

Small molecule drug absorption in inflammatory bowel disease and current implementation in PBPK models

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Introduction

Inflammatory bowel disease (IBD) is characterized by a chronic inflammation of the intestinal mucosa, with predominant localization in the colon in ulcerative colitis (UC) or affecting the entire length of the gastrointestinal tract in Crohn's disease (CD). Current mainstay treatment for this disease consists predominately of anti-tumor necrosis factor alpha (TNF- α) monoclonal antibodies. However, initial nonresponse to anti-TNF biologics has been reported to range from 10% to 80% with loss of response over time in around one third of initial responders. Therefore, recent advances in the drug development space have been marked by a return to orally administered small molecules. Additionally, the prevalence of certain chronic conditions is higher in IBD patients, many of which are treated with orally administered drugs. Given the pathophysiology and localization of IBD, altered drug absorption from the gastrointestinal tract can be expected.

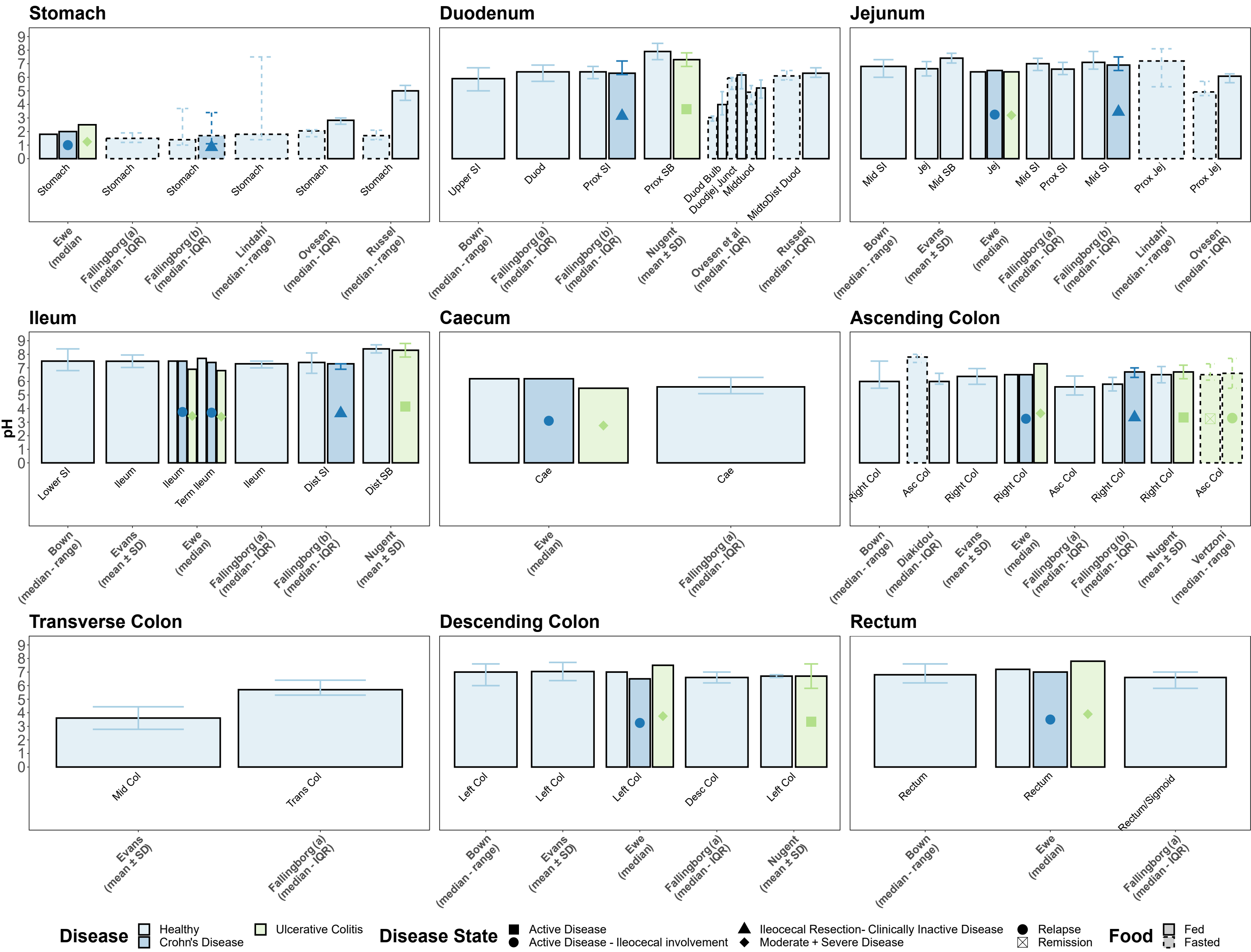
Methods

Databases Searched - PubMed - Web of Science - Embase	Aims - Determine factors influencing oral drug absorption in the small and large intestine in healthy volunteers and IBD patients - Find PBPK models describing oral drug absorption in IBD patients
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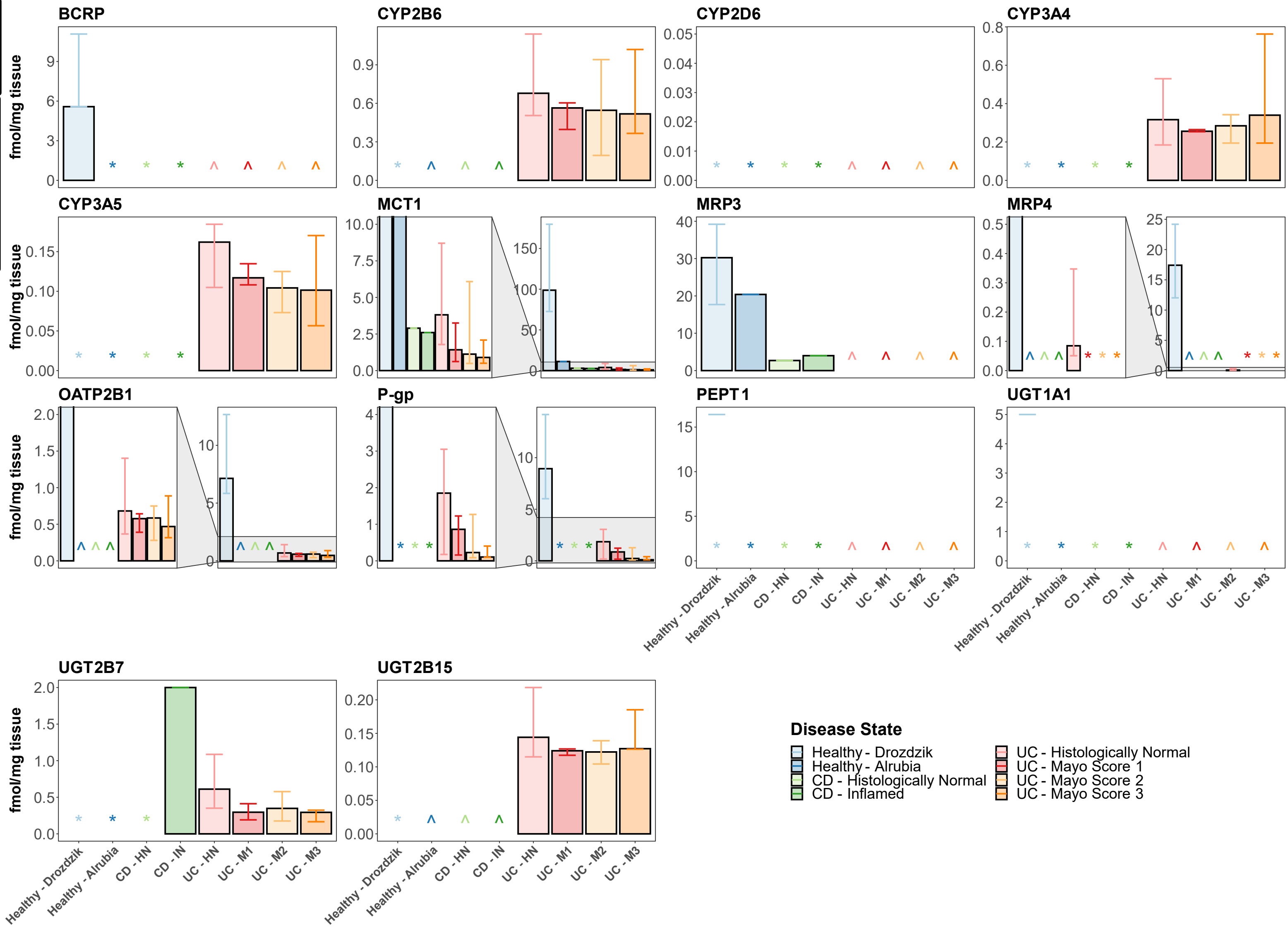
Results

