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Using PBPK to Establish In Vitro-In Vivo Relationship for Budesonide Delayed Release Oral Drug Product

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PURPOSE

- Budesonide is a corticosteroid used to treat inflammatory bowel diseases (IBD) (1).
- Budesonide undergoes extensive intestinal metabolism contributing to its low oral bioavailability (~9%) (2).
- Controlled-release formulations have been developed to target a drug release at pertinent GI segments.
- ENTOCORT® is a multi-particulate delayed-release (DR) drug product designed to release budesonide to the terminal ileum segment.
- Developing DR formulations can be challenging due to the numerous layers of complexity related to their in vivo behavior, rendering it difficult to predict the pharmacokinetic of drugs administered as DR (3).
- Modeling and simulation can support the development and regulatory assessment of DR formulations

OBJECTIVE

- To develop an oral absorption physiologically based pharmacokinetic (PBPK) model/physiologically based biopharmaceutics model (PBBM) for budesonide.
- To validate in vitro to in vivo relationships (IVIVRs) for ENTOCORT® to assess if different in vitro dissolution methods are biopredictive.

METHODS

A mechanistic PBBM for budesonide was built using GastroPlus® v.9.8.2 (beta version of extended ACAT model, including transverse colon, descending colon, sigmoid colon, and rectum) (Simulations Plus, Inc., Lancaster, CA, USA).

- Physicochemical, biopharmaceutical, and enzymatic clearance parameters were obtained from the literature (4-11); or predicted from budesonide chemical structure using the ADMET Predictor® module v.11 (Simulations Plus, Inc., Lancaster, CA, USA).
- The budesonide disposition model was validated against intravenous (IV) and oral immediate-release data (9-14). The oral IR data was mechanistically described using the Johnson dissolution model.
- ENTOCORT® dissolution profiles were obtained from literature (2) or measured in vitro. Two dissolution methods were used: single-phase USP-2 with biorelevant media (FaSSIF-V2 and FaSSCoF), and USP-4 with sequential media change (FaSSGF -> FaSSIF v2 -> FaSSCoF).
- All the results obtained using these dissolution methods were used to validate IVIVRs using the PBBM.
- Validation was performed using data from eight PK studies in healthy subjects (12,14–20).

PBBM model validation

The developed PBBM model for budesonide adequately described the plasma PK profile following IV and PO (immediate release (IR)) in healthy subjects (Table 1 and Figure 1).

Table 1: Predicted vs. observed C_{max} and AUC_{0-t} ratio for IV and immediate release oral formulations

	IV			Oral		
	0.1mg	0.4mg	0.5mg	3mg Cap	4.82mg Cap	3mg IR Susp
C_{max} ratio	N/A	N/A	N/A	0.82	0.83	1.04
AUC_{0-t} ratio	1.12	1.51	1.39	0.96	0.95	0.90

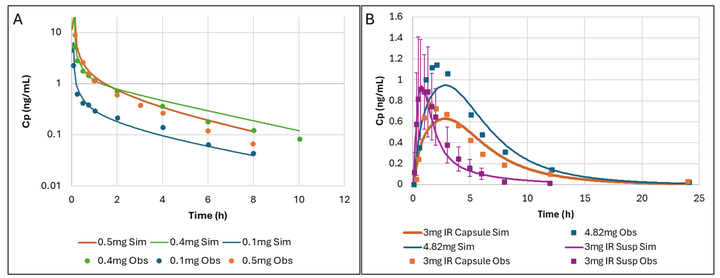

Figure 1: Prediction of mean systemic budesonide concentration in healthy subjects after (A) IV and (B) oral immediate release formulations. Lines represent model simulations and symbols are observed data (9-14). Sim: Simulated. Obs: Observed; Susp: Suspension

PBBM - IVIVR

- The validated disposition parameters (e.g., clearance and volume of distribution) were used in the PBBM to predict the plasma PK profile of budesonide following ENTOCORT® administrations.
- IVIVR using the in vitro single phase USP 2 FaSSIF v2 dissolution data (Figure 2) resulted in an overprediction of C_{max} and earlier T_{max} than observed data (Table 2).
- IVIVR using the single phase USP 2 FaSSCoF dissolution data (Figure 2) resulted in an underprediction of C_{max}, a reasonable T_{max} prediction (Table 2), but an overall misprediction of the PK profile shapes (data not shown).
- Hence, using directly in vitro dissolution data obtained with a USP 2 apparatus did not allow the validation of an IVIVR.
- In contrast, the PBBM, informed by in vitro dissolution data obtained using a USP 4 apparatus with sequential media change, generally described the PK profiles accordingly (Table 2 and Figure 3). Therefore, this in vitro system was defined as biopredictive in healthy subjects.

