Integration of Biopredictive Dissolution and PBPK Models for Evaluation of GI Locally Acting Products

FDA/ CRCG workshop: Advances in PBPK Modeling and its Regulatory Utility for Oral Drug Product Development
Rockville, October 12, 2023

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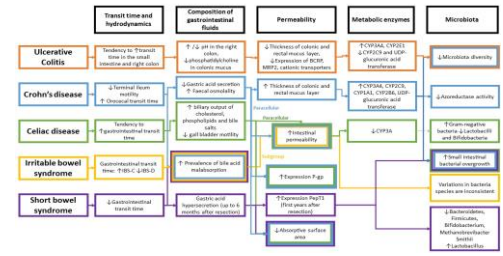
GI Diseases and Oral Drug Absorption



Effinger A, O'Driscoll CM, McAllister M, Fotaki N- J Pharm Pharmacol. 2019;71(4):674-698

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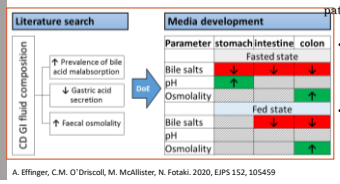
Biorelevant media for patients with CD

Identify differences between GI patients and healthy subjects in literature

Development of biorelevant media for patients with CD using a Design of Experiment approach

To take into account the interindividual variability in CD patients



- a low and a high concentration level was defined based on the available data
- differences were integrated as factors with 2 levels in the DoE.

A. Effinger, C.M. O'Driscoll, M. McAllister, N. Fotaki. 2020, EJPS 152, 105459

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Risk for altered drug solubilisation in CD patients

Stomach	Ionisable compounds	Altered gastric pH
Intestine	Moderate to Highly Lipophilic compounds	CD patients with low bile salt and lecithin concentrations
Colon	Lipophilic compounds, + Ionisable compounds	CD patients with low bile salt and lecithin concentrations

*Based on PLS analysis

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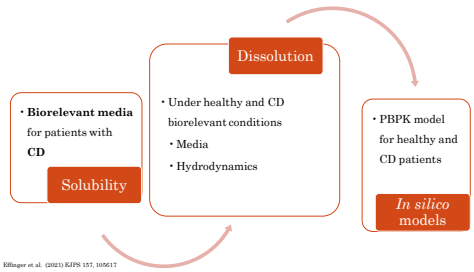
Prediction of oral absorption in CD patients



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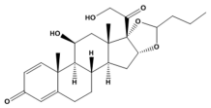
Budesonide

- BCS class II
- Log P 2.6
- Acidic pKa 12.0



- Locally-acting corticosteroid due to its high ratio of topical to systemic activity → low oral bioavailability (~10%)
- Metabolism: mainly CYP3A4, to a smaller extent CYP1A2 and CYP2C9
- Protein binding: 85-90% bound to albumin

Bhatt H *et al.*, 2014; Bharate SS, 2016; Corey EJ, 2014; Edsbacker S et al, 2003; Lu C et al., 2008; Public Assessment report (MHRA) Budenofalk

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Controlled-release formulation Entocort®

Formulation	Entocort® CR (Tillotts Pharma UK Ltd., UK)
Dose	3 mg
Description	Multi-particulate controlled-release formulations Gelatine capsule and enteric coated pellets with L 100-55 Eudragit® granules
Releasing pH	≥5.5
Target site	Terminal ileum and/or ascending colon

Iborra et al., 2014

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Crohn's disease

Parameter	Change in Crohn's disease compared to healthy subjects
GI transit time	↑ Orocaecal transit time
Composition of GI fluids	Bile acid malabsorption: ↓Bile acid pool ↓ Gastric acid secretion, amylase/trypase/lipase activity ↑ Faecal osmolality
Enzyme abundance	Liver: ↓ CYP3A4 Colon: ↑ CYP3A4, CYP2C9, CYP1A1, CYP2B6, GST, UGT
Permeation and transporter abundance	↑ Intestinal permeability for various compounds ↑ Expression of P-gp Mutations in genes for OCTN1 and OCTN2
Microbiota	↑ Small intestinal bacterial overgrowth ↓ Diversity, azoreductase activity

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In vitro release/ dissolution testing

USP IV apparatus (flow through cell apparatus)

Healthy conditions		
Medium	**Time from start [min]**	**Flow rate [mL/min]**
FaSSGF	0 - 60	6
FaSSIF-V2	60 - 270	4
FaSSCoF	270 - 420	4

Crohn's disease conditions		
Medium	**Time from start [min]**	**Flow rate [mL/min]**
CD-FaSSGF low/high level	0 - 30	12
CD-FaSSIF low/high level	30 – 300	4
CD-FaSSCoF low/high level	300 - 450	4

- Gastric residence time reduced
- Small intestinal phase increased (active disease state)

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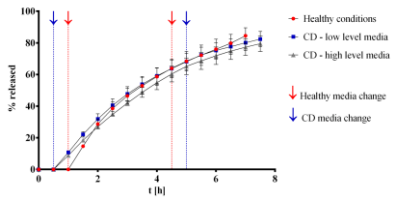
Entocort® *In vitro* dissolution



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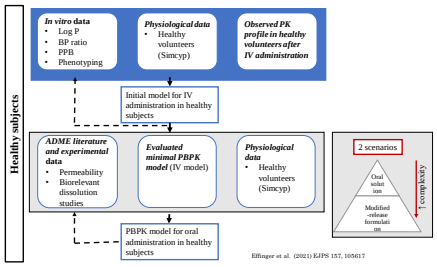
PBPK workflow for budesonide Healthy subjects



