USE OF PBBM-PBPK TO PREDICT MESALAMINE DELAYED-RELEASE ORAL DRUG PRODUCTS PERFORMANCE IN BOTH HEALTHY AND DISEASE PHYSIOLOGIES

T1330-09-60

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PURPOSE

Mesalamine (5-aminosalicylic acid (5-ASA)) is an anti-inflammatory drug indicated for the treatment of ulcerative colitis (UC) and Crohn's disease (CD). 5-ASA acts locally in the intestines [1] and is primarily metabolized to the N-acetyl metabolite (N-Ac-5-ASA) by N-acetyltransferase 1 (NAT1) in the intestinal wall and liver. The efficacy of 5-ASA treatment can be optimized by using modified release formulations, which maximizes the local drug concentration at the site of inflammation [2]. Asacol® and Mesasal® are examples of commercially available delayed-release 5-ASA formulations. [3]. Predicting the *in vivo* behavior of such formulations can be challenging since many factors other than lumen pH play a role.

OBJECTIVE

This study aims to develop an oral absorption physiologically based pharmacokinetic (PBPK) / physiologically based biopharmaceutics model (PBBM) for 5-ASA and N-Ac-5-ASA, to predict the in vivo exposure of 5-ASA and N-Ac-5-ASA from Asacol® in healthy subjects and Mesasal® in healthy and UC or CD patients.

METHODS

- PBPK models for 5-ASA and N-Ac-5-ASA were built using GastroPlus® v.9.8.2 (beta version including the extended Advanced Compartmental Absorption and Transit (ACAT) model and UC and CD physiologies).
- All tissues were modeled as perfusion-limited and the Kp's were calculated using the default Lukacova method for both parent drug and its metabolite [4,5].
- *In vitro* Km for an analogue (para-aminobenzoic acid) [6] was used as a surrogate and converted to an *in vivo* Km for 5-ASA. Vmax for NAT1 was then optimized using intravenous (IV) [7–9] and immediate-release oral (PO) pharmacokinetic (PK) data [8,10]. 5-ASA renal filtration clearance was defined as fraction unbound x glomerular filtration rate.
- Asacol® dissolution profile was measured *in vitro* in fasted state simulated colonic fluid (FaSSCoF) and an *in vitro-in vivo* relationship (IVIVR) was explored with the available data [11,12].
- The *in vivo* dissolution was mechanistically deconvoluted from the PK profile after administration of 800 mg Asacol® [11]. This profile was then correlated with FaSSCoF *in vitro* dissolution to establish a preliminary second order IVIVR (Figure 2). The IVIVR was used to scale the FaSSCoF *in vitro* dissolution which was used as a direct input in the model.
- Mesasal® dissolution profile in simulated intestinal fluid (SIFsp pH 6.8) was obtained from the literature [13]. Due to sparse *in vitro* sampling and very fast dissolution profile, it was not possible to establish an IVIVR for Mesasal®. Rather, the *in vivo* dissolution deconvoluted from the PK profile in healthy subjects was used to model Mesasal® administration to healthy subjects and patients [14].

RESULTS

The developed PBPK model for 5-ASA and N-Ac-5-ASA adequately described the plasma PK profile following IV and immediate-release PO in healthy subjects, as shown in Figure 1.

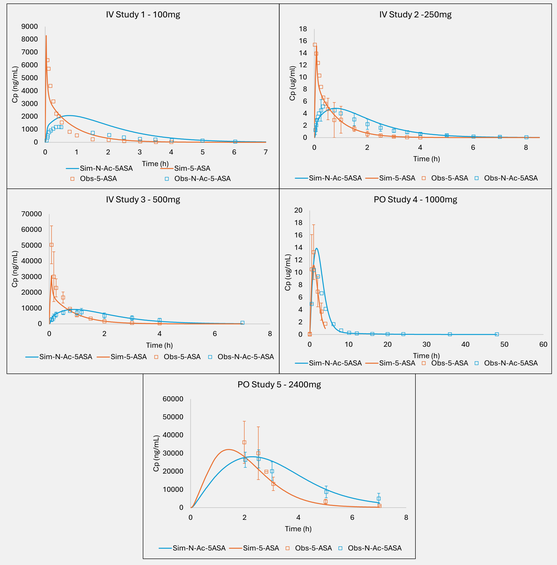

Figure 1: *Prediction of mean systemic 5-ASA and metabolite N-Ac-ASA concentrations in healthy subjects after intravenous (IV) administration and immediate-release oral (PO) administration.*

