Impact of gastrointestinal physiology on drug absorption in special populations—an UNGAP review

Cordula Stillhart, Katarina Vučićević, Patrick Augustijns, Abdul W. Basit, Hannah Batchelor, Talia R. Flanagan, Ina Gesquiere, Rick Greupink, Daniel Keszthelyi, Mikko Koskinen, Christine M. Madla, Christophe Matthys, Goran Miljuš, Miriam G. Mooij, Neil Parrott, Anna-Lena Ungell, Saskia N. de Wildt, Mine Orlu, Sandra Klein, Anette Müllertz

ARTICLE INFO

Keywords:
Oral drug absorption
Special populations
Gastrointestinal tract physiology
Biopharmaceutics
Oral bioavailability

ABSTRACT

The release and absorption profile of an oral medication is influenced by the physicochemical properties of the drug and its formulation, as well as by the anatomy and physiology of the gastrointestinal (GI) tract. During drug development, the bioavailability of a new drug is typically assessed in early clinical studies in a healthy adult population. However, many disease conditions are associated with an alteration of the anatomy and/or physiology of the GI tract. The same holds true for some subpopulations, such as pediatric or elderly patients, or populations with different ethnicity. The variation in GI tract conditions compared to healthy adults can directly affect the kinetic of drug absorption, and thus, safety and efficacy of an oral medication.

This review provides an overview of GI tract properties in special populations compared to healthy adults and discusses how drug absorption is affected by these conditions. Particular focus is directed towards non-disease dependent conditions (age, sex, ethnicity, genetic factors, obesity, pregnancy), GI diseases (ulcerative colitis and Crohn’s disease, celiac disease, cancer in the GI tract, Roux-en-Y gastric bypass, lactose intolerance, Helicobacter pylori infection, and infectious diseases of the GI tract), as well as systemic diseases that change the GI tract conditions (cystic fibrosis, diabetes, Parkinson’s disease, HIV enteropathy, and critical illness).

The current knowledge about GI conditions in special populations and their impact on drug absorption is still...
Intestinal absorption can occur through passive permeation (paracellular or transcellular) or active uptake via intestinal transporters.

The possible interaction between co-administered drugs (polypharmacy), between the drug and the excipients in its formulation, as well as the drug-mediated effect on the GI tract physiology further add to the complexity of drug absorption. An example is cyclosporine A, which is known to inhibit cytochrome P450 isoenzymes, particularly CYP 3A4, 2D6, and 2C19 (Niwa et al., 2007); however, it has also shown a potential effect on the small intestinal transit time (Buggins et al., 2007), suggesting a rather complex impact of cyclosporine A on the overall GI tract physiology.

The dosage forms are typically selected based on the biopharmaceutical behaviour anticipated in healthy adults and are in many cases used in patients irrespective of the physiological differences between these populations. These differences may strongly influence the drug performance and result in large variability in exposure, which in turn could result in reduced efficacy, higher incidence of adverse events, and/or impaired compliance during clinical use. Thus, the characteristics of the targeted population and possible differences in GI tract physiology compared to healthy adults have to be considered from the outset start of drug and formulation development.

During drug development physiologically based pharmacokinetic (PBPK) modelling software tools are increasingly used for predicting pharmacokinetic (PK) profiles or performance of dosage forms. The strengths of these models lies in the possibility to include altered physiological parameters to mechanistically predict drug disposition. A major limitation of such models is, however, the lack of quantitative data describing variation in all processes involved and the validation of these models (Peters et al., 2016).

Recently, several reviews on the relation between drug absorption and systemic diseases (Hatton et al., 2019) or GI diseases and disorders (Effinger et al., 2019; Hatton et al., 2018), have been published and provide a good overview of these areas. In contrast, this review aims to cover changes in oral drug absorption in both non-disease and disease related conditions that can influence the physiology of the GI tract, and thereby absorption of drugs. After a short introduction to GI physiology in the healthy adult, the present review is divided into three sections, including non-disease dependent conditions, diseases in the GI tract, and systemic diseases, all with the aim of providing a comprehensive overview of the influence of different GI conditions on drug absorption.

1. Introduction

Oral dosing is the preferred route of administration as it is convenient and safe for most populations (Stewart et al., 2016). Upon oral administration, the drug is passing through the stomach to the small intestine where most of the drugs are absorbed. Poorly absorbed drugs, or drugs in modified release formulations will pass to the colon, where further absorption can occur. During the development of new medicines, the absorption behaviour of oral compounds is usually studied in healthy adults. However, the morphology and physiology of the gastrointestinal (GI) tract is influenced by multiple factors such as age, sex, ethnicity, genome, or the disease state of the treated patient. These factors can significantly alter the kinetics of drug absorption, as well as the total amount of drug absorbed, thereby changing the pharmacokinetics of a drug and possibly its effect compared to the observed behaviour in healthy adults.

The main physiological parameters that are often altered in patients compared to healthy populations are the gastric emptying rate and pH, transit times across the different intestinal segments, intestinal surface area, epithelial permeability, as well as intestinal enzyme and transporter expression. Further differences may be observed with regard to the volume and composition of luminal fluids and of the intestinal microbiota (Fleisher et al., 1999; Bai et al., 2016; Effinger et al., 2019).

The possible interaction between co-administered drugs (polypharmacy), between the drug and the excipients in its formulation, as well as the drug-mediated effect on the GI tract physiology further add to the complexity of drug absorption. An example is cyclosporine A, which is known to inhibit cytochrome P450 (CYP) isoenzymes, particularly CYP 3A4, 2D6, and 2C19 (Niwa et al., 2007); however, it has also shown a potential effect on the small intestinal transit time (Buggins et al., 2007), suggesting a rather complex impact of cyclosporine A on the overall GI tract physiology.

The dosage forms are typically selected based on the biopharmaceutical behaviour anticipated in healthy adults and are in many cases used in patients irrespective of the physiological differences between these populations. These differences may strongly influence the drug performance and result in large variability in exposure, which in turn could result in reduced efficacy, higher incidence of adverse events, and/or impaired compliance during clinical use. Thus, the characteristics of the targeted population and possible differences in GI tract physiology compared to healthy adults have to be considered from the outset start of drug and formulation development.

During drug development physiologically based pharmacokinetic (PBPK) modelling software tools are increasingly used for predicting pharmacokinetic (PK) profiles or performance of dosage forms. The strengths of these models lies in the possibility to include altered physiological parameters to mechanistically predict drug disposition. A major limitation of such models is, however, the lack of quantitative data describing variation in all processes involved and the validation of these models (Peters et al., 2016).

Recently, several reviews on the relation between drug absorption and systemic diseases (Hatton et al., 2019) or GI diseases and disorders (Effinger et al., 2019; Hatton et al., 2018), have been published and provide a good overview of these areas. In contrast, this review aims to cover changes in oral drug absorption in both non-disease and disease related conditions that can influence the physiology of the GI tract, and thereby absorption of drugs. After a short introduction to GI physiology in the healthy adult, the present review is divided into three sections, including non-disease dependent conditions, diseases in the GI tract, and systemic diseases, all with the aim of providing a comprehensive overview of the influence of different GI conditions on drug absorption.

2. GI tract physiology in healthy adults

The GI tract physiology in healthy adult subjects and its impact on oral drug absorption has been extensively studied in the past decades and comprehensive reviews can be found in the literature (Bergstrom et al., 2014; Dressman and Reppas, 2010). A brief overview of the main physiological parameters of the human GI tract is presented here.

The pH of luminal fluids is acidic in the stomach (pH 1.5–3.5), and increases to approximately pH 5-6 in the duodenum and pH 7-8 in the distal jejunum and ileum, before dropping to pH 6 in the colon with high interindividual variability (Evans et al., 1988; Koziolek et al., 2015). The pH affects the degree of ionization of drug molecules, influencing their dissolution and permeation behaviour, as well as the performance of some drug delivery systems, such as modified-release formulations.

The gastric emptying time, measured by magnetic resonance imaging as the time to get back to fasted gastric volumes, is approximately 45 min after a glass of water (240 mL) and more than 6 h after a standardized Food and Drug Administration (FDA) high-caloric breakfast (Koziolek et al., 2014; Mudie et al., 2014). The small intestinal transit time has been reported to be relatively constant between 4.3 and 4.6 h, whereas the colonic transit time is very variable between ~18 and 34.2 h (Becker et al., 2014; Sarosiek et al., 2010; Maharaj and Edginton, 2016).

Intestinal absorption can occur through passive permeation (paracellular or transcellular) or active uptake via intestinal transporters.
depending on both the physicochemical characteristics of the drug and the properties of the intestinal membrane in different regions of the GI tract. Polar molecules pass through the passive paracellular route depending on their molecular size and charge, while more hydrophobic molecules tend to be absorbed via the transcellular route. Since the epithelial membrane composition, surface area, and pore size, are varying along the GI tract, polar molecules tend to be absorbed in the upper small intestine while hydrophobic molecules can penetrate across the membrane throughout the intestine (Sarosiek et al., 2010).

Reviews of intestinal transporter expression and specificity have been published recently (Drozdzik et al., 2014; Estudante et al., 2013). Some uptake transporters (monocarboxylate transporter 1 and organic cation transporter 1) are expressed along the whole GI tract (Sjoberg et al., 2013) while others are located in a specific region: peptide transporter protein 1 mainly in the jejunum and organic anion transporting polypeptides 2B1 (OATP2B1) mainly in the colon (Sjoberg et al., 2013). Overall the expression of efflux transporters, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug-resistance-associated protein 2, increases from the proximal to the distal small intestine (Peters et al., 2016; Gutmann et al., 2005; Berggren et al., 2007), which is opposite to the expression of cytochrome P450 enzymes being highest in the duodenum/jejunum (Peters et al., 2016; Stappaerts et al., 2013).

The volume of GI fluids determines the local drug concentrations in the GI tract, and thus, it affects the dissolution behaviour as well as the driving force for permeation. Several studies using magnetic resonance imaging can be found in the literature (Grimm et al., 2018; Mudie et al., 2014; Perez de la Cruz Moreno et al., 2006; Schiller et al., 2005). In the fasted stomach, resting gastric fluid volumes between 25 and 45 mL have been reported with significant interindividual variability (Grimm et al., 2018; Mudie et al., 2014; Schiller et al., 2006). In contrast, the volume in the fed state is dependent on the volume of the ingested food, and the time after ingestion. In the small intestine the fasted state volume has been reported to be 43 ± 14 mL (range 5–159 mL), which was non-evenly distributed in small pockets (Mudie et al., 2014). In the ascending colon, mean fluid volumes of 7 to 22.3 mL were measured in the fasted state and 29.9 mL the fed state, respectively (Murray et al., 2017; Diakidou et al., 2009).

The composition of bile salts and pancreatic enzymes can affect the solubility and dissolution rate especially of hydrophobic drugs in the gut. The overall composition of intestinal fluids changes during intestinal transit due to digestion and absorption processes, as well as the secretion of bile and pancreatic fluids into the intestinal lumen. In the fasted state, the concentration of bile salts ranges from 2.5 to 5.9 mM in the duodenum and from 1.4 mM to 5.5 mM in the jejunum. Only few studies have determined the regional bile salt level in the fed state, and reported values between 3.6 and 24.0 mM in the duodenum and 4.5 and 8.0 mM in the jejunum. The large variability also reflects the effect of different food types ingested (Bergstrom et al., 2014). In the fasted state, the rank order of relative bile salt concentration in the duodenum was reported as follows: taurocholic acid > glycocholate > glycochenodeoxycholate > glycodeoxycholate > taurochenodeoxycholate > taurodeoxycholate. The concentration of cholic acid, tauroursodeoxycholate, chenodeoxycholic acid, and deoxycholic acid was less than 1% of the total bile salts (Perez de la Cruz Moreno et al., 2006). Other minor components of luminal fluids can be found in Diakidou et al. (2009) and Perez de la Cruz Moreno et al. (2006). Interestingly, the relative composition of bile salts is similar between fasted and fed state in the upper GI tract as well as in the lower bowel (Diakidou et al., 2009; Perez de la Cruz Moreno et al., 2006; Riehorst et al., 2016). However, some disease states have been associated with erroneous synthesis of bile acids resulting in different relative concentrations compared to healthy subjects (Sundaram et al., 2008).

