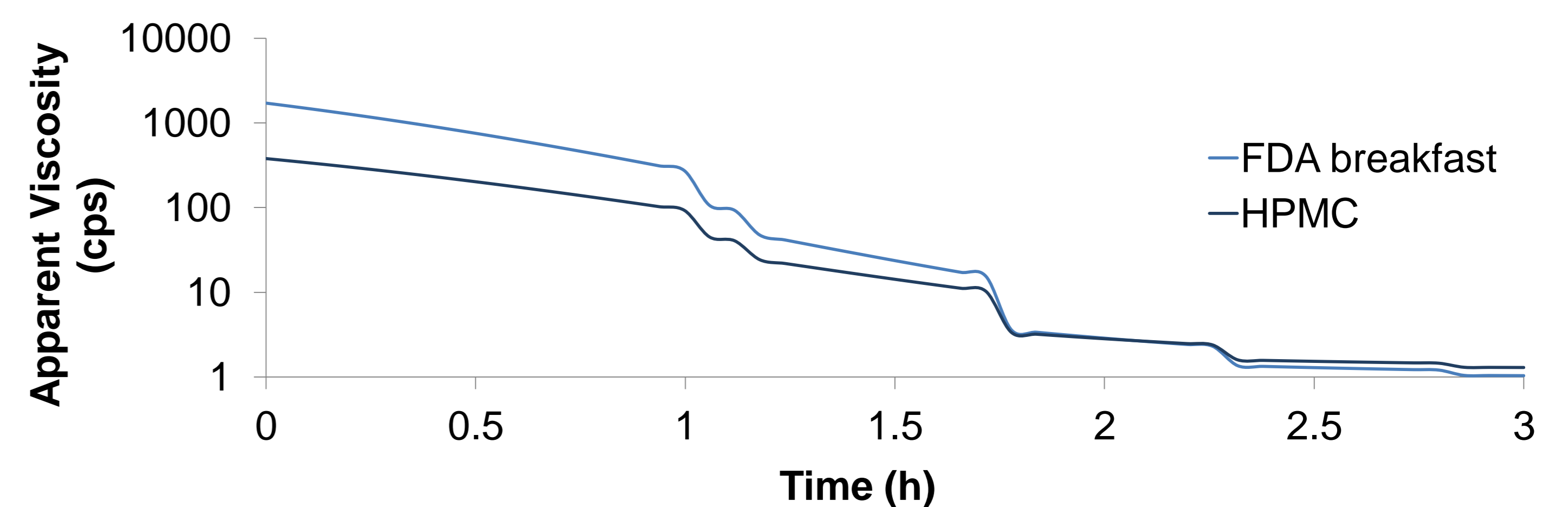


Figure 2: (above) Predicted *in vivo* Food and HPMC viscosity change based upon the ADAM fluid volume dynamics model.