For Asacol®, the direct use of FaSSCoF *in vitro* dissolution data resulted in overprediction of PK profiles (AUC and Cmax fold errors 2.63 and 2.15, respectively).
The mechanistically deconvoluted *in vivo* dissolution from the PK profile after administration of 800 mg Asacol® and its comparison to FaSSCoF *in vitro* dissolution data is shown in Figure 2. This profile was then correlated with FaSSCoF *in vitro* dissolution to establish a preliminary second order IVIVR (Figure 2).

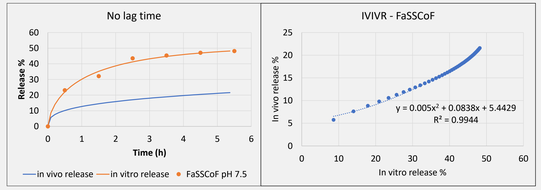

Figure 2. *Deconvoluted in vivo dissolution profile and* FaSSCoF *in vitro* dissolution data *(Left panel). In vitro-in vivo relationship between deconvoluted in vivo dissolution and in vitro dissolution in fasted state simulated colonic fluid (FaSSCoF) for Asacol® 800mg administration [11] (Right panel).*

The scaled dissolution profile via IVIVR resulted in reasonable PK profile prediction for Asacol® administration, shown in Figure 3.

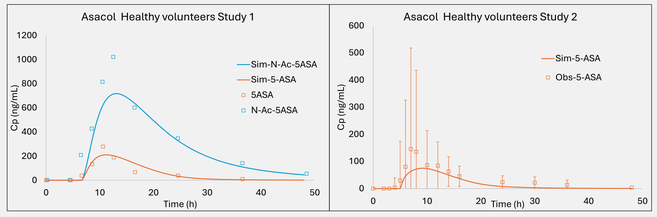

Figure 3: *Prediction of mean systemic 5-ASA and metabolite N-Ac-ASA concentrations in healthy subjects after Asacol® administration using the scaled dissolution profile via IVIVR as direct input.*

Likewise, for Mesasal®, the direct use of SIFsp *in vitro* dissolution data resulted in overprediction of PK profiles (AUC and Cmax fold errors 3.2 and 3.42, respectively).
The healthy subject prediction using the deconvoluted *in vivo* dissolution profile is shown in Figure 4. Disease physiologies were generated to account for blood flow, stomach pH and intestine transit time differences between healthy subjects and patients. Since the NAT1 expression in disease condition is not known, the same expression level as in healthy was assumed. The developed PBBM-PBPK model for CD adequately described the plasma PK profile following administration of Mesasal® in CD patients (Figure 4). All subjects in the UC groups were in remission, and using the UC gut physiology resulted in an overall overprediction (data not shown). Using healthy gut physiology adequately described the plasma PK profile in UC patients (Figure 4).

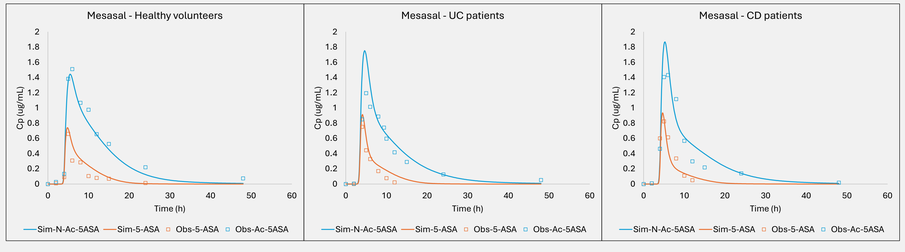

Figure 4: *Prediction of mean systemic 5-ASA and metabolite N-Ac-ASA after Mesasal® administration in healthy volunteers, UC and CD patients*

CONCLUSIONS

The developed PBBM-PBPK models resulted in reasonable prediction of 5-ASA and N-Ac-5-ASA PK profiles from the different clinical PK studies. The *in vivo* release for both Asacol® and Mesasal® was lower than the *in vitro* dissolution data. This highlights the need for more biopredictive dissolution methods. The PBBM-PBPK approach presented herein can be used for assessing the biorelevance of different *in vitro* dissolution methods for delayed-release formulations and can serve as an aid in new and generic drug development.