The healthy human gut is populated with billions of microbes, the microbiome, that contributes to a dynamic relationship between immune and metabolic function. The weight of the intestinal microbiome amounts to around 1.8 kg in adults and every individual has a unique mix of microbial species. The diversity of microbes within a given body can be defined as the number and abundance distribution of distinct types of organisms. An imbalance in this diversity has been linked to several human diseases, such as obesity and inflammatory bowel disease (Human Microbiome Project Consortium, 2012). In addition, many bacteria in the gut microbiome have been shown to metabolise drugs, with potential consequences for the pharmacokinetics and effect of the drug (Zimmermann et al., 2019). A large database on the human microbiome, including a variety of species for healthy and diseased humans can be found in the Human Microbiome Project Consortium report (Human Microbiome Project, 2012).

3. Non-disease dependent conditions

3.1. Paediatric age groups

The paediatric population is a diverse ‘special’ population as it includes sub-populations including pre-term and term neonates, infants, children and adolescents. The impact of age on drug absorption has been reviewed recently for children (Guimaraes et al., 2019; Johnson et al., 2018) and neonates (Neal-Kruever et al., 2019; Somani et al., 2016). Both the rate and the extent of absorption of drugs in children is different than in adults with the greatest differences from the adult being observed in neonates (Batchelor et al., 2014). The difficulties of extrapolation of oral absorption data from adult data into paediatric populations is further complicated by the dose adjustment made for the population. For a long time, the standard approach for dose adjustments was based on the weight or by body surface area of the patient with no regard to the overall absorptive capacity of the paediatric intestine and age-related changes of oral drug absorption processes in the intestine. Since more recently, paediatric dose adjustment based on allometric concepts and ontogeny is considered more appropriate, but to date no final consensus on the suitability of different methodologies for dose adjustment in children has been reached.

When dosing oral medicines it is important to recognise that most oral processes are present from birth (rooting, lip, lateral tongue, mouth opening, biting, and emerging chewing behaviours) (Sheppard and Mysak, 1984). However, functionality is not fully matured: e.g., oral syrups are incompletely swallowed when administered to neonates and infants (Klingmann et al., 2018).

Key findings from recent reviews on the ontogeny of oral drug absorption processes are presented in summary here and, where available, newer data is included (Mooij et al., 2012). In contrast to what has been echoed in multiple reviews, the gastric pH is only high directly after birth, likely due to buffering of remaining amniotic fluid, and rapidly decreases to pH 1 to 3 in children of all ages (Mooij et al., 2012). Collection of paediatric gastric fluids have shown pH values ranges from 2.0 to 2.7 in neonates and typically <3 in children and adolescents (Van Den Abeele et al., 2018). The postprandial buffering effect of a milk-based diet in frequently-fed neonates results in a higher percentage of time at higher gastric pH.

The paediatric gastric emptying time is highly variable in children younger than 6 months and paracetamol absorption kinetics have revealed delayed gastric emptying in the first few days of life. Intestinal transit time is also slower in neonates and infants yet reaches adult values by the age of 2 years (Bonner et al., 2015).

To study the effect of age and feeding in vitro, simulated paediatric fasted- and fed-state gastric and intestinal fluids have been developed based on literature data to inform their composition, although the evidence-base is limited (Maharaj et al., 2016). The solubility of six drugs were evaluated in these new paediatric media and compared to values from adult simulated media; key differences in solubility were found for neonatal media where milk was a component. Typically, the differences in solubility were outside the nominal 80–125% bioequivalence criteria for neonatal media compared to adults (Maharaj et al., 2016).
Very recent work has shown that the total bile salt concentration in gastric fluids collected from neonates and infants was low with 31.2 and 9.2 µM, respectively; whereas higher values were found in children (99.5 µM) and adolescents (763.6 µM) (Van Den Abeele et al., 2018). Small intestinal pH has only been studied in older children and showed adult values; bile acid concentrations are reported to reach adult values around the age of 4 years. Pancreatic function appears to be sufficient in healthy neonates, independent of gestational age (Zoppi et al., 1972).

Drug absorption in the intestine may be affected by age-related changes in intestinal permeability, as well as activity of drug metabolizing enzymes and membrane transporters. Intestinal permeability is reported to be higher in neonates compared to adults with factors relating to the three-dimensional shape of the intestinal mucosal surface as well as the high nutritional need of this sub-population (Bezerra et al., 1990). The ontogeny of intestinal and hepatic drug metabolizing enzymes and transporters, both impacting oral bioavailability, shows age-dependent and transporter-specific profiles (Brouwer et al., 2015; Mooij et al., 2016a; Mooij et al., 2016b; Mooij et al., 2016c; Cheung et al., 2019; van Groen et al., 2018). For example, hepatic ATP-binding cassette B1 (ABCB1) expression appears low at birth as compared to adults, but stable in the intestine. In contrast to the stable intestinal ABCB1 expression, OATP2B1 expression in the intestine appears higher in neonates than in older children and adults. By combining the existing physiological data from children across the paediatric life span and PK data of oral and intravenous administration, physiology based (population) PK studies aimed to elucidate the relative contribution of intestinal and hepatic drug metabolism during growth and maturation (Brussee et al., 2018a; Brussee et al., 2018b). While very informative, these models are still hampered by limited data on age-related physiological parameters, including intestinal drug metabolizing enzyme and transporter expression (Kodidela et al., 2017).

The impact of food and nutrition can influence the absorption of drugs as the diet particularly in neonates and infants with milk-based feeding is different to that in adults (Batchelor et al., 2018; Karkossa et al., 2017). Not only buffering of gastric pH by milk, as discussed above, but dietary conditions, may also change drug metabolizing enzyme and maybe transporter maturation, as for example CYP 1A2 and CYP 3A4 activity appears to be higher in formula fed than in breast-milk fed neonates (Blake et al., 2006). However, it is not yet clear if this is caused by the presence of an inducer in formula or an inhibitory factor in breast milk. In young children, manipulations with drugs (i.e., crushing, dissolving tablets) or co-administering with food to enhance ingestion by children may affect drug bioavailability.

In conclusion, gaps in knowledge are related to the composition and volume of fluids present in the small intestine, the expression of intestinal transporters and metabolizing enzymes, and methods to understand permeability in paediatric intestine and pathways relevant to intestinal wall metabolism. Major knowledge gaps were identified in the most vulnerable groups of neonates and infants under 6 months of age. In addition, there is a critical need for PK data from these young populations to better understand the implications of GI differences on the absorption of drugs.

3.2. Advanced age

As age advances, the GI tract undergoes a variety of morphological and functional changes that result in a general decline in bodily function. The complex deterioration of normal GI parameters can therefore compromise effective drug absorption in the elderly population, who is often subject to polypharmacy. The impact of advanced age on GI physiological factors including GI transit, pH, expression of metabolising enzymes and membrane transporters, permeability and the microbiome are limited (Khan and Roberts, 2018), but studies have demonstrated minor differences when compared with healthy adults (Brogna et al., 1999; Carrion, 2017; Fakhoury et al., 2005; Holt, 2018; Russell et al., 1993).

There is an important interaction between drug absorption and nutritional practice prevalent in the older population. For example, the limited fluid intake in the geriatrics in particular has the potential to influence the intestinal absorption process. In addition, the thirst sensation is diminished in elderly (Carrion, 2017; Kenney and Chiu, 2001). The consequence of the reduced fluid intake in the longer term, however, may be associated with the impaired drug absorption. Further research is required to generate evidence-based data to understand: (i) whether the alteration in thirst physiology is associated with changes in intestinal absorption and (ii) if it is associated, which drugs are subject to altered absorption profiles in older people with diminished thirst.

Nutritional intake is also subject to change at advanced age. Fibre-based enteral nutrition is often administered to improve bowel function in the elderly. Hence, age-related motility changes as a result or in combination with these formulations may elicit varying intestinal drug absorption profiles. More importantly, the geriatric population is the main user of thickening agents to manage dysphagia. The administration of a drug product mixed with thickening agents may present an unforeseen reason for changes in the bioavailability profile (McKinley et al., 2006).

Drug absorption in the GI tract should be investigated thoroughly in the presence of disease. The incidence of disease is higher in the elderly although this factor is rarely considered as the primary cause of variability in drug absorption as drug bioavailability may further be perturbed due to advanced age or a combination of both. Therefore, it is more complicated to understand the intestinal absorption profile of a drug in an older individual with a clinical condition.

Polypharmacy may further contribute to varied absorption in the intestine, for example due to drugs that increase the risk of constipation. As multi-morbidity, and consequently polypharmacy, is predominant in the elderly, the use of drugs with an effect on the GI pattern is more frequent than in younger subjects (Cichero, 2013; Perini et al., 2019).

Overall, there is a lack of consensus regarding the independent effects of ageing on intestinal absorption due to: (i) the challenge in investigating the aged intestine that is free of disease; (ii) the lack of harmonisation in the applied methods and tools to study drug absorption from the intestine at old age and; (iii) the scattered approach in reporting the GI physiology related factors as the main drivers for drug absorption. Clinical studies including healthy elderly subjects should be encouraged to understand GI tract physiology and drug absorption in this population.

3.3. Sex differences

Men and women respond differently to medicines. These sex differences, however, have largely been neglected in the drug development arena. Many pharmaceutical scientists can attest that for decades, the default human model subject was a “70 kg Caucasian male” (Beery et al., 2011; Yoon et al., 2014). With the effort to overcome the disparity between sexes in biomedical research, the FDA and the National Institutes of Health mandated for the inclusion of women in clinical trials in the U.S. in 1993. Nonetheless, following the review of ten drugs that were withdrawn from the market from 1997 to 2000, it was found that withdrawal of eight of the ten drugs were due to greater risks of adverse effects in women (GAO, 2001). In addition, out of 67 new molecular entities approved by the U.S. FDA between 2000 and 2002, 25 compounds demonstrated significant sex-specific differences in PK and efficacy (Yang, 2009). Ignoring female participants in clinical trials has backfired and has resulted in the significant implications in women directly related to drug use. For example, only identified during post-market drug surveillance, women were more susceptible to next-day effects following the administration of the sedative zolpidem as drug elimination was slower in women than in men. The FDA subsequently recommended that immediate-release and extended-release
products were to reduce the dose from 10 mg to 5 mg and 12.5 mg to 6.25 mg respectively for women (Norman et al., 2017). In addition, women are also at a greater risk (50–70%) of experiencing adverse side effects (Rademaker, 2001), which may be directly linked to distinct GI physiological differences between the sexes.

Drug dissolution is often the rate limiting step in drug absorption, however, it was identified that fluid volumes in the stomach and small intestine (following the normalisation of body weight) were higher in men than in women (Gotch et al., 1957; Soldin and Mattison, 2009). In terms of gastric pH, the fastest state pH is higher in females than in males (2.79 ± 0.18 and 2.16 ± 0.09, respectively), which may be attributed to reduced acid secretion and smaller sized female stomach (Feldman and Barnett, 1991; Phan et al., 2015). Lowered gastric acid secretion may influence drug ionisation and solubility of pH-sensitive drugs, thereby impairing absorption and consequently, oral drug bioavailability (Lahner et al., 2014).

With regards to motility, pre-menopausal women have a significantly longer gastric emptying time when compared with their male counterparts for solids and carbonic liquids, however, in post-menopausal women, gastric emptying time decreases and becomes similar to that in men (Bennink et al., 1998). Variabilities in drug PK can be attributed to differences in gastric emptying time as a shorter absorption lag time of an enteric-coated aspirin tablet was demonstrated in males than females (Mojaverian et al., 1988; Fischer and Fadda, 2016). Colonic transit time is also significantly longer in women than in males (ascending colon: 13.3 ± 1.6 h; 8.9 ± 1.1 h and transverse colon: 13.7 ± 2.1 h; 8.7 ± 1.5 h; descending colon: 11.8 ± 1.6 h; 13.0 ± 1.7 h in women and men respectively) (Metcalfe et al., 1987; Rao et al., 2009). The increased total intestinal transit time in women would have significant implications to oral drug bioavailability. The longer GI residence time for sustained-release dosage forms may facilitate enhanced drug absorption in women as demonstrated with the PK profile of an extended-release formulation of diltiazem, which was demonstrated to be sensitive to GI transit time (Zimmermann et al., 1999). This, however, may further be implicated by the regulation of intestinal membrane transporters and metabolising enzymes located in the GI mucosa.