Table 2: C_{max} and AUC_{0-inf} ratio range of predicted vs. observed for each dissolution input

	C_{max} ratio range	AUC_{0-inf} ratio range	T_{max}
USP 2 FaSSIF v2	1.31 – 1.99	0.57 - 0.97	0.17 – 0.37
USP 2 FaSSCoF	0.53 – 0.82	0.77-1.62	0.8 – 1.56
USP 4	0.87 – 1.33	0.80 – 1.56	0.7 – 1.4

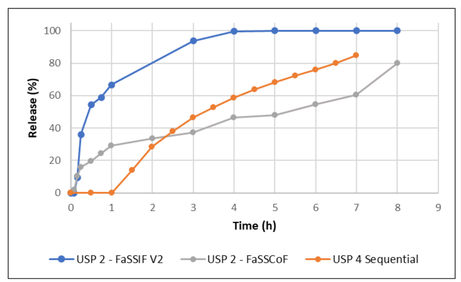

Figure 2: In vitro release of ENTOCORT® in USP-2 with biorelevant media (FaSSIF-V2 - blue and FaSSCoF - gray), and in USP-4 with sequential media change (orange) (FaSSGF -> FaSSIF v2 -> FaSSCoF). The first in vitro media change was at 1 hour and the second at 4.5 hours.

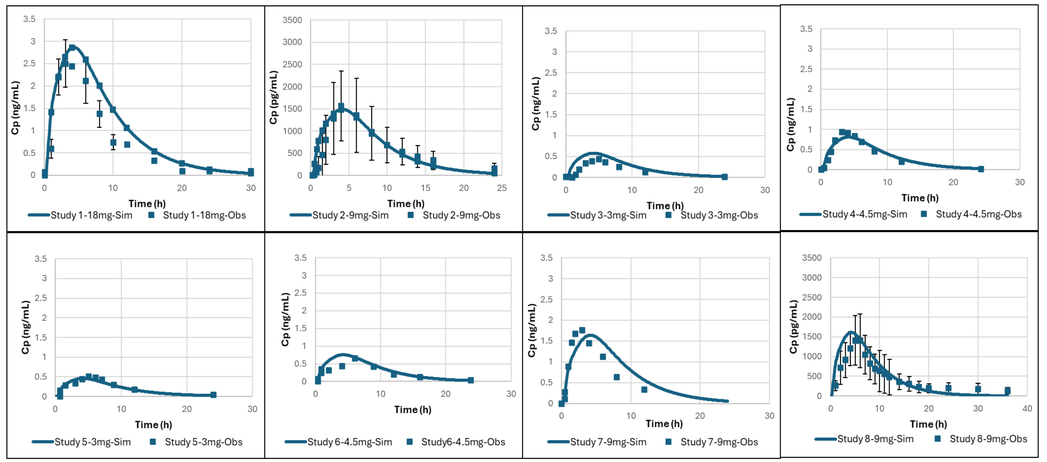

Figure 3: Prediction of mean systemic budesonide PK profiles in healthy subjects after ENTOCORT® administration (eight studies) using a USP 4 apparatus with sequential media change data. Lines represent model simulations and symbols are observed data (12, 14-20) Sim: Simulated. Obs: Observed

CONCLUSIONS

- An IVIVR of ENTOCORT® was validated utilizing an USP 4 apparatus with sequential media change dissolution data.
- It resulted in the reasonable prediction of budesonide PK profiles from the different clinical PK studies in healthy subjects.
- The validated PBBM-based IVIVR will be used to predict budesonide PK in IBD patients
- This method can assess the biopredictive nature of different in vitro dissolution methods for DR formulations and support the development of new and generic drug products for IBD.

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