	Crohn's disease	Ulcerative colitis	Effect on drug absorption
Fluid volume	↑	↑	Increased solubility
pH	↑↓	↑↓	Altered solubility and/or permeability
Transit time	↑↓	↑	Altered f_a due to altered residence time
Bile salt concentration	↓	=	Decreased solubility of lipophilic compounds
Microbiome	↑	=	Bacterial degradation in the distal small intestine
Absorptive surface area	↓	↓	Reduced f_a due to reduced area available for absorption
Permeability	↑	↑	Increased paracellular permeability for small hydrophilic compounds
Metabolizing enzymes and transporters	↑↓	↑↓	Altered f_a and/or f_g for substrates of gut enzymes/transporters

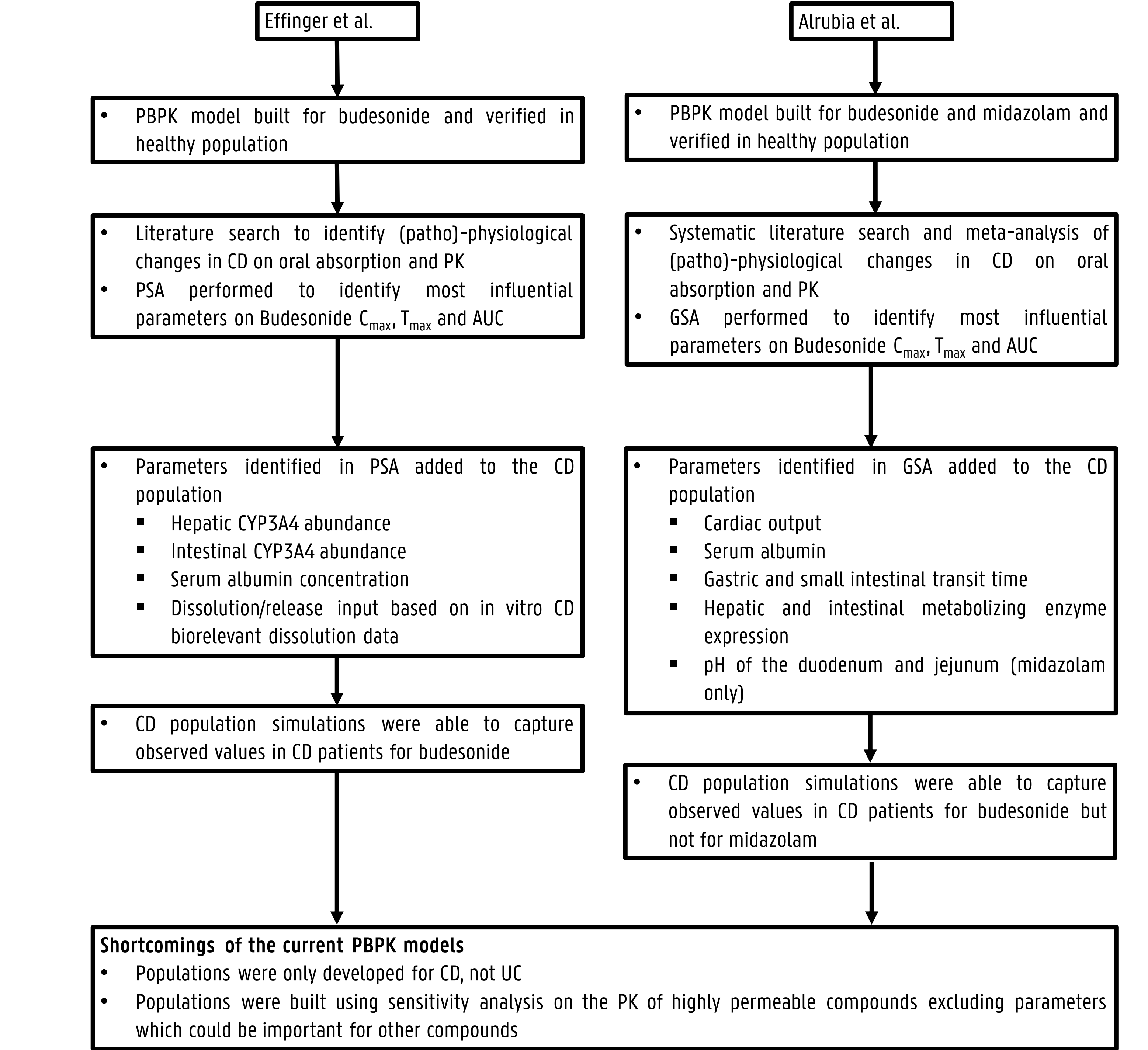
Pathophysiological differences in CD and UC and their expected effect on oral drug absorption. Compared to healthy volunteers: ↑ = increased, ↓ = decreased, ↑↓ : altered, different values reported across studies, different regions of the intestine or related to disease severity. Red: effects of disease not quantitatively assessed. f_a : fraction absorbed, f_g : fraction escaping gut wall metabolism.