CYP enzymes are responsible for the metabolism of a number of drug substrates of which CYP2C and 3A are most commonly expressed in the small intestine. For example, the oral bioavailability of verapamil (a CYP3A substrate) was higher in women than in men (Krecic-Shepard et al., 2000) due to higher intestinal CYP3A expression and activity (Tamargo et al., 2017). P-gp, the most studied efflux membrane transporter in the GI tract, has been shown to differentially affect oral drug absorption in males and females in the presence of so-called “inert” excipients. A human study firstly identified that when formulated with 0.5 g polyethylene glycol 400 (PEG 400), the bioavailability of ranitidine (a P-gp substrate) significantly increased by 63% in males. In females, however, ranitidine bioavailability decreased by 8% when compared with the control (Ashiru et al., 2008). As aforementioned, the National Institute of Health mandated for women to be included in clinical trials in 1993. No such initiatives, however, have been implemented to investigate sex differences in pre-clinical research, i.e., cell and animal models. As early drug development often uses rats as animal models, the sex differences at a rodent physiological level can translate the oral drug performance in humans. A rat study was subsequently developed to explore the levels of P-gp along the gastrointestinal tract. Afonso-Pereira et al. identified that female rats displayed significantly higher relative P-gp expression levels than male rats throughout the small intestine (Afonso-Pereira et al., 2018). Excipients have since been identified to directly interact with the gene and protein expression of P-gp differently between males and females (Maï et al., 2017). The presence of PEG 400 and its potential interaction with P-gp was assessed for its gene and protein expression in the presence of a P-gp substrate (ranitidine and ampicillin), a non-P-gp substrate (metformin) and a P-gp inhibitor (cyclosporine A) in male and female rats. The study showed that the bioavailability of ampicillin significantly increased (p < 0.05) in the presence of PEG 400 in male, but not female, rats. No sex differences were reported in the bioavailability of metformin in the presence of PEG 400. When formulated with a P-gp inhibitor (cyclosporine A), the bioavailability of ampicillin and ranitidine increased in males to a greater extent but showed no influence on metformin bioavailability. There is, therefore, a potential sex-specific effect of PEG 400 on the bioavailability of certain drugs due to the interaction of PEG 400 with the P-gp efflux transporter (Maï et al., 2018a). A recent study established an in vitro permeation model for the prediction of the in vivo sex-related influence of PEG 400 mediated by P-gp. The study identified a good in vivo-in vitro correlation for the influence of PEG 400 on the absorption of ranitidine in different segments of the small intestine which can predict drug bioavailability in human subjects (Maï et al., 2018b).

Advancements in the research has since revealed that the sex-specific influence of excipients on drug bioavailability is not limited to PEG 400 alone. Other solubilising excipients including PEG 2000, Cremophor RH 40, Poloxamer 188 and Tween 80 have shown to significantly increase ranitidine bioavailability, although this was only apparent in males but not in female rats (Maï et al., 2019). The effect of Span 20 was also studied on the oral bioavailability of ranitidine; although this solubilising agent was able to significantly increase ranitidine bioavailability, its effects were in a non-sex dependent manner. Consequently, sex-specific effects may be attributed to the presence of a polyoxyethylated group in PEG 2000, Cremophor RH 40, Poloxamer 188 and Tween 80, but not for Span 20.

Food intake has recently been discovered to affect the intestinal expression of P-gp in males and females. Dou et al. identified that relative P-gp levels decreased in all segments of the intestine (bar duodenum) in male rats following food intake. A fundamentally different outcome, however, was observed in female rats where the fed state resulted to a significant increase in P-gp expression in the small intestine. Specifically, a six-fold increase in jejunal P-gp expression occurred from the fasted to fed state in female rats. As such, intestinal permeability studies in an Ussing chamber showed that ganciclovir and ranitidine (both P-gp drug substrates) exhibited a sex difference in intestinal permeability from the fasted to fed state (Dou et al., 2018).

Adding further to the complexity of varying drug response between the sexes may be governed by the intestinal microbiome. The increasing number of microbiome studies have revealed the importance of the gut-brain axis namely the microbiota and the endocrine system with bacteria being able to produce hormones (e.g., serotonin and dopamine), respond to host hormones (e.g., oestrogen) and regulate the homeostasis of host hormones by inhibiting gene transcription (e.g., prolactin) (Edwards et al., 2018). A study demonstrated that women appear to have significantly higher levels of faecal bifidobacteria and Bilophila than men (Cross et al., 2018; Haro et al., 2016). The diversity seen in the gut microbiota between the sexes may have a dominant role in defining the sex-specific response to medications or provide the foundation to understanding the pathology of disease.

Although men are subject to higher mortality rates, the prevalence of morbidity is higher in women (Singh-Manoux et al., 2008). The onset of disease has also recently been identified to affect normal gut physiology and function between the sexes which consequently alter drug absorption and bioavailability (Freire et al., 2011). For example, the erratic gastric emptying of levodopa in Parkinson’s disease patients can reduce the dissolution time of the tablets in the stomach resulting in delayed and incomplete absorption (Deleu et al., 1991). A study showed that a significantly higher bioavailability of levodopa was found in all female patients with Parkinson’s disease (PARDK) where the area under the curve was almost 1.6 times higher than in their male counterparts (Kumagai et al., 2014). The study did not investigate further into why sex differences were found, but hypothesised the potentially negative influence of oestrogen in patients with PARDK. Although the underlying mechanism of PARDK is still unclear, the effects of oestrogen on
PARKD symptoms that are mediated by the modulation of the basal ganglia have been shown to exacerbate classic Parkinsonism disorders in human PARKD patients (Van Hartesveldt et al., 1986; McEwen, 2014).

Research invested in to understanding the differences between the sexes in the main site of drug absorption continue to be very limited. It is clear that males and females differently respond to medicines due to the dynamic interplay of GI fluid volumes, luminal pH, transit time, expression of membrane transporters, the microbiome and the onset of disease. As such, drug development is required to invest in specialised sex-specific studies to fully understand the mechanism of the gut and to maximise effective oral drug bioavailability.

### 3.4. Ethnic and genetic factors

Ethnicity can be considered as an important demographic variable that may contribute to significant interindividual variability in PK and pharmacodynamics of several drugs. Regulatory authorities are expecting a sponsor developing a medicine for a new geographical region to consider how to “deal with the possibility that ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations” (ICH, 1998). Ethnic variation in drug absorption may be attributed to intrinsic factors such as variation in the genetics or physiology, or to extrinsic factors such as socioeconomic background, culture and environment with major differences in the diet (Chen, 2006; ICH, 1998; Johnson, 1997).

When considering passive processes in intestinal absorption, ethnic differences as such are not anticipated (Johnson, 1997). However, with drugs undergoing active transport and metabolism in the gut there is more potential for differences. An example is the active calcium absorption with fractional absorption of calcium in premenarchal girls of more potential for differences. An example is the active calcium absorption with fractional absorption of calcium in premenarchal girls of African origin being significantly higher compared to Caucasian girls (Johnson, 1997). Apart from CYP3A4, also CYP2C9 and CYP3A5 are considerably expressed along the GI tract (Drosdzik et al., 2018). CYP3A4 is known to have largely variable expression between subjects, but limited information is available comparing the CYP3A4 expression or activity in different ethnic groups. Further, little evidence is available regarding clinically significant polymorphisms in the CYP3A4 gene. However, polymorphism in the CYP3A4 gene can make a significant contribution to the variability in drug absorption in different ethnic groups, particularly for substrates with preferential metabolism by CYP3A5 over CYP3A4, such as tacrolimus (Zanger and Schwab, 2013). The ethnic differences in tacrolimus PK were suggested to be related to intestinal metabolism rather than hepatic elimination, and thus the CYP3A5 genotype can affect absorption profiles of extended-release and immediate-release oral formulations (Chen and Prasad, 2018). The most studied polymorphism is CYP3A5*3, and those with homozygous condition are considered as non-expressor. This polymorphism is less frequent in populations of African origin as compared to Caucasians (Chen and Prasad, 2018). Indeed, the prescribing information of orally dosed tacrolimus capsules advice African American patients to receive a higher dose to attain comparable plasma trough concentrations compared to Caucasian patients (FDA, 1994).

For the efflux transporter P-gp, many polymorphisms in the ABCB1 gene have been associated with altered expression of P-gp, potentially leading to changes in drug PK (Wolking et al., 2015). One of the most common variants, 3435 C>T, shows remarkable interethnic variability, and people of African origin due to their lower allele frequency could be expected to have higher plasma concentrations for P-gp substrates than other ethnic groups, such as East Asians, Indians, and Caucasians. However, the clinical significance remains inconsistent and equivocal (Cascorbi, 2006; Wolking et al., 2015).

In addition to P-gp, BCRP, another efflux transporter expressed in the GI tract, can have a clinically significant effect on drug absorption. For the gene coding for BCRP, ABCG2, a much studied single nucleotide polymorphism, Q141K (421C>A), has been shown to decrease BCRP expression and activity, and this polymorphism has a highly variable frequency depending on ethnicity (Heyes et al., 2018). It is common in Asian populations, where about one third of Japanese and Chinese subjects are affected, while more rare in Caucasian, Sub-Saharan, or African American populations (Heyes et al., 2018). As BCRP is expressed in many tissues, including the intestine, it is complicated to interpret the role of the transporter on the PK. Examples where altered PK is considered to be due to tissue-specific BCRP interaction is atorvastatin and rosuvastatin, where a change in absorption parameters has been observed, but no effect on the elimination half-life (Heyes et al., 2018; Li and Barton, 2018). The FDA label of rosuvastatin states "PK studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls” (FDA, 2003c). Consequently, a lower rosuvastatin dose is suggested for Asian subjects. What complicates the assessment of the precise mechanism for this ethnic difference is that not only the polymorphism of ABCG2, but also that of SLCO1B1, a gene coding a hepatic transporter OATP1B1, can have an effect on rosuvastatin PK (Li and Barton, 2018; Wu et al., 2017).

Even though there is limited evidence for clinically meaningful ethnic disparities in gastric pH, emptying, intestinal motility, transit time or mucus properties, ethnicity may be associated to these properties through extrinsic factors such as the diet. For example, some ethnic groups may have more vegetarians than others. Vegetarians, compared with non-vegetarians, are expected to have more rapid GI transit time, thus impacting the residence time of the dosage form in the intestine (Chen, 2006). However, ethnic differences in gastric pH can exist as lower gastric acidity has been found in the Japanese population (Tamboli et al., 2010). Implications of specific pharmaceutical product designs on the PK of drugs prescribed for various ethnic groups and genetic variants need to be considered, especially for the drugs that exhibit active processes in absorption and have narrow therapeutic index. More mechanistic studies are needed for detailing the contribution of various factors. Especially, the interrelationship between P-gp and CYP3A, with a highly variable interindividual expression, and potential food-drug interactions, makes it difficult to elucidate the precise ethnic differences in drug absorption.

### 3.5. Diet

The interaction between food ingestion and drug absorption is well described in several recent review papers (Deng et al., 2017; Mouly et al., 2017; Peter et al., 2017; Van Orten-Luiten, 2017; Witkamp and van Norren, 2018). The postprandial effect of food intake in the GI tract is complex and includes increased viscosity of luminal contents, delay in gastric emptying, elevation of gastric pH, enhancement of splanchnic blood flow and stimulation of bile secretion (Deng et al., 2017). The interaction between food components and drugs mainly takes place in the GI tract before absorption and thus can affect the PK profile of the drug. The effect on a specific drug is dependent on the physico-chemical characteristics of the drug and also the nature of the food. For lipophilic drugs, a positive food effect, i.e., increased absorption upon ingestion of, especially, a high-fat meal, is expected to have more rapid GI transit time or mucus properties, ethnicity may be associated to these properties through extrinsic factors such as the diet. For example, some ethnic groups may have more vegetarians than others. Vegetarians, compared with non-vegetarians, are expected to have more rapid GI transit time, thus impacting the residence time of the dosage form in the intestine (Chen, 2006). However, ethnic differences in gastric pH can exist as lower gastric acidity has been found in the Japanese population (Tamboli et al., 2010). Implications of specific pharmaceutical product designs on the PK of drugs prescribed for various ethnic groups and ethnic differences in drug absorption.
its postprandial absorption of bile acids and stimulation of fermentation in the gut lumen, influencing the gut microbiota. High-carbohydrate food, like high-fat meals, retards the gastric emptying. Thus, Deng and colleagues conclude that one food item or a specific diet can interact through different mechanisms, thus having diverse effect on different drugs (Deng et al., 2017).

