Development of a PBPK Model for Mesalamine Using ACATPlus to Support Prediction of Local Gut Tissue Exposure

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Purpose

- Mesalamine is a locally acting anti-inflammatory drug used to treat inflammatory bowel disease, where efficacy depends on achieving adequate concentrations in the terminal ileum and colonic tissues.
- Predicting local gut tissue exposure remains challenging because conventional PBPK models primarily describe systemic plasma pharmacokinetics (PK).

Objective

This work aimed to extend a previously developed mesalamine PBPK model to predict local gut tissue concentrations using the ACATPlus model in GastroPlus® . Unlike the standard ACAT model, ACATPlus incorporates detailed colonic anatomy and multiple gut wall tissue layers (mucus, mucosa, submucosa, and muscularis propria), enabling mechanistic prediction of local drug disposition.

Methods

- A mesalamine PBPK model was built in GastroPlus® v10.2 to simulate plasma and local gut tissue concentrations, using physicochemical properties from the literature[1,2,3,4] or *in vitro* measurements, supplemented with ACATPlus-specific parameters (mucus binding, luminal content binding, tissue partitioning, mucus diffusivity) where available and *in silico* predictions otherwise.
- For the delayed-release (DR) Asacol® tablet, an *in vitro-in vivo* relationship (IVIVR) was developed by deconvoluting the *in vivo* dissolution profile from observed PK data and using the derived dissolution profile as a direct model input.
- The previously validated model[5] was verified against published plasma PK data[6,7] after single 400 and 800 mg oral doses of Asacol® in healthy subjects. Then, the healthy physiology was updated to the Crohn's disease physiology, where stomach and small intestine transit times and pH are increased compared to healthy subjects. The model was used to predict colonic tissue concentrations after administration of Asacol® 400 mg 3 times/day for one week in patients, which were compared with published biopsy data[8]. Development and validation of the PBPK models were done following the workflow presented in Figure 1.

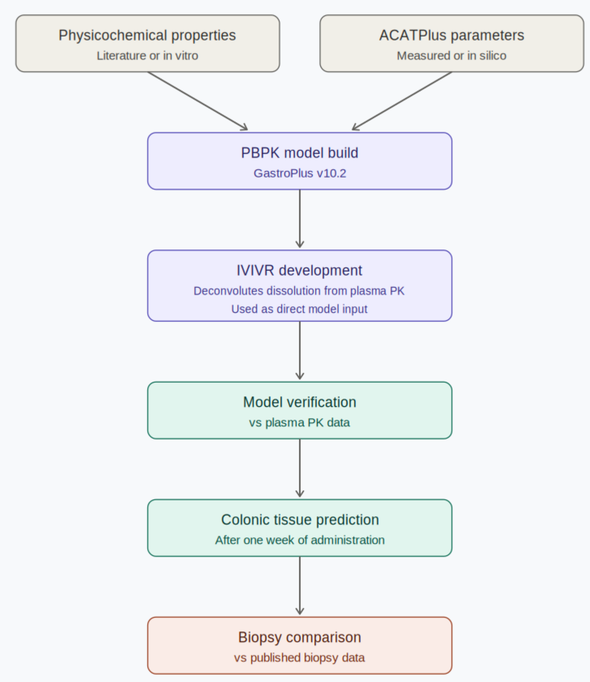


Figure 1: Mesalamine PBPK models development and validation workflow

Results

- The final PBPK model incorporating the Asacol® DR tablet formulation reasonably predicted the observed mesalamine PK profile (Figure 2).
- Simulated mesalamine concentrations in colonic tissue were consistent with the magnitude and regional distribution of tissue concentrations measured in biopsy samples after one week of administration (Figure 3, Table 1).

