Development of a mechanistic *in vitro* - *in vivo* correlation for theophylline

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Introduction

Theophylline is used to prevent and treat wheezing, shortness of breath, and difficulty breathing caused by asthma, chronic bronchitis, emphesema, and other lung diseases. Immediate release oral theophylline preparations have a higher incidence of side effects due to its rapid absorption, short elimination half-life, and narrow therapeutic index. For these reasons, sustained-release formulations of theophylline are desirable.

It has been reported that theophylline's rate of absorption (as measured by the absorption half-life) decreases along the GI tract, particularly when it is dosed into the colon.

Convolution methods that assume the same absorption rate along the GI tract over-predict the theophylline absorption rate in the lower GI tract making it difficult to develop an *in vitro-in vivo* correlation (IVIVC). The objective of this study is to utilize the mechanistic ACAT™ model within GastroPlus to develop an IVIVC for theophylline.

Methods

A theophylline pharmacokinetic (PK) model that takes into account the absorption profile along the entire GI tract was developed using GastroPlus™ v7.0 (Simulations Plus, Inc.). Simulated theophylline plasma concentration-time profiles for different doses ranging from 125-500 mg with both intravenous (*i.v.*) dosing and immediate release (IR) tablets were compared with published plasma concentration-time profiles[1-3]. Plasma concentration-time data after theophylline solution was released into the stomach, terminal ileum and ascending colon of the GI tract by a remote-controlled drug release system was also obtained from the literature[4] and compared to simulated plasma concentration-time profiles for theophylline solution directly dosed to the different regions. *In vitro* release and plasma concentration-time profiles for a theophylline sustained-release dosage form were obtained from the literature[5]. Deconvolution of the *in vivo* release profile for the theophylline sustained-release dosage form, construction of a Levy Plot, formation of an IVIVC, and convolution were all performed within the IVIVCPlus™ Module of GastroPlus.

Results

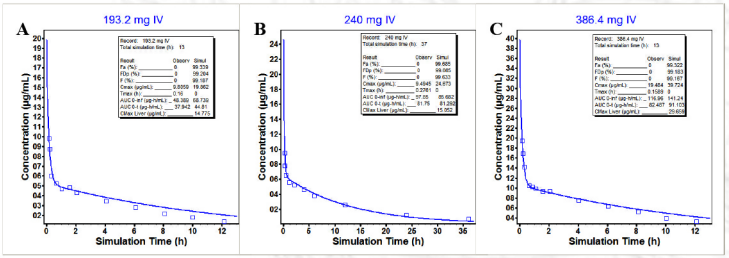

Fig. 1. Simulated (solid line) and observed (squares) Cp-time profiles after IV administration of theophylline: A) 193.2 mg B) 240 mg C) 386.4 mg. All simulations use the same 2-compartment PK model with saturable enzymatic clearance in the liver and fixed renal clearance.

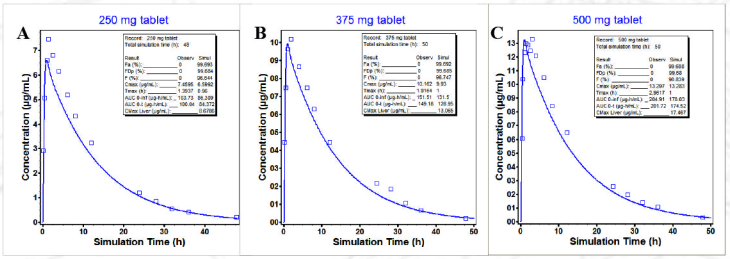

Fig. 2. Simulated (solid line) and observed (squares) Cp-time profiles after administration of theophylline IR tablet: A) 250 mg B) 375 mg C) 500 mg

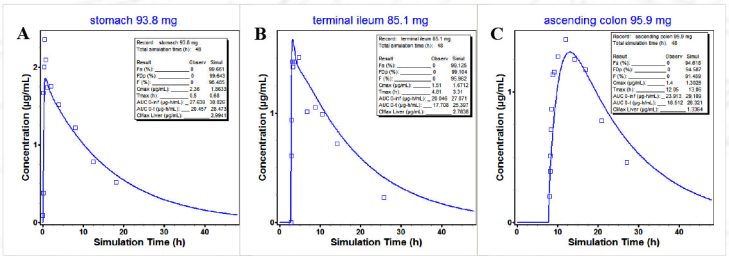

Fig. 3. Simulated (solid line) and observed (squares) Cp-time profiles after administration of theophylline solution in different regions of the GI tract via a remote-controlled capsule A) 93.8 mg dosed into stomach B) 85.1 mg dosed into terminal ileum C) 95.9 mg dosed into ascending colon.

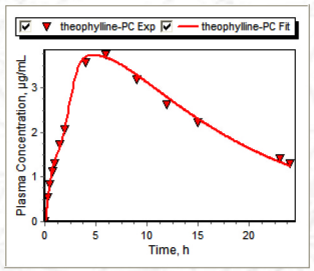

Fig. 4. Simulated (solid line) and observed (triangles) Cp-time profile after deconvolution of *in vivo* release profile for the sustained-release formulation.

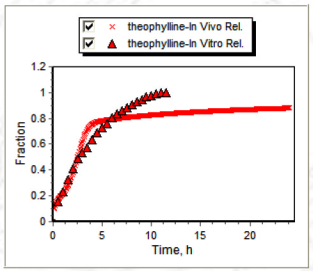

Fig. 5. *In vitro* dissolution profile (triangles) vs. deconvoluted *in vivo* release profile for the sustained-release formulation.

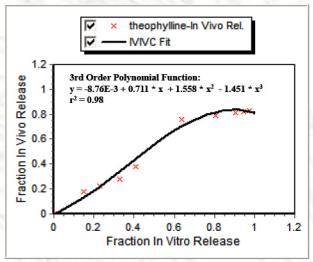

Fig. 6. IVIVC with fit for the sustained-release formulation

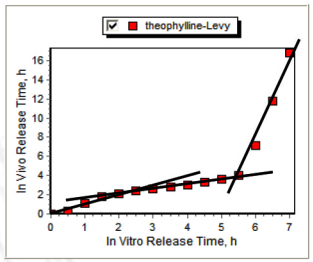

Fig. 7. Levy Plot for the sustained-release formulation.

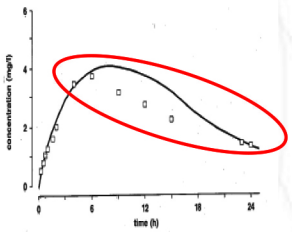

Fig. 8. Published results of convolution using constant absorption approach[6].

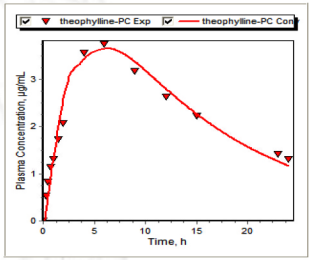

Fig. 9. Convolution result using mechanistic IVIVC approach.

Conclusions

- Developing an IVIVC for the theophylline sustained-release formulation that accounted for slower theophylline absorption in the distal region of the GI tract led to an improved convoluted Cp-time profile.
- The deconvoluted *in vivo* release profile and Levy Plot suggest that multiple dissolution experimental conditions are necessary to sufficiently mimic the *in vivo* release of this product.

References

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3. Rovei et al., *Br J Clin Pharmacol* 1982, 14, 769-778.
4. Staib A.H. *Eur J Clin Pharmacol* 1986, 30, 691-697.
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6. Brockmeier D. Colonic Drug Absorption and Metabolism 1993, 109-135.

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