Food components can also impact drug absorption via metabolising enzymes and transporters (Wen et al., 2012). The most well-known specific interaction here is the inhibition of intestinal CYP3A expression and activity by grapefruit juice (Mouly et al., 2017). Similar interaction is assumed with P-gp transporters, which were shown to be inhibited by citrus juices in vitro (Soldner et al., 1999), but the in vivo relevance has not been fully demonstrated (Becquemont et al., 2001).

Moreover, the gut microbiome and postprandially produced metabolites can affect the absorption of nutrients and pharmaceutical compounds. (Zimmermann et al., 2019) describe that the gut microbiota can modify drug absorption and drugs biotransformation and suggest to take the role of the gut microbiota into account when considering bioavailability and efficacy of drugs. The gut microbiota does not only modify drug absorption, but can be a therapeutic target as well. Food components and diet influence the composition of the gut microbiota and therefore will interact with drug absorption (Falony et al., 2019). Nevertheless, the clinical relevance of all these interactions could be questioned and are often not clear and unexpected interactions could occur (Witkamp and van Norren, 2018).

3.6. Obesity

The prevalence of obesity is increasing and it is now estimated that more than six million adults in Europe are obese (Webber et al., 2014). Obesity is associated with co-morbidities that include type 2 diabetes mellitus (T2DM), ischaemic heart disease, cancer, depression and hypertension, all of which require therapy (Brandt, 2013). Previous work exploring the impact of obesity on drug PK have focused on distribution, metabolism, and elimination aspects rather than absorption (Hanley et al., 2010; Smit et al., 2018). There have also been reviews describing the impact of GI surgery as a treatment for obesity, for example bariatric surgery and Roux-en-Y gastric bypass (Santamaría et al., 2018). Obesity is associated with GI complications which are further described in a recent review (Camilleri et al., 2017).

Obesity has been reported to increase the prevalence of oesophageal disorders; there is a documented link between gastroesophageal reflux disease and obesity in adults, which is likely due to the increased pressure on the stomach and oesophagus due to excess weight (Zacchi et al., 1991). Abdominal obesity has been linked to increased intra-abdominal pressure in subjects whose body mass index (BMI) had increased gastric pH during pregnancy (Costantine, 2014; Pariente et al., 2015). Those studies report that gastric volumes also reported gastric pH in lean patients (BMI = 18–25 kg/m²) versus obese patients (BMI = ≥35 kg/m²) and reported larger gastric volumes in the obese (26.9 ± 14.6 mL) compared to lean (6.3 ± 7.4 mL) (Mahajan et al., 2015). Those studies reporting gastric volumes also reported gastric pH with values of 2.8 and 4.3 in lean participants and values of 2.3 and 3.5 in obese participants by Juvin et al. (2001) and Mahajan et al. (2015), respectively.

The impact of obesity on gastric emptying is complex with some studies showing no difference (Buchholz et al., 2013; Zahorska-Markiewicz et al., 1986), some showing slower (Jackson et al., 2004) and others showing faster gastric emptying in obese subjects (BMI = 45.3–58.0 kg/m²) compared to controls (BMI = 20.3–24.8 kg/m²) (Tosetti et al., 1996).

Intestinal transit has been measured in obese (BMI = 34.0–43.6 kg/m²) and normal-weight subjects (BMI = 20.0–26.6 kg/m²) and similar intestinal transit times have been reported (Wisen and Johansson, 1992). However, the same study showed that the obese population absorbed 74 ± 4% of the total liquid test meal compared to 50 ± 5% absorbed in the lean control group. This increased energy uptake may be related to the need for energy transfer to the relatively larger organs present in the obese subjects (Wisen and Johansson, 1992).

The total bile acid concentration was comparable between normal weight (mean BMI = 23.2 kg/m²) and obese populations (mean BMI = 47.2 kg/m²) in the fasted state (Diakidou et al., 2009). However, the postprandial concentrations of bile salts were much reduced in obese compared to control populations (Glicksman et al., 2010).

Intestinal transporter expression was investigated in obese compared to non-obese subjects and the following differences were reported: decreased glucose transporter 5 expression (Deal et al., 2018), reduced amino acid nutrient transporter expression (Irving et al., 2016), increased short-chain fatty monocarboxylate acid transporter expression (Irving et al., 2016), increased levels of CYP1A2 and glucose transporter 4 (Miyachi et al., 2016).

The above differences in GI physiology between normal weight and obese, can indicate potential differences in drug absorption. However, to date there are no reports on the impact of obesity on drug absorption, whereas there are several studies reporting on the distribution and clearance of drugs in obese patients (e.g., Abdussalam et al., 2018; Greenblatt et al., 2018; van Rongen et al., 2018).

3.7. Pregnancy

The effect of pregnancy on drug absorption has been studied using clinical pharmacological tools (i.e., by studying the PK of drugs that are metabolized or transported by a specific enzyme or transporter, and can therefore serve as probe substrates to reflect the activities of the involved enzyme/transporter), as well as via physiological measurements of relevant mechanistic determinants of the absorption process. In terms of gastric acid secretion, several previous reviews report increased gastric pH during pregnancy (Costantine, 2014; Pariente et al., 2016). However, looking back to several original studies, which addressed heartburn during pregnancy, learns that there are also reports of no major changes in gastric pH taking place between the different trimesters of pregnancy and the non-pregnant situation. In these studies also no significant effect of pregnancy on basal and peak acid outputs could be found, suggesting that changes in gastric acidity may not be that prominent (O’Sullivan and Bullingham, 1984; Van Thiel et al., 1977).

In terms of gastric emptying, it has been demonstrated using ultrasound studies that gastric emptying time for liquids does not appear to be affected by pregnancy (Chiloiró et al., 2001). In line with this, it was found that the absorption of acetaminophen (maximum plasma concentration (Cmax), time to Cmax (Tmax)), was not altered by pregnancy over the trimesters and compared to non-pregnant women (Whitehead et al., 1993). The authors reasoned that due to the very rapid absorption of this drug from the small intestine, gastric emptying will be absorption-limiting. Hence, the fact that no differences occur in absorption profile also led them to conclude that gastric emptying times are not very different between trimesters. Nevertheless, overall GI transit time was found to be longer in the third trimester, indicative of an overall lower intestinal motility (Chiloiró et al., 2001). Consequently, intestinal absorption may be delayed during pregnancy
possibly resulting in slower $T_{\text{max}}$ and lower $C_{\text{max}}$ values for drugs in which the intestinal transit time is the rate-limiting step.

The ultimate bioavailability of drugs is also determined by enteric first pass metabolism, the extent of which can be affected by changes in the expression of drug metabolizing enzymes. The same holds true for compounds that are subject to active transport. The changes in expression of metabolizing enzymes and transporters are in many cases secondary to changes in hormone levels, such as progesterone, oestrogens or cortisol. Substrates of CYP3A4 (e.g., midazolam), CYP2D6 (e.g., fluoxetine), CYP2C9 (e.g., glibenclamide), as well as UGT1A1 (labetalol) and UGT1A4 (lamotrigine), experience increased enzyme activity during pregnancy, which may result in lower bioavailabilities. In contrast, activity of CYP1A2 (caffeine) and CYP2C19 (proguanil) decline during pregnancy, hence an opposite effect may be expected (Fischer et al., 2014; Hebert et al., 2008; Hebert et al., 2009; Heikkinen et al., 2003; Knutti et al., 1981; McGready et al., 2003; Ohman et al., 2008; Wangboonskul et al., 1993). However, as overall oral bioavailability is also determined by hepatic first pass metabolism, it remains difficult to delineate to which extent the changes in PK are the result of changes in enzyme expression occurring in the gut. Although limited direct data is available on the expression of drug metabolising enzymes and transporters in the intestine during pregnancy, changes in activity may be derived from clinical PK studies that have investigated drug disposition after oral administration during pregnancy and the non-pregnant situation (Broe et al., 2014; Deligiannidis et al., 2014; Leke et al., 2018; van der Galiën et al., 2019). Quantitative proteomic analysis of the expression levels of transporter and different CYP and uridine 5’-diphospho-glucuronosyltransferase (UGT) enzymes in the intestine of pregnant women will help to address this question further (Groer et al., 2014; Miyauchi et al., 2016).

An improved understanding of quantitative changes in the expression levels of enzymes and drug transporters or the availability of useful probe substrates or endogenous markers that reflect enzyme and transporter activity would further improve our understanding of the impact of pregnancy on drug absorption. At the same time, this type of mechanistic information is useful to build better in silico PBPK models for prediction of oral absorption and bioavailability in this specific patient population, as reviewed in Section 6 of this paper and by others (Abduljalil et al., 2012; Ke et al., 2018).

4. Diseases in the GI tract

4.1. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is an umbrella term for inflammatory conditions that affect the GI tract, mainly the small intestine and the colon. The aetiology of IBD is not fully understood (Bilsborough et al., 2016). IBD includes two major inflammatory conditions of unknown aetiology, Crohn’s disease (CD) and ulcerative colitis (UC). Both are associated with a variety of intestinal and extra-intestinal features. Extra-intestinal manifestations are usually related to intestinal disease activity and may precede or develop concurrently. However, the GI areas that are affected can be quite different in CD and UC (Hendrickson et al., 2002).

Fig. 1. Components of the mucosal barrier in healthy gut (left) and inflammatory bowel disease (IBD) (right). For detailed explanation, please refer to (Michielan and D’Inca, 2015). The basic structure of tight junctions and other junctional complexes are shown in the bottom-right box. JAM: junctional adhesion (copied from (Michielan and D’Inca, 2015) with permission).
Numerous review and research articles on the pathology, clinical presentation and treatment of CD and UC can be found in the literature. The major treatment goals of current therapies are to decrease the inflammatory reaction, minimize symptoms, improve quality of life, and minimize progression and complications of disease (Sairenji et al., 2017). Even though in many patients it is possible to induce and maintain phases of remission, in both diseases, chronic inflammatory changes of the intestinal epithelium dominate epithelial histology.

CD is a chronic transmural inflammation, i.e., it can affect the entire thickness of the bowel wall, and also any segment of the GI tract from mouth to anus. The inflammation pattern is usually discontinuous with inflamed segments and so called “skip areas” of healthy tissue. The initial location of CD is most commonly in the distal ileum and the earliest mucosal lesions often appear over Peyer’s patches (Xavier and Podolsky, 2007). Approximately half of the patients suffer from inflammations that are localized in the distal ileum and proximal colon. The inflammatory reaction can also appear in the proximal parts of the small intestine and/or the colon and, in some patients, also the upper GI tract can be involved. Inflammation can decrease the functional surface area of the intestines, but results from various studies indicate that it also can increase intestinal tight junction permeability (Michielan and D’Incà, 2015). Increasing the pore size of intestinal tight junctions contributes to an increased tight junction permeation of larger molecules, but also bacteria. According to Michielan and D’Incà, CD patients display several defects in the many specialized components of mucosal barrier that regulate paracellular permeability (Michielan and D’Incà, 2015). A schematic comparison of the components of the mucosal barrier in the gut of a healthy subject and an IBD patient is given in Fig. 1 (Michielan and D’Incà, 2015).

UC shows a continuous distribution in the intestinal mucosa and is generally confined to the colon (Stein et al., 1999). It includes diffuse mucosal inflammation that extends proximally from the rectum to a varying degree (Xavier and Podosky, 2007). Occasionally, it extends into the terminal ileum (Hazlett et al., 2005). Histologically, UC involves the innermost lining of the colon. In conjunction with severe inflammation, an extensive superficial mucosal ulceration can be observed (Xavier and Podosky, 2007). Due to the presence of a significant number of neutrophils within the lamina propria and the crypts, microabscesses are formed and another common feature is the depletion of goblet cell mucin (Xavier and Podosky, 2007). Even though the inflammation is mainly restricted to the colon, there is evidence for some functional small intestinal abnormalities as well. Mourad et al. reported that small intestinal dysfunction is a common feature in UC patients (Mourad et al., 2017). With the intention of better understanding the impairment of small intestinal function in UC, they screened the relevant literature for case studies focusing on intestinal dysfunction in UC and summarized that even though the pathophysiology of the dysfunction has not been elucidated, there is evidence for a decrease in fluid, electrolyte, amino acid, fat, and carbohydrate absorption, as well as for a deranged intestinal motility (Xavier and Podosky, 2007).