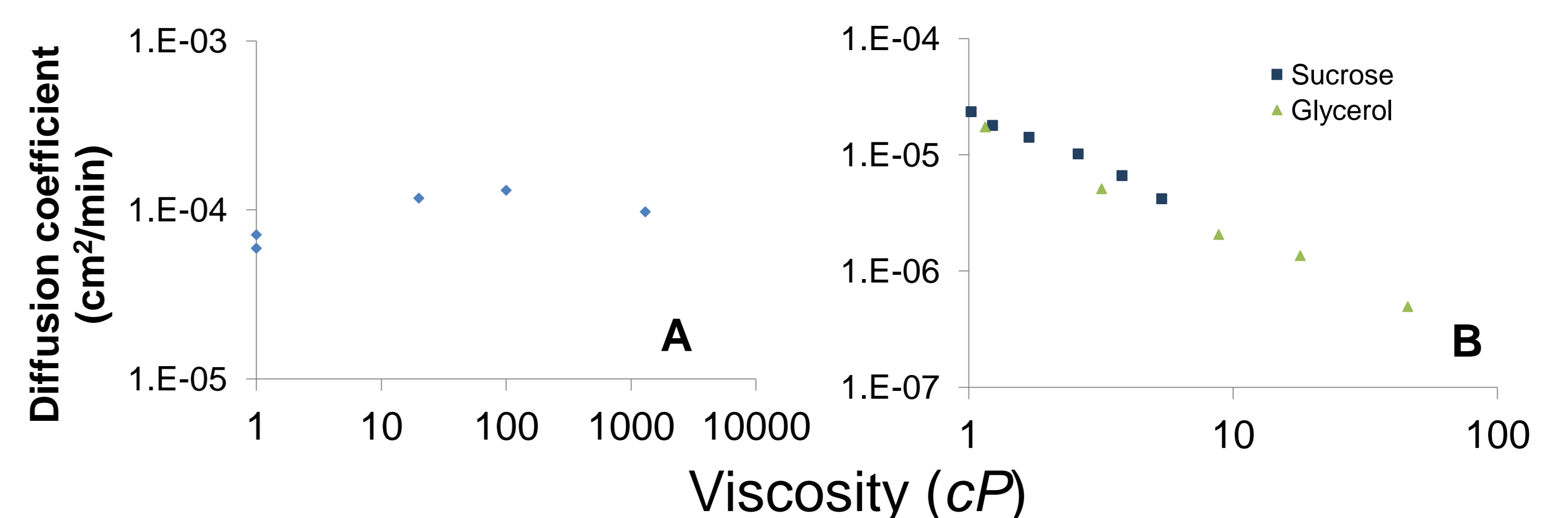


Figure 3. (above) A: The calculated diffusivity of TC in HPMC solution at 75 rpm. B: The calculated diffusivity of PA in sucrose and glycerol, respectively in a flow-through apparatus.

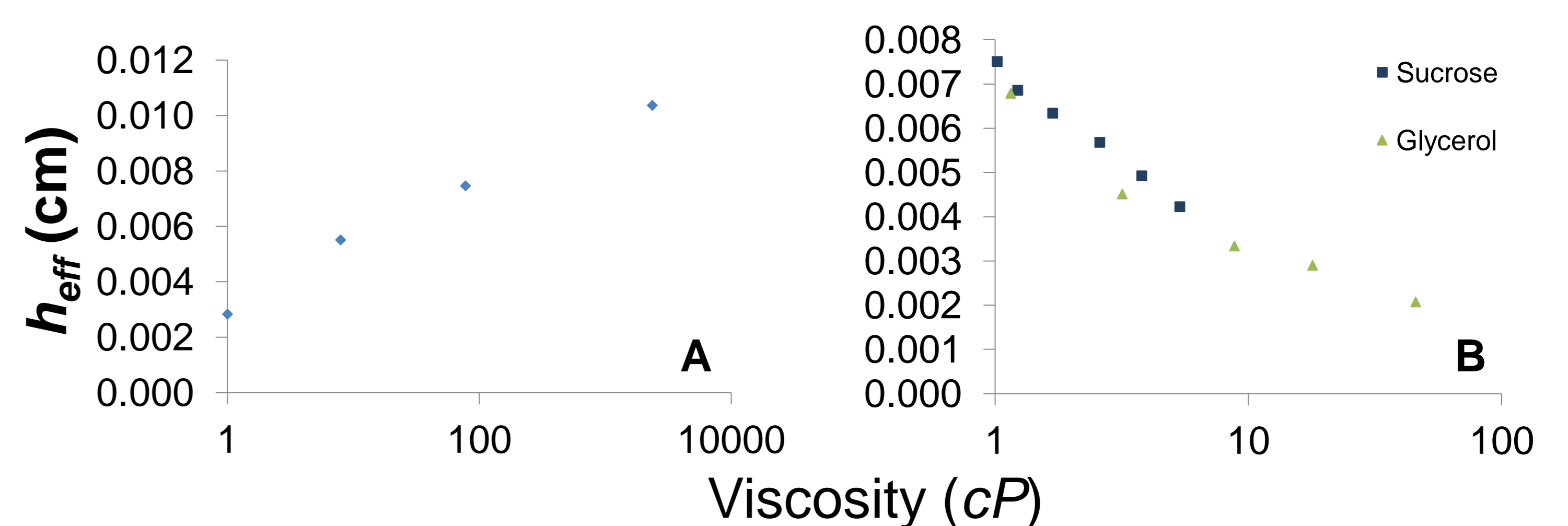


Figure 4. (above) A: The calculated h_{eff} of TC in HPMC solution at 75 rpm. B: The calculated h_{eff} of PA in sucrose and glycerol, respectively in a flow-through apparatus

Both the FDA breakfast and a viscosity-matched HPMC solution were predicted to be rapidly diluted in the GI tract resulting in significant time-dependency of viscosity. Due to the differential impact of dilution upon viscosity HPMC was found not to be a good surrogate for food and therefore unlikely to be suitable for predicting food effects. In terms of surrogates suitable for mimicking digesta viscosity, D is *not* sensitive to viscosity at relevant concentrations of HPMC polymer but is *inversely correlated* to viscosity at different concentrations sucrose or glycerol monomers. This has implications for the design of media mimicking the viscosity of digesta in terms of the balance between small molecule and polymer concentrations. However, in all cases h_{eff} is linked to the viscosity.

Conclusion

A model has been developed to anticipate dynamic changes of physicochemical properties of the GI tract lumen contents linked to dilutive viscosity change after food intake. It provides a mechanistic basis for the return of viscosity from the fed to the fasted state which may be of particular significance for modeling controlled release formulations. It provides a useful addition to existing food-effects within the ADAM model *viz.* pH/solubility effects, bile salt concentration changes linked to changes in biliary secretion patterns, delays to gastric emptying, villous blood flow increase *etc*. Further work may include consideration of other meal types and other factors potentially impacting upon the time-dependence of digesta viscosity.

References

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