Example studies reporting pH values across the gastro-intestinal tract. Naming of the intestinal segments differed across studies, these were assigned to a general segment mentioned above the panels based on the methodology of the study wherever possible. The original name of the segments in the articles are specified underneath the respective bars on the plots. Bars with full lines represent pH values recorded under fed state, the dotted bars represent pH values in the fasted state. Lightblue bars represent pH values in healthy volunteers, darkblue bars are pH values in CD patients and lightgreen bars in UC patients. The disease states mentioned in the studies are assigned a symbol which is plotted on the respective bars.



Metabolic enzyme and drug transporter expression in the colon determined by quantitative proteomics using LC-MS/MS. The bars represent median values, while errorbars represent the minimum and maximum reported value. Lightblue bars represent protein abundance in healthy volunteers from Drozdik et al. (1,2), Darkblue bars represent the protein abundance in healthy volunteers determined by Alrubia et al. (3). Lightgreen bars signify protein abundance in histologically normal tissue from CD patients and darkgreen bars are inflamed tissue from CD patients by Alrubia et al. (3). Lightpink bars represent protein abundance in histologically normal tissue from UC patients, while lightred, lightyellow and lightorange bars represent protein abundance in tissues from UC patients with disease classified as Mayo score 1, 2 and 3 respectively determined by de Waal et al. (4).



Conclusion

The factors which can affect oral drug absorption are numerous and differ regionally even within the small and the large intestine. This review described the influence of IBD on these factors both in UC and CD. Two PBPK models attempted to describe the pharmacokinetics of midazolam and budesonide in the CD population. Model performance would need to be assessed using other BCS class type drugs to determine whether membrane and luminal alterations in IBD are adequately incorporated into the model and capable of describing absorption kinetics for these low permeability and/or low solubility drugs as well.

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