Oral drug absorption in IBD patients is altered due to impaired mucosal barrier function. The type, pattern and severity of the disease is likely to determine whether the reduced total absorptive surface area, or the increased tight junction permeability, also referred to as “leaky-gut-syndrome”, will be the major determinant of the plasma profile of orally administered drugs. However, gut wall permeability is only one factor to consider when discussing oral drug exposure. GI parameters that affect rate, timing and site of in vivo drug release are of equal importance. Surprisingly, even though numerous articles and guidelines have been published on various aspects of diagnosing and treating IBD, a systematic review of how IBD affects GI parameters relevant to oral drug exposure is not available.

One of the major GI symptoms in both CD and UC is diarrhoea. Patients often present with severe and chronic diarrhoea. Consequently, GI transit in these patients can significantly differ from that in healthy patients. However, in CD patients, constipation is also a common symptom. It results from a so-called stricture resulting from thickening of the intestinal wall. Stricture involves narrowing of a small intestinal section and in the worst case can block the flow of digestive contents. GI transit of the luminal contents and dosage forms in IBD patients can thus be significantly different from healthy subjects.

In the recent past, several review and research articles on GI motility in IBD patients have been published. Bassotti et al. reviewed results from studies focusing on colonic motility in UC patients and summarized that UC patients present colonic motor abnormalities, including a lack of contractility and an increase in propulsive contractile waves (Bassotti et al., 2014). Yung et al. assessed GI pH, transit, and motility in 12 patients with known or suspected CD using a wireless-motility capsule (Yung et al., 2016). The motility index in stomach, SI and colon was significantly lower in patients with CD. Since this was the very first study with a wireless-motility capsule in CD patients, at this stage, these observations can only indicate a potential trend, but with the wireless-motility capsule technology, it should be possible to gain a much better insight into GI motility and transit in IBD patients in the near future.

Nugent et al. reviewed the literature with regard to intestinal luminal pH in IBD and concluded that some data indicate that colonic pH is reduced in UC patients, particularly in active disease (Nugent et al., 2001). They could not draw a definite conclusion on intraluminal pH in CD patients, but overall, pH conditions reported in the articles reviewed by Nugent et al. were quite similar to those in healthy controls.

There is currently next to no information available on small intestinal fluid properties and composition in IBD patients (Barkas et al., 2013). A bit more information is already available on colonic fluid properties. With the aim of characterizing the fluid composition in the ascending colon of fasted UC patients in relapse and in remission, Vertzoni et al. analysed the properties of ascending colonic fluid of twelve UC patients (Vertzoni et al., 2010). Of potential relevance for drug absorption, the pH was lower and the buffer capacity higher in IBD patients compared with healthy subjects. More recently, Müller et al. presented results from a study on assessing ascending colonic fluid composition, which indicate the presence and structure of some remnants of lipolytic products in the ascending colon of UC patients (Müller et al., 2013). However, as for the small intestine, there are still a lot of knowledge gaps to be filled and the same is true for gastric conditions.

In summary, it is obvious that IBD can affect oral drug absorption significantly, but there is a need to fill several essential knowledge gaps. When designing experiments for assessing essential GI parameters, the large inter- and intraindividual variability in pattern and severity of the inflammation in both CD and UC will require particular attention. Moreover, the increasing number of paediatric and adolescent patients, in whom IBD is often following a more complicated and aggressive course than in adult onset (Grover et al., 2017; Rosen et al., 2015), should be properly addressed.

4.2. Cancer in the GI tract

The GLOBOCAN statistic report for 2018 predicted a total of 18.1 millions newly diagnosed cases of cancer, together with expected 9.6 millions cancer-related deaths worldwide (Bray et al., 2018). Out of those numbers, colorectal cancer and gastric cancer rank third (10.2%) and fifth (5.7%) in total cancer incidence, respectively, while they are positioned as second (9.2%) and third (8.2%) cause of death among cancer patients (with pancreatic cancer causing 4.5% of deaths globally).

Primary treatments for GI cancer include surgical removal of the tumor tissue, chemotherapy, radiotherapy and targeted therapy (Gulbake et al., 2016; Orditura et al., 2014). Usual intravenous administration of chemotherapy causes various side effects like nausea, vomiting, neutropenia, hematological disorders, and general fatigue (Lin et al., 2015) due to unspecific activity of drugs on both cancer and healthy cells. In order to avoid these effects, targeted
delivery of drugs to the GI tract could offer a much-needed replacement, also with the convenience of patients in mind (Amidon et al., 2015; Banerjee et al., 2017; Derakhshanbakh et al., 2017). Well-designed oral chemotherapy can result in low plasma drug concentrations, and concomitantly achieve a prolonged drug exposure to the cancerous cells in the GI tract, resulting in better efficacy and fewer side effects than an intermittent parenteral chemotherapy (Joshi et al., 2014).

Gastric cancer causes changes in physiological function of the stomach manifested as delayed gastric emptying. While delayed gastric emptying has been reported as one of the features of gastric cancer (Tatsuta et al., 1990), it is also one of the most common postoperative syndromes of (partial) gastrectomy, which is a treatment for gastric cancer. As reported in several studies (Kim et al., 2017; Pradhan et al., 2017) delayed gastric emptying develops in 7% to 52% of patients that underwent distal gastrectomy, with this time declining in the post-operative period. However, a study by Chang et al. including 28 patients with non-obstructive gastric cancer, showed no difference in water gastric emptying time compared to control group (15.51 +/- 2.21 and 16.82 +/- 2.13 min, respectively) (Chang et al., 2004). Delayed gastric emptying represents burden for the patients, but also an important fact for the physicians in determining the medication dosage.

The gastric pH has been found to be as high as pH 6–7 in gastric cancer patients (n = 89) (Lu et al., 2010). This increase in the pH of gastric juices is explained by gastric atrophy, which results in reduction of parietal cell mass and cause reduction or absence of detectable gastric acid (Ghosh et al., 2011). Human gastric cancer cell lines were found to have an increased expression of membrane transporters belonging to ABC and the family of efflux proteins, such as multidrug-resistance-associated protein 1 (Obuchi et al., 2013). Inhibition of these and other efflux carriers (e.g., reduced folate carrier 1, multidrug-resistance-associated protein 5, monocarboxylate transporter 4) represents an option to increase cancer cell susceptibility to locally acting cancer drugs (Lee et al., 2016). Other potential targets of drug action, besides efflux transporters, are proposed in reviews by Yu and Xie (2008). Increased expression of drug efflux transporters (P-gp, BCRP, multidrug-resistance-associated protein) in colorectal cancer cells (Hu et al., 2016) accompanied with increased glycosylation of the transporters and other molecules on the cancer cell membrane (Very et al., 2018) has been reported. The expression of certain drug transporters also correlates with the progression of the disease (Gotanda et al., 2013; Havata et al., 2012). In vitro models of drug absorption in cancer have been developed based on the expression of transporters in cancer cells in order to predict the absorption of drugs dosed in combination therapies (Bekusova et al., 2018).

Bekusova et al. found that the paracellular permeability (opening of tight junctions) in colorectal cancer varies depending on the tumour location. The tumour tissues were less permeable than the intact intestinal membrane, while the tumour-adjacent tissues exhibited an increased paracellular permeability (Bekusova et al., 2018). Passive transcellular absorption of drugs is also affected by neoplastic changes of the colonic cells. Changes in the properties of the transcellular transport systems in cancer cells should be considered when designing the new molecular entities intended for treatment of colon cancer.

As presented, cancer pathologies of the GI tract do affect drug absorption through the alteration of the GI tract physiology, in particular the modification or damage of the GI epithelium. These alterations require careful consideration when patients are treated with oral therapeutics to treat the disease itself or associated comorbidities such as diabetes or hypertension.

4.3. Roux-en-Y gastric bypass

The prevalence of obesity is growing (see above), and it is associated with an increased demand for bariatric surgery; especially Roux-en-Y gastric bypass (RYGB, Fig. 2) and sleeve gastrectomy are gaining ground. With a sleeve gastrectomy, there is only a restriction of the size of the stomach by creating a gastric tube (Neff and le Roux, 2014). When performing a RYGB, a small gastric pouch is formed and the proximal part of the small intestine is bypassed. The gastric remnant and bypassed biliary limb is reconnected to the intestine 75 to 150 cm distal to the anastomosis between the gastric pouch and distal part of the
the jejunum. These anatomical and physiological changes of the GI tract including changes in volume of the stomach, gastric pH, gastric emptying, inlet of bile acids, surface area for absorption and transit time, can all affect the intestinal drug absorption. This can result in altered drug disposition, namely decreased (Gesquiere et al., 2016), increased (Padwal et al., 2011) or comparable (Gesquiere et al., 2015) bioavailability after RYGB. A good insight into these changes is important as they can result in potentially dangerous over- or under-dosing. In this section, we focus on the changes following RYGB.

Gastric mixing promotes disintegration, which is required for drug absorption. Gastric mixing, and thus disintegration, may be reduced as the stomach volume is reduced after RYGB (Padwal et al., 2010). To avoid the need for disintegration, drugs can be administered as a liquid formulation, crushing/chewing solid formulation or as an odispersible formulation, if this is available for the drug involved.

A small gastric pouch, which is separated from the native stomach, is created in patients with a gastric bypass. In the study of Smith et al. (patients with RYGB: n = 10; controls: n = 15), the gastric acid secretion from the gastric pouch was markedly reduced compared to the gastric acid secretion from the total stomach of age- and sex-matched control subjects (Smith et al., 1993). This was the case for both the basal secretion (mean ± Standard error of the mean: 0.01 ± 0.01 mEq/h post-RYGB vs. 4.97 ± 0.66 mEq/h in the control group) and the pentagastrin-based stimulated secretion (0.08 ± 0.04 mEq/h post-RYGB vs. 12.11 ± 1.34 mEq/h in the control group) (Smith et al., 1993). These findings were confirmed by Behrens et al. (Behrens et al., 1994), indicating that the gastric acid secretion after gastric bypass is negligible as most of the parietal cells (i.e., acid-producing cells) are bypassed. This results in an elevated gastric pH, which will have an impact on the solubility of drugs as it influences the ionization (De Smet et al., 2013). Basic drugs will have a decreased solubility after RYGB as there is less ionization, and acidic drugs will have an increased solubility, as there is more ionization. In modelling studies, an average pH of 6.6 was set to stimulate the gastric pouch after RYGB in fasted state (Darwich et al., 2012; Seaman et al., 2005). An in vitro analysis of the dissolution of psychiatric medications after RYGB showed that the dissolution of 10 out of 22 drugs was significantly reduced, while two drugs had significantly greater dissolution in a post-RYGB environment in comparison with a control environment (Seaman et al., 2005). The level of dissolution gives no direct information on the therapeutic effect of drugs, but it provides already an indication of the level of absorption since the absorption of drugs is often limited by the dissolution rate.

Gastric content, hormones and neural influences regulate gastric emptying. It has been shown by different methods (e.g., D-xylene test, paracetamol test and scintigraphic measurements) that gastric emptying for liquids is accelerated after RYGB (Dirksen et al., 2013; Horowitz et al., 1982; Mornigo et al., 2006; Näslund and Beckman, 1987; Wang et al., 2012). Oral administration of a liquid drug may therefore result in faster absorption and in a shorter time to reach Cmax. The influence of RYG on gastric emptying for solids is more controversial, as Horowitz et al. have shown that the gastric emptying for solids is slower postoperatively, while Dirksen et al. have shown that it is faster (Dirksen et al., 2013; Horowitz et al., 1982).

RYGB is associated with alterations of the anatomical structure of the upper intestinal tract, which could affect the enterohepatic re-circulation of bile acids. The inlet of bile acids and pancreatic juices in the small intestine is delayed, thus the interaction between these compounds and food/drugs is delayed (Neff et al., 2013). These changes have mainly an impact on lipophilic drugs as they depend on bile acids for their dissolution/solubility. Furthermore, lipophilic drugs often undergo enterohepatic recirculation, influencing its steady-state concentration (Padwal et al., 2010). Patti et al. showed that, in individuals who had undergone a RYGB 2–4 years before (n = 9), the serum concentration of bile acids was more than twofold higher than in overweight (n = 10) or severely obese individuals (n = 5) without bariatric surgery (Patti et al., 2009). This was the same for the individual bile salts taurodeoxycholic, glycocholic, glycochenodeoxycholic, and glycocoxycholic acids. This has been confirmed by Simonen et al. (n = 30) (Simonen et al., 2012), who have also shown that the total serum bile acid concentration in fasted state was twofold increased post-RYGB. However, the increased secretion of bile acids may not be sufficient to compensate the delayed inlet as it has been shown that the absorption of fat is reduced after RYG, as mentioned before (Carswell et al., 2014; Kumar et al., 2011; Odstrcil et al., 2010).