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Input of dissolution data

	Options		
Dissolution start	Discrete profile →first measuring points 0	Weibull fitting, t lag	Triggering pH
Dissolution input	Discrete profile – linear interpolation	Discrete profile – piecewise cubic	Weibull fitting

Selected:

- Triggering pH plus Weibull →Advantage: Includes variability for time that subjects reach the triggering pH in their GI tract
- Discrete dissolution profile with linear interpolation

Comparison against mean data from 10 different studies

Edsbaecker, 2003; Seidegard, 2009; Seidegard, 2000; Edsbaecker, 2002; Seidegard, 2000; Edsbaecker, 2003; Nicholls, 2013; Assessment report Entocort

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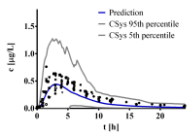
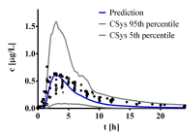
PBPK model for healthy subjects -Entocort®

Triggering pH plus Weibull



	Predicted	Observed	Ratio
$AUC_{0,\infty}$ [ug/L*h]	3.47	5.19	0.67
Cmax [ug/L]	0.44	0.54	0.81
Tmax [h]	3.00	1.60	

Discrete dissolution input



	Predicted	Observed	Ratio
$AUC_{0,\infty}$ [ug/L*h]	3.54	5.19	0.68
Cmax [ug/L]	0.62	0.54	1.15
Tmax [h]	3.00	1.60	

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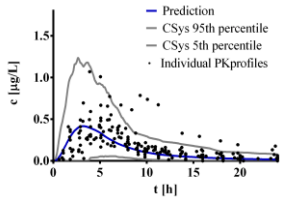
Does the PBPK model also capture interpatient variability?



Effinger et al. (2021) EJPS 157, 105617; Nicholls, 2013

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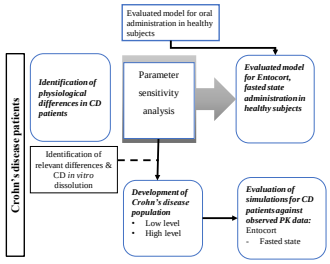
PBPK workflow for budesonide CD patients



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Investigated parameters in CD

- **CYP3A4 activity**
  - Based on hepatic and intestinal extraction ratio of midazolam (CYP3A4 substrate)
  - Hepatic: 25-31% of healthy activity
  - Intestinal: 91-149% of healthy activity
- **Plasma proteins: Human serum albumin**
  - Decreased by up to -44% (female) and -37% (male)
- **GI transit time**
- **Gastric pH**

Wilson *et al*, 2017; Lenz *et al*, 1976; Yadav *et al*, 2017, Effinger *et al*, 2018

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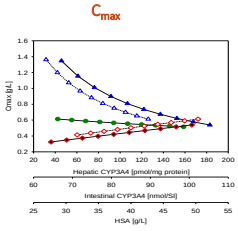
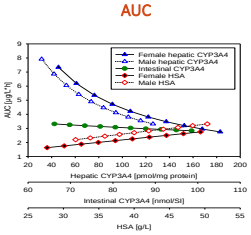
Parameter sensitivity analysis

C_{max}



AUC



HSA: Human serum albumin

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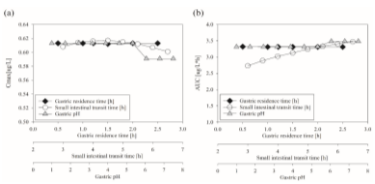
Parameter sensitivity analysis



- increased gastric pH impact when exceeding the triggering pH of 5.5
- gastric and intestinal transit times expected to have a limited effect on budesonide performance

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Crohn's disease population

	CD Low level	CD High level	Healthy population
Hepatic CYP3A4 male [pmol/mg protein]	31.50	38.49	126.00
Hepatic CYP3A4 female [pmol/mg protein]	45.75	55.91	183.00
Intestinal CYP3A4 [nmol/SI]	60.53	98.53	66.20
HSA male [g/L]	31.72	41.00	50.34
HSA female [g/L]	27.70	41.00	49.38
Dissolution input	Profile in CD biorelevant media with low levels of all factors	Profile in CD biorelevant media with high levels of all factors	

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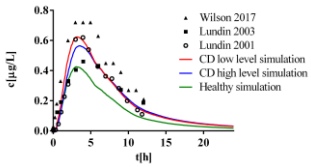
Prediction of Entocort® performance in CD patients



	Cmax [ug/L]	$AUC_{0\text{-}inf}$ [ug/L*h]	Tmax [h]
CD Low level	0.62	5.41	3.24
CD High level	0.55	5.13	3.48
Healthy	0.43	3.56	3.12
Observed	0.60	5.73	3.63

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Conclusion

- Pathophysiological changes in CD patients may alter properties of gastrointestinal fluids
- Solubility of poorly soluble compounds in CD biorelevant media is altered revealing implications for absorption in patients with CD (risk assessment tool)
- Successful predictions for oral performance in CD patients can be achieved with biopharmaceutics tools (biorelevant solubility/dissolution tests + PBPK modeling)
- PBPK models could indicate when GI diseases pose a risk for safety and efficacy and dose adjustments are needed

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