FUNDING

This project was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award U01FD007660 totaling $484,699 with 100 percent funded by FDA/HHS. The poster reflects the views of the author and should not be construed to represent FDA's views or policies.

REFERENCES

1. Garbacz G, Rappen G-M, Koziolek M, Weitschies W. Dissolution of mesalazine modified release tablets under standard and bio-relevant test conditions. Journal of Pharmacy and Pharmacology. 2015;67:199–208. https://doi.org/10.1111/jphp.12332
2. Hausmann M, Paul G, Menzel K, Brunner-Ploss R, Falk W, Schölmerich J, et al. NAT1 Genotypes Do not Predict Response to Mesalamine in Patients with Ulcerative Colitis. Z Gastroenterol. 2008;46:259–65. https://doi.org/10.1055/s-2007-963673
3. Sandborn WJ, Hanauer SB. The pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. Aliment Pharmacol Ther. 2003;17:29–42. https://doi.org/10.1046/j.1365-2036.2003.01408.x
4. French DL, Mauger JW. Evaluation of the physicochemical properties and dissolution characteristics of mesalamine: relevance to controlled intestinal drug delivery. Pharm Res. 1993;10:1285–90. https://doi.org/10.1023/A:1018909527659
5. Jung YJ, Lee JS, Kim HH, Kim YM, Han SK. Synthesis and evaluation of 5-aminosalicyl-glycine as a potential colon-specific prodrug of 5-aminosalicylic acid. Arch Pharm Res. 1998;21:174–8. https://doi.org/10.1007/BF02974024
6. Stevens GJ, Payton M, Sim E, McQueen CA. N-acetylation of the heterocyclic amine batracylin by human liver. Drug Metab Dispos. 1999;27:966–71.
7. Bondesen S, Hegnhoj J, Larsen F, Hansen SH, Hansen CP, Rasmussen SN. Pharmacokinetics of 5-aminosalicylic acid in man following administration of intravenous bolus andper os slow-release formulation. Dig Dis Sci. 1991;36:1735–40. https://doi.org/10.1007/BF01296618
8. Myers B, Evans DN, Rhodes J, Evans BK, Hughes BR, Lee MG, et al. Metabolism and urinary excretion of 5-amino salicylic acid in healthy volunteers when given intravenously or released for absorption at different sites in the gastrointestinal tract. Gut. 1987;28:196–200. https://doi.org/10.1136/gut.28.2.196
9. Vree TB, Dammers E, Exler PS, Sorgel F, Maes RAA. Saturable Active Tubular Reabsorption in the Renal Clearance of Mesalazine in Human Volunteers. Clin Drug Investig. 2000;20:35–42. https://doi.org/10.2165/00044011-200020010-00005
10. Yu DK, Elvin AT, Morrill B, Eichmeier LS, Lanman RC, Lanman MB, et al. Effect of food coadministration on 5-aminosalicylic acid oral suspension bioavailability. Clin Pharmacol Ther. 1990;48:26–33. https://doi.org/10.1038/clpt.1990.113
11. Sandborn WJ, Hanauer SB, Buch A. Comparative pharmacokinetics of equimolar doses of 5-aminosalicylate administered as oral mesalamine (Asacol) and balsalazide: a randomized, single-dose, crossover study in healthy volunteers [1]. Aliment Pharmacol Ther. 2004;19:1089–98. https://doi.org/10.1111/j.1365-2036.2004.01964.x
12. NDA 204-412 (eCTD 0017).
13. Klein S, Rudolph MW, Dressman JB. Drug Release Characteristics of Different Mesalazine Products Using USP Apparatus 3 to Simulate Passage Through the GI Tract. Dissolut Technol. 2002;9:6–12. https://doi.org/10.14227/DT090402P6
14. NORLANDER B, GOTTHARD R, STRÖM M. Pharmacokinetics of a 5-aminosalicylic acid enteric-coated tablet in patients with Crohn's disease or ulcerative colitis and in healthy volunteers. Aliment Pharmacol Ther. 1990;4:497–505. https://doi.org/10.1111/j.1365-2036.1990.tb00496.x