Dirksen et al. have studied the small intestinal transit time after a meal by a scintigraphic technique in 17 patients who had undergone a RYG more than a year before and in 9 healthy control subjects. They have shown that the small intestinal transit time was longer in patients with RYGB compared to control subjects (Dirksen et al., 2013). This does not entirely correspond with the findings of Morinigo et al., who observed that, by performing a lactulose breath test, the oro-caecal transit time was shorter in RYGB-patients. However, the oro-caecal transit includes pouch emptying and small intestinal transit, so it reflects not only the intestinal transit time (Morinigo et al., 2006). Carswell et al. have also measured the oro-caecal transit time using sulphalamazine. In this study, RYG had no impact on the oro-caecal transit time (Carswell et al., 2014). Dirksen et al. have also determined the colonic transit time, which was unaltered after RYG (Dirksen et al., 2013).

By performing a RYGB, a part of the stomach and the proximal small intestine is bypassed resulting in a reduction of the functional GI length (Neff et al., 2013). Moreover, the proximal small intestine has the largest surface area of the GI tract by the presence of villi and microvilli. A bypass of the duodenum and the proximal part of the jejunum results in a large reduction of the surface area for absorption (Miller and Smith, 2006; Spak et al., 2010). This can have an impact on the bioavailability of drugs, especially since most of the orally administered drugs are maximally absorbed in the small intestine (Padwal et al., 2010). Besides, Spak et al. have shown that the appearance of the mucosa of the Roux-limb is altered 6–8 months after the surgery (Spak et al., 2010). They showed that the height of the villi was decreased after RYG, which also contributes to the reduction of the surface area. However, cell proliferation was increased, which might be a compensatory mechanism for the loss of cells at the tips of the villi.

The influence of drug metabolism and drug efflux may vary over distinct parts of the intestine (Padwal et al., 2010). The expression of P-gp increases from the proximal to the distal small intestine, while the expression of CYP450 enzymes is the highest in the duodenum and jejunum and decreases to more distal sites (Stappaerts et al., 2013). Bypassing parts of the small intestine with a high abundance of CYP450 iso-enzymes can therefore lead to alterations in oral drug bioavailability as there will be less metabolism and may thus increase the relative influence of P-gp. The majority of drugs enter into the systemic circulation by passive diffusion from the GI tract, provided that they are non-
Celiac disease

Celiac disease is an autoimmune disorder occurring in genetically predisposed individuals, in whom the ingestion of gluten, a protein from wheat, barley and rye, leads to an immune reaction in the small intestine. Celiac disease generally affects around 1% of the population worldwide (Lebwohl et al., 2018). The occurrence has increased over the past 50 years, and is higher in some countries, e.g., Finland, than in others, e.g., Germany (Lebwohl et al., 2018; Mustalahti et al., 2010). It is estimated that more than two million Americans with celiac disease are not diagnosed and can be at risk for long-term health complications. Prolonged gluten intake in undiagnosed patients can lead to an increase in the incidence of autoimmune diseases such as T1DM, IBD, autoimmune thyroiditis, and also an increased mortality rate (Ludvigsson et al., 2015; Rubio-Tapia and Murray, 2010). The current treatment of celiac disease is a gluten-free diet, and hereby most symptoms, but not all, can be alleviated (Lebwohl et al., 2018; Rubio-Tapia and Murray, 2010; Samsel and Seneff, 2013).

The classical symptoms of celiac disease include chronic diarrhoea and weight loss, but also symptoms like bloating, constipation, chronic fatigue, headache, abdominal pain, and osteoporosis are prevalent (Downey et al., 2015). Celiac disease is manifested in the small intestine as an increased number of intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy (Lebwohl et al., 2018; Rubio-Tapia and Murray, 2010). Most often, villous atrophy is found in the duodenum, but it can also affect more distal parts of the small intestine. The areas of villous atrophy tends to be patchy and are dispersed between regions of normal mucosa (Giacco et al., 2016). Villous atrophy results in a flattening of the microvilli, which in turn gives a decreased absorptive surface area in the intestine, which can impair the ability to absorb nutrients (Giacco et al., 2016; Samsel and Seneff, 2013). Accordingly, celiac disease is associated with deficiencies in iron, vitamin D3, molybdenum, selenium, and cobalamin (Samsel and Seneff, 2013). It is therefore possible that intestinal drug absorption will also be negatively affected. However, it is also well accepted that the intestinal permeability is increased, in part due to opening of tight junctions, which can potentially increase drug absorption (Heyman et al., 2012; Kuitunen and Savilahti, 1996; Vilela et al., 2008).

Details on other changes in the small intestine in untreated celiac disease are scarce. A single study has examined the pH on the jejunal surface in untreated patients and compared it with the pH of patients on a gluten-free diet. The study showed a significantly higher pH in untreated celiac disease patients, which also might impact absorption of ionizable drugs (Kitis et al., 1982). Another study by Lang et al. (1996) found that the activity of CYP3A4 was decreased in adult untreated patients, compared to healthy subjects, and Johnson et al. found the same for paediatric celiac disease patients (Johnson et al., 2001). This is likely to be related to the villus atrophy, as the CYP enzymes are primarily located in the apex of the enterocytes, in a band just below the microvillar border (Lang et al., 1996). This decrease in CYP3A4 is normalized when patients where on a gluten-free diet (Lang et al., 1996; Samsel and Seneff, 2013).

Celiac disease is associated with delayed gall bladder emptying and decreased pancreatic secretions (Benini et al., 2012). The fasting gall bladder volume and the post prandial residual volume are significantly higher in celiac disease patients compared to controls. These symptoms are reversible and disappear when celiac disease patients get on a gluten free diet. Unfortunately, the intestinal bile salt concentrations have not been determined in any of these patient groups (Benini et al., 2012; Usai-Satta et al., 2018).

In general, the mouth-to-caecum transit time has been reported to be slower in untreated celiac disease patients, compared to healthy controls, but the literature does not agree as to whether this is normalized when patients are on a gluten-free diet (Benini et al., 2012; Chiarioni et al., 1997). The gastric emptying time is prolonged in untreated celiac disease patients, but is normalized upon intake of a gluten-free diet (Benini et al., 2012; Elli and Bardella, 2005; Perri et al., 2000). In addition, the transit time of a meal through the small intestine is delayed in celiac disease patients, probably due to functional alteration of small intestinal motility, whereas there are no changes in the colonic transit time (Benini et al., 2012; Usai-Satta et al., 2018). An abnormal gastrointestinal motor activity, indicating a neuropathic disorder, in untreated celiac disease patients has been observed and this is persisting in most adult celiac disease patients also during a gluten free diet (Bassotti et al., 2008; Benini et al., 2012). The mechanism involved in this remains unclear, but there might be a low-grade mucosal inflammation even on a gluten-free diet. This in turn has recently been connected to an intestinal sensorimotor dysfunction (Usai-Satta et al., 2018).

The microbiota in celiac disease patients has been shown to be altered, as compared to healthy subjects. Often reduced levels of the commensal bacteria Enterococcus, Bifidobacteria and Lactobacillus are found, together with an overgrowth of pathogenic gram-negative bacteria (Di Cagno et al., 2011; Sanz et al., 2011). A gluten-free diet will change the microbiome, but this is also the case in healthy individuals.

Drug absorption studies in treated and untreated celiac disease patients mostly date back to the 70ties and 80ties and all involve a rather low number of patients (up to 14), and often lack proper controls. In these studies, many drugs showed a higher absorption in celiac disease patients, as compared to control subjects (propranolol, cephalaxin, clindamycin, sulfamethoxazole, trimethoprim and methyldopa), whereas paracetamol and practolol displayed a lower absorption (Tran et al., 2013). Thus, a conclusion on the impact of celiac disease on drug absorption cannot be drawn on this point. However, the physiological changes described above make it possible that drug absorption is altered, but more clinical studies in untreated celiac disease patients are needed.

4.5. Lactose intolerance

Lactose intolerance is the consequence of decreased or absent lactase activity in the brush border of the small intestinal epithelium resulting in malabsorption of lactose in the small intestine and fermentation of it in the large intestine. The primary effect concerning drug absorption is related to the osmotic effect of the non-absorbed lactose that also results in diarrheal symptoms. The prevalence of lactase deficiency has been described in most regions of the world and in people with diverse ethnic backgrounds. However, the prevalence of lactose malabsorption and lactose intolerance is unclear due to methodological limitations. The lowest prevalence was seen in Europeans and European Americans and higher prevalence in African Americans, Hispanics, Asians, Asian Americans, and Native Americans (Suchy et al., 2010). Particularly, Asian populations present higher prevalence of lactose intolerance, which originates from the high prevalence of lactase deficiency in these populations (Goh et al., 2018).

The effect of lactose intolerance has most extensively been investigated in patients undergoing thyroid hormone replacement therapy. Lactose intolerance can cause malabsorption of levothyroxine: eliminating lactose from the diet leads to decreased values of thyroid-stimulating hormone in the serum of patients with both Hashimoto thyroiditis and lactose intolerance, indicating less effective absorption of the drug (Asik et al., 2014; Cellini et al., 2014; Munoz-Torres et al., 2006). Therefore, in patients resistant to levothyroxine therapy, lactose intolerance should be considered as a cause. The most recent advance concerning levothyroxine therapy is the development of a novel oral...
liquid preparation that has been shown to overcome different malabsorption conditions (Fallahi et al., 2017).

Another study investigated the absorption of isoflavones, which have preventive effects against loss of bone mass and cardiovascular diseases. Serum isoflavone metabolites were measured in participants with and without evidence for lactose malabsorption. Interestingly, the lower absorption of isoflavone glucosides induced by low lactase activity was compensated by bacterial deglycosylation in the large intestine in humans. Therefore, the effect of lactose intolerance on drug absorption depends on the chemical properties of the drug in question, as well as the extent to which the colon participates in drug assimilation processes (Tamura et al., 2008).

4.6. Infectious diseases of the gastrointestinal tract

GI tract infections include acute and chronic disorders of the digestive apparatus induced by viruses, bacteria, and parasites. Most GI tract infections are self-limiting and exhibit acute symptoms lasting 5 to 7 days. However, in some cases the symptoms can persist over a longer period of time and result in a prolonged, persistent, or even chronic disease state. Typical symptoms comprise diarrhea, nausea, vomiting, abdominal cramping, fever, and/or dysentery. Nausea is typically associated with an increased stomach emptying time. In case of diarrhea the intestinal motility is often increased which results in a shorter intestinal transit time (Higgs et al., 1975; Spiller, 2006). The overall stool volume is increased and the viscosity of intestinal contents decreased compared to a healthy gut (Schiller, 1999). Finally, GI tract infections can also result in the damage of the intestinal membrane barrier (Barnes and Townley, 1973; Ford et al., 1985) and are often linked to the disruption of the intestinal microbiota system (Aebischer et al., 2006; Kuehl et al., 2005; Sekirov and Finlay, 2009).

The impact of the pathophysiology of GI tract infections on oral drug absorption largely depends on the type, severity, and duration of symptoms. The increased stomach emptying time, associated with nausea and vomiting, delays the onset of action of medications and may result in uncontrolled or sub-therapeutic plasma concentrations. The selection of appropriate dosage forms, such as sublingual or orally disintegrating tablets, suppositories, or parenteral formulations is therefore particularly important in the treatment of patients exhibiting nausea or concomitant diseases.

The decrease in intestinal transit time can significantly affect the absorption of drugs exhibiting an absorption window or pre-systemic metabolism as observed with tacrolimus and cyclosporine. Tacrolimus is rapidly absorbed in the duodenum and jejunum. The absorption is limited by the efflux-transporter P-gp, and tacrolimus undergoes extensive pre-systemic metabolism by CYP3A4 in the gut wall, which both reduce the oral bioavailability to approximately 20%. In gastroenteritis patients, P-gp-mediated efflux and pre-systemic metabolism are reduced due to impaired enterocytes. This results in significantly higher tacrolimus trough levels (Eades et al., 2000; Hochleitner et al., 2001). The opposite effect is observed with cyclosporine A. Cyclosporine A is subject to an absorption window in the small intestine, and the residence time in this segment was shown to be an important determinant of oral cyclosporine exposure (Drewle et al., 1992). In gastroenteritis patients, the increased GI motility and reduced residence time in the gut was shown to significantly reduce the oral cyclosporine exposure.