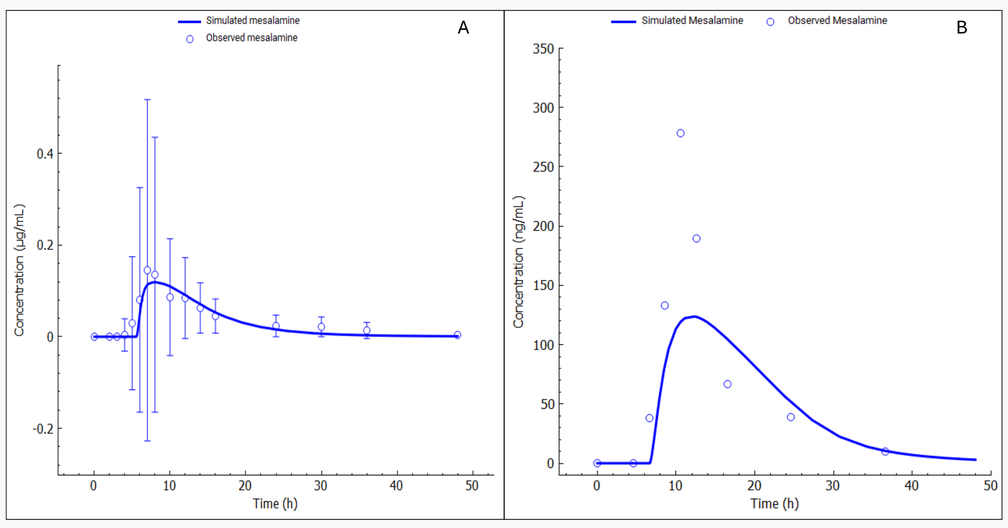


Figure 2: Observed (circles) and simulated (line) mesalamine plasma concentration-time courses in healthy subjects following a single administration of a 400-mg DR tablet (A) and an 800-mg DR tablet (B) of Asacol®.

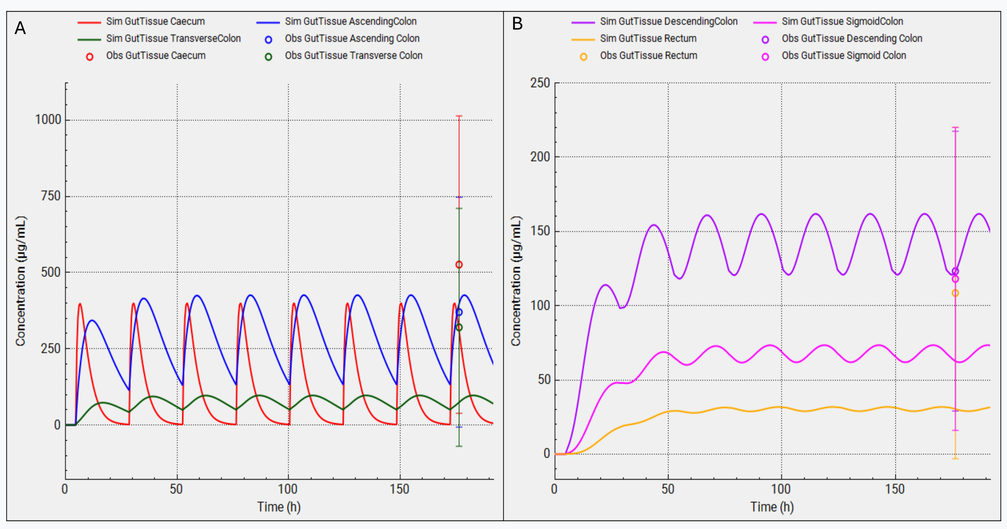


Figure 3: Observed (circles) and simulated (lines) mesalamine local gut concentration–time profiles in the caecum, ascending colon, transverse colon (A), descending colon, sigmoid colon, and rectum (B) following administration of Asacol® 400 mg three times daily for one week in patients. Observed data are presented with associated CV% (error bars).

Table 1: Observed and simulated mesalamine local gut concentration values (µg/mL) following administration of Asacol® 400 mg three times daily for one week.

	Caecum	Asc colon	Trans colon	Desc colon	Sigm colon	Rectum
Simulated	309.3	397.3	74.3	122.9	62.6	30.3
Observed	525.9	370	320.1	123.2	118	108.5
Sim/Obs	**0.59**	**1.07**	**0.23**	**1.00**	**0.53**	**0.28**

Conclusion

- The ACATPlus model enabled mechanistic prediction of both systemic and local gut tissue exposure of mesalamine.
- Although validation is limited by the scarcity of human tissue data and the lack of layer-specific biopsy measurements, predicted tissue concentrations agreed with published observations, mainly for ascending and descending colon sections.
- These results demonstrate the potential of ACATPlus to support the development of locally acting colon-targeted therapies, formulation optimization, dose selection, and future translational applications as more tissue-specific data become available.

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