The impact of membrane damage on oral exposure is difficult to predict and can result in either an increase or a decrease in drug absorption. The loss in mucosal integrity results in an increased permeation of compounds, while villous shortening reduces the absorptive surface area and thus may reduce the total absorption of compounds (Ford et al., 1985). This severe condition directly influences the absorption of oral compounds exhibiting permeability-limited exposure or which are intended for local activity, such as vancomycin (Oami et al., 2017). Such damage typically occurs in case of prolonged symptoms or massive diarrhea, and therefore, it must be kept in mind that a specific drug may show different absorption behaviour depending on the length and severity of the GI tract infection (Bolme and Margareta, 1975; Nelson John et al., 1972). Little is known about the impact of GI tract infections on the expression and activity of membrane transporters. The intestinal gut membrane typically regenerates within 2-4 weeks and the absorption of oral compounds may still be altered after the recovery from clinically evident GI tract symptoms.

The microbial imbalance occurring during GI tract infections is critical for drugs that are activated or inactivated by the intestinal microbiome (Li et al., 2016), as reported for several compounds including immunosuppressant, antineoplastic, and cardiovascular medicines (Enright et al., 2016). The impact of the intestinal microbiota system on oral drug absorption is particularly critical for low solubility and/or low permeability compounds, as well as for extended release formulations, which are subject to long residence time in the gut and may therefore interact with the intestinal microbiome.

The impact of infectious GI tract diseases on oral drug absorption is very variable and difficult to predict a priori. It does not only depend on the type, severity, and duration of GI symptoms, but also the specific biopharmaceutical properties of the compound and its dosage form. In the absence of predictive biopharmaceutical methods simulating such altered GI tract conditions, a good mechanistic understanding of the absorption behaviour of the drug (e.g., absorption window, permeability- vs. solubility-limited absorption etc.) is key for estimating the impact of GI tract infections on oral exposure. Attention must be directed towards medicines with a narrow therapeutic index, for which careful plasma concentration monitoring should be considered to ensure safety and efficacy.

4.7. Helicobacter pylori infection

_Helicobacter pylori_ (H. pylori) is a highly prevalent pathogen causing a chronic inflammation of the gastric mucosa. The clinical outcome ranges from an asymptomatic gastritis to serious conditions such as peptic ulcer or gastric cancer.

_H. pylori_ infection is known to induce alterations in some physiological functions of the stomach, particularly affecting gastric acid secretion and GI motility. The impact on gastric acidity depends on the severity of the infection and distribution of the affected tissue in the stomach. Inflammation in the antral region is associated with increased production of gastrin, which in turn increases acid secretion in the gastric corpus. However, if the corpus is affected by severe inflammation, the response to gastrin is greatly reduced, resulting in reduced capacity to secrete acid (El-Omar, 2006). Thus, _H. pylori_ positive subjects can exhibit either increased or decreased stomach acidity. Between 25 and 40% of patients also exhibit antral hypomotility and a delayed gastric emptying (Mearin et al., 1995; Miyaji et al., 1999; Thor et al., 1996). Furthermore, there is increasing evidence that _H. pylori_ infection affects the GI functions indirectly by influencing the brain-gut axis (Budzynski and Klopacka, 2014). This may have an impact on the pathophysiology of other organs than the stomach, and generate disturbances in permeability, motility and secretion along the entire GI tract (Budzynski and Klopacka, 2014; Gerards et al., 2001; Su et al., 2000).

The physiological changes induced by _H. pylori_ infection can have a significant impact on the drug absorption process and thus important clinical implications as highlighted in several systematic reviews (Fiorini et al., 2015; Lahner et al., 2009; Lahner et al., 2014). Particularly, oral compounds and formulations with pH-dependent solubility need careful evaluation when administered to _H. pylori_ positive patients, as observed with thyroxine (Centanni et al., 2006), L-dopa (Pierantozzi et al., 2006; Pierantozzi et al., 2001), and delavirdin (Shelton et al., 2000; Shelton et al., 2003). However, more research is needed to capture the pathophysiology of _H. pylori_ infections, its impact on the function of the entire GI tract, and thus, the clinical implications on oral drug absorption.
5. Systemic diseases that change GI conditions

5.1. Parkinson's disease

Parkinson's disease (PARKD) is a progressive neurodegenerative disease that is classically diagnosed after the manifestation of visible motor symptoms such as rigidity, bradykinesia, tremor and postural instability. However, there is a growing body of evidence supporting the hypothesis that non-motor features, especially a variety of GI symptoms could be considered as early biomarkers since they are prevalent among confirmed patients and occur much earlier than the cardinal signs of PARKD, i.e., the motor symptoms (Pfeiffer, 1998; Poirier et al., 2016).

A thorough understanding of the broad spectrum of clinical manifestations of PARKD is essential for a proper diagnosis of the disease. There is evidence that pathological processes that lead to PARKD could be initiated in the enteric nervous system before spreading to the central nervous system. This would be an explanation for the early occurrence of GI symptoms, but to date the pathophysiology of the enteric nervous system component in the aetiology of PARKD is not completely understood (Poirier et al., 2016). According to numerous review articles on GI dysfunctions in PARKD patients published in the recent past, a more detailed picture of the presence and extent of GI dysfunction in PARKD is emerging and over the last decades many abnormalities or disturbances in function at virtually all levels of the GI system have been identified (Fasano et al., 2015; Jost, 2010; Kim and Sung, 2015; Pfeiffer, 2011; Poirier et al., 2016; Su et al., 2017).

A detailed understanding of how and to which extent the GI system is affected in which state of the disease would be essential for developing better oral PARKD medications. It would improve the estimation of how dosing regimens for orally administered drug might be affected by the stage of the disease (Wollmer and Klein, 2017) and the development of appropriate experimental models when the aim is to predict drug release and absorption in PARKD patients using in vitro and in silico tools.

With the aim of better predicting in vivo drug release and absorption of orally administered drugs in PARKD patients, Wollmer and Klein recently reviewed the literature for a reliable set of PARKD-specific GI parameters (Wollmer and Klein, 2017). They found that the level of detail of information available is limited and that reports focus on the discussion of general GI symptoms rather than specific GI parameters.

Typical PARKD-related GI symptoms range from oral issues, including drooling, swallowing problems, nausea, vomiting, early satiety, bloating and weight loss to constipation which is regarded as one of the most common symptoms (Fasano et al., 2015; Pfeiffer, 2011; Su et al., 2017). These symptoms are, however, just indicators of serious physiological alterations of several GI parameters including a reduced salivary secretion rate and an impaired motility of oesophagus, stomach, and the intestines amongst others. An altered GI environment and transit time may seriously affect PK of orally administered drugs. To date, this issue has been mainly discussed for orally administered PARKD drugs (Fasano et al., 2015; Pfeiffer, 2011), but is of equal importance for all other oral medications taken by a PARKD patient, not only in an advanced stage of the disease, but particularly in early phases, when motor symptoms are not yet developed and the patient is sometimes not even diagnosed with PARKD.

Based on their literature review Wollmer and Klein concluded that even though there is quite a reasonable set of data available on parameters, such as salivary secretion, oropharyngeal and oesophageal passage and gastric emptying, there is still a big lack in knowledge that would be required for addressing all parameters that might be relevant for drug release and absorption during a GI passage in a PARKD patient. The latter is particularly true for contractile motility patterns and pressures in the entire GI tract as well as for the small intestinal transit time. Moreover, it seems that to date next to no attention has been given to potential disease-related changes in GI fluid composition (Wollmer and Klein, 2017). With the availability of novel non-invasive diagnostic options, such as for instance the wireless motility capsule and magnetic resonance imaging and a proper test design, it will hopefully be possible to gather the required information in the near future.

5.2. Cystic fibrosis

Cystic fibrosis (CF) is an autosomal genetic disorder, caused by mutations in the CF transmembrane conductance regulator (CFTR) gene (Gelfond and Borowitz, 2013). World-wide, around 70-80.000 people suffer from CF. In the past, life expectancy for a CF patient was 15-20 years and it was therefore considered a fatal paediatric disease. However, in the last decades life expectancy has increased to 40-50 years, especially in developed countries (Bowen and Hull, 2015; Elborn, 2016). This is partly caused by prophylactic use of oral antibiotics to avoid pulmonary infections (Elborn, 2016).

The CFTR protein is responsible for ion transport across the epithelium, i.e., the lungs and the GI tract, including the pancreatic and hepatobiliary systems (Gelfond and Borowitz, 2013). Mutations in the
C. Stillhart, et al.  

European Journal of Pharmaceutical Sciences 147 (2020) 105280

CFTR protein results in an abnormal chloride and bicarbonate transport across the apical membrane of the epithelial cells. This in turn leads to the formation of thick, viscous mucus secretions in, e.g., the lungs and the GI tract (Fig. 3) (Bowen and Hull, 2015; Elborn, 2016; Gelfond and Borowitz, 2013). Most CF patients also have pancreatic insufficiency, as well as GI dysmotility disorders, such as gastroesophageal reflux, distal intestinal obstruction syndrome, and chronic constipation (Corral et al., 2016; Gelfond and Borowitz, 2013). Corral and co-workers recently reviewed gastric emptying and incidence of gastroparesis in CF patients. In general, a more rapid gastric emptying was seen in younger patients, whereas the overall CF population had a gastroparesis frequency of 38%, and this was higher for patients >18 years, and especially patients with diabetes (Corral et al., 2016).

The impaired pancreatic and intestinal bicarbonate secretion can lead to a decreased duodenal and jejunal pH, which influences the effect of the enterocoated pancreatic enzyme supplements, taken by CF patients to improve food digestion (Tang et al., 2009). The decreased duodenal and jejunal pH can therefore lead to low and variable absorption of drugs dosed in enterocoated formulations. All in all, the GI symptoms of CF patients often lead to poor nutrient and fat absorption (Duffield, 1996; Elborn, 2016), which in turn could be associated with a reduced absorption of orally dosed drugs, however, this is not clear from the literature. For example, lower and more variable drug absorption for lung transplanted CF patients, compared to non-CF lung transplanted patients has been observed for tacrolimus (Saint-Marcoux et al., 2005), whereas no difference in oral absorption compared to healthy volunteers was found for doxycycline (Beringer et al., 2012). Often studies of oral drug pharmacokinetics in CF patients are carried out without proper control groups (Touw et al., 2000), thus better controlled studies are needed in order to conclude if CF patients in general have impaired drug absorption.

5.3. Diabetes mellitus

Diabetes mellitus is a significant issue with approximately 8.5% of the adult population being affected (Sarwar et al., 2010). There are two main types of diabetes: Type 1 (T1DM), an autoimmune disease, where the body is unable to produce insulin, and Type 2 (T2DM) where insulin secretion is deficient or there is insulin resistance. T2DM is the dominant form in adults and is strongly linked to obesity.

Several authors have recently reviewed gastric emptying in T1DM and T2DM (Chang et al., 2010; Kashyap and Farrugia, 2010; Marathe et al., 2013). Delayed gastric emptying (diabetic gastroparesis) is observed in 30-50% of diabetic patients, with a similar prevalence between T1DM and T2DM. However, in some diabetic subjects, abnormally rapid gastric emptying can also occur (Chang et al., 2010; Marathe et al., 2013). Alterations in plasma glucose levels also have an impact on gastric emptying: severe hyperglycaemia slows gastric emptying of solids and liquids, whereas insulin-induced hypoglycaemia increases the gastric emptying rate, even in subjects with an underlying delay in gastric emptying (Chang et al., 2010). An increase in gastric pH is associated with diabetic gastroparesis (Hasler et al., 2008).

Wegener et al. investigated GI transit in insulin-treated diabetic patients (Wegener et al., 1990). Three aspects of GI transit were studied, i.e., gastric emptying (using scintigraphy), oro-caecal transit time (using a hydrogen breath test), and whole gut transit time (using appearance of indigocarmine in the stool). Both T1DM and T2DM patients were enrolled in the study, which was performed in the fed state. Gastric emptying was significantly delayed in diabetic patients compared to healthy controls. While the difference in median % gastric retention at 60 min was modest (approximately 69% vs. 72% in healthy controls), 35% of diabetic patients had a % retention at 60 min that was higher than the upper limit of the normal range. For oro-caecal and whole gut transit time, there was no significant overall increase in the diabetic group, although the proportion of subjects with prolonged oro-caecal transit time (>135 min) or prolonged whole gut transit time (>29 h) was higher in the diabetic group than in the control group (23.0% vs. 3.6% for oro-caecal, and 25.6% vs. 3.0% for whole gut transit time). This remained significant when patients with prolonged gastric emptying time were removed from the analysis. No patient had abnormal transit times in all three compartments reported (gastric, small intestinal, and mouth to caecum), suggesting that there was an impact on specific segments of the intestine rather than an overall effect on the whole GI tract. The presence of autonomic neuropathy correlated significantly with delayed gastric emptying, although there was no significant difference in oro-caecal or whole gut transit time in patients with or without autonomic neuropathy. This is in contrast to the work of Scarpello et al., who reported a significant prolongation of oro-caecal transit time in diabetic patients with autonomic neuropathy versus patients without autonomic neuropathy or healthy volunteers (hydrogen appearance time 140.2 min compared to 69.8 or 70.8 min, respectively) (Scarpello et al., 1976). This study was performed in the fasted state.

Increased intestinal permeability has been reported in patients with T1DM and T2DM and in animal models of the disease, as assessed by sugar permeability tests (Vaarala et al., 2008; Zhong et al., 2016). This is attributed to a more permeable mucosal barrier (‘leaky gut’), due to intestinal inflammation and altered interepithelial tight junctions caused by hyperglycaemia (Thaiss et al., 2018).

Chronic diarrhoea is a common symptom of diabetes, occurring in 10–22% of patients. 43% of patients presenting chronic diarrhoea show evidence of small intestinal bacterial overgrowth (Virally-Moned et al., 1998). Cuoco et al. demonstrated that treatment of small intestinal bacterial overgrowth with antibiotics accelerated oro-caecal transit time in the majority of diabetic patients (62%) (Cuoco et al., 2002). There is growing evidence that the composition of the intestinal microbiota in T2DM patients is different compared to healthy controls, e.g., a lower amount of butyrate-producing bacteria is reported (Tilg and Moschen, 2014). Disebios of the microbiota caused by, e.g., antibiotic therapies and low-fibre diet, results in reduced production of short-chain fatty acids, which impacts the pathogenesis of T2DM (Aw and Fukuda, 2018).

Antidiabetic agents can also have a significant impact on GI conditions. Metformin is widely prescribed in T2DM, and up to 25% of subjects suffer from GI side effects (McCredie et al., 2016). Its effects on the GI tract were recently reviewed by McCredie et al. (2016); key mechanisms of interest form a biopharmaceutics perspective are briefly summarised here. Metformin increases intestinal glucose uptake, which is the basis of an interaction with the imaging agent F-18-fluorodeoxyglucose. However, the mechanism by which metformin increases glucose uptake is currently unclear. Metformin was also shown to increase glucagon-like peptide 1 (GLP-1) concentration in mice and in humans, probably through an increase in GLP-1 secretion. GLP-1 can slow down gastric emptying (Marathe et al., 2013), although there do not appear to be any reports that directly make this link for metformin. Metformin has structural similarities to 5-hydroxytryptamine agonists, and stimulates the intestinal release of 5-hydroxytryptamine in vitro. 5-hydroxytryptamine release in the intestine is associated with nausea, vomiting and diarrhoea, and it is hypothesised that this could be one mechanism responsible for the GI side effects observed with metformin. Finally, metformin increases the concentration of bile acids in the small intestine by reducing their ideal absorption and it alters the gut microbiome in mouse and human.

GLP-1 agonists used to treat T2DM, such as exendin, have GI side effects including nausea and diarrhoea. These agents can slow down gastric emptying through their pharmacological action on GLP-1 receptors (Marathe et al., 2013). Exendin administered twice daily delays gastric emptying in a dose-dependent manner; the half-emptying time for the solid component of a test meal was increased by 1.9- and 2.8-fold for 5 μg and 10 μg exendin doses, respectively, and for the liquid meal components increased by 2.6- and 3.4-fold, respectively (Linnebjerg et al., 2008). The impact of long-acting GLP-1 agonists on
gastric emptying appears to diminish with time, whereas this is not the case for short-acting GLP-1 agonists (Marathe et al., 2013).

In summary, several aspects of GI conditions can differ between diabetic patients and healthy subjects, which could impact drug product performance in this patient group. Delayed gastric emptying could lead to reduced or delayed Cmax. The longer time spent in the gastric environment could alter dissolution for drugs with pH-dependent solubility, increasing the time available for dissolution of basic compounds in an acidic environment where they are more soluble, and delaying the arrival of weakly acid drugs in the small intestine where the majority of dissolution will occur for these compounds. There could also be an increase in degradation of drugs which are unstable in an acidic environment. Increased rate and extent of absorption may be observed for compounds that normally exhibit permeability-limited absorption. For drugs which are subject to bacterial metabolism (either for activation or clearance), the presence of small intestinal bacterial overgrowth could result in increased bacterial degradation, and occurring at an earlier site in the small intestine before significant absorption has occurred, and the potentially altered microbiome composition could result in different metabolic profiles. The side effects of antidiabetic medications can also affect several aspects of GI functions, representing an additional source of absorption variability in this patient population.

5.4. HIV enteropathy

Patients infected with human immunodeficiency virus (HIV) or patients who develop acquired immunodeficiency syndrome (AIDS) have reduced immune response that often leads to other comorbidities. The most common ones are of GI origin, including symptoms such as diarrhea, weight loss, vomiting, nausea, and dysphagia (Lim et al., 1993; Malebranche et al., 1983). In addition, patients with HIV/AIDS develop certain types of cancer, among which GI malignancies, more often compared to non-HIV infected patients (Coghill et al., 2015).

HIV enteropathy is a condition characterized by persistent diarrhea, without a pathogen isolated in the stool (Slavik, 2012). Many theories have been formulated to explain the possible cause(s) of diarrhea in HIV patients, however it remains unclear.

As previously shown, HIV affects the mucosal immune system of the GI tract mostly during the acute infection period, but then again the influence of HIV on lamina propria immune cells in later stages of the disease is also confirmed (Dikman et al., 2015). Consequently, the number of mucosal CD4+ lymphocytes is reduced as compared with peripheral CD4+ cells in the early stage of HIV infection, and the immune response to usual pathogens decreases (Mehandru et al., 2004). The number of CD4+ T cells correlates well with GI symptoms (Thompson et al., 2012). Mucosal CD4+ cells are more susceptible to depletion in contrast to peripheral CD4+ cells because of the expression of the specific co-receptor CCR5 (Brenchley and Douek, 2008; Poles et al., 2001). Inflammation and damaged epithelium (villous atrophy and blunting and crypt hyperplasia) altogether increase intestinal permeability (Batman et al., 2007; Brenchley and Douek, 2008; Sharpestone et al., 1999). Hence, studies have shown that HIV-positive patients have vitamin B12 deficiency due to the reduced permeation in intestines and steatorrhea as a result of decreased fat absorption (Ehrenpreis et al., 1994). Likewise, the changes in intestinal absorption can reduce the AUC or Cmax of some antituberculosis drugs, as tuberculosis represents a common comorbidity in HIV-positive patients (Gurumurthy et al., 2004; McLellan et al., 2012). On the other hand, in HIV-positive patients without chronic diarrhea, no significant change in plasma concentrations of antituberculosis drugs was observed (van Oosterhout et al., 2015). In addition, proton pump inhibitors or H2 antagonists, often administered to HIV positive patients, can decrease the absorption of antiretroviral agents by changing gastric pH, and consequently drugs solubility (Hughes et al., 2015).

Altered absorption in HIV infected patients may also be caused by the changes in the microbiota. Recent research suggests that microbiota can be considered as an organ, and as such it has its own pathology that can influence the functioning of other systems (Baquero and Nombela, 2012). HIV causes a decrease in certain types of gut bacteria such as Bacteroides, Lactobacillus and Clostridia. On the other hand, pathogenic bacteria like Prevotella and Proteobacteria are abundant resulting in an imbalance in the gut flora. Furthermore, the altered microbiota induces inflammation that affects the GI mucosa (Zevin et al., 2016). These can potentially lead to changes in drug absorption.

5.5. Critical Illness

Critically ill patients often depend on pharmacotherapy, however, they are in a condition in which drug disposition might have changed and pharmacotherapy might become erratic. Although oral drug administration is generally not the preferred route especially for life-saving drugs, there are nevertheless several reasons for selecting oral medications, i.e., absence of intravenous access, higher occurrence of side-effects with intravenous administration, absence of appropriate intravenous formulations (especially for the paediatric population).

Roberts and Hall reviewed drug absorption considerations in critically ill adults and identified mesenteric hypoperfusion, increased intestinal permeability, decreased functional absorptive capacity, and delayed gastric emptying leading to significant changes in oral drug absorption with higher and lower bioavailability (Kar et al., 2015; Roberts and Hall, 2013).

As inflammation has shown to alter drug metabolism and transport in the liver, it can be expected that this is also the case for the intestine (Aitken et al., 2006; Evers et al., 2018; Vet et al., 2016). Indeed, in vitro studies also show mostly a decrease in transporter gene and protein expression with inflammatory states as proinflammatory cytokine-induction, high altitude or response to enteropathogenic bacteria (Evers et al., 2018). At the same time, the complexity and interplay of drug metabolizing enzymes and transporters make it difficult at this time to predict the effect on drug bioavailability.

When drugs are given orally to sedated and non-sedated critically ill patients they are most often administered through gastric or duodenal feeding tubes. This might impose problems for some drugs, as the need to be crushed and suspended or dissolved, potentially can reduce stability or induce chemical characteristics resulting in sticking to tubes. Enteral administration and the alteration of the drug product may also significantly modify the rate and/or extent of drug release and absorption causing wide variability in serum concentrations, as described for different antibiotics (Roberts and Hall, 2013). A change in phenytoin plasma levels was found in patients after starting or discontinuing enteral feeding compared to normal oral administration, exposing them to increased risk of seizures. This observation suggests an interaction with enteral feeding, although the mechanism is not fully understood (Au Yeung and Ensom, 2000).

Besides the processes specific to oral absorption, other processes involved in drug disposition (i.e., distribution, metabolism, elimination) may be altered in the critically ill due to, e.g., body fluid shifts, alteration in protein binding or pH, renal or hepatic failure, or the need for life-sustaining measures as extracorporeal membrane oxygenation or dialysis (Thakkar et al., 2017). Polypharmacy is common in the Intensive Care Unit and further contributes to possible changes in oral drug absorption, e.g., by delaying gastric emptying, altering gastric and enteric pH, or inducing drug-drug interactions.

In summary, altered oral drug absorption has been observed in critically ill patients in the past. For these patients there are several disease-, co-medication-, and medical care-related factors that may affect oral exposure. This complexity represents a major challenge in predicting drug absorption or making dosing recommendations in this group of patients.
European Medicines Agency (EMA, 2016) have recently produced sorption such as formulation, and both the FDA (FDA, 2018) and the questions around intrinsic and extrinsic factors influencing oral ab-

chanistic absorption models (Agoram et al., 2001; Jamei et al., 2009) 
mimic the time-course of drug concentrations in plasma and tissues. 
integrate this physiological description with drug specific data to si-

mentalized based on known physiological data such as tissue composi-
tion, tissue volumes and blood flows (Jones et al., 2015). PBPK models 
intebrate this physiological description with drug specific data to si-
mulate the time-course of drug concentrations in plasma and tissues. 
PBPK models can also describe the processes of drug absorption with 
mechanistic absorption models. Commercial implementations of me-
chanistic absorption models (Agoram et al., 2001; Jamei et al., 2009) 
are now routinely used in the pharmaceutical industry to address 
questions around intrinsic and extrinsic factors influencing oral ab-
sorption such as formulation, and both the FDA (FDA, 2018) and the 
European Medicines Agency (EMA, 2016) have recently produced 
guidance documents on appropriate use of PBPK models. 

Since PBPK models follow a systems pharmacology approach, they 
include both system specific and drug specific data where system spe-
cific data refers to the physiology being simulated. When sufficient 
knowledge on the influence of disease or non-disease-related conditions 
on the GI physiology exists, this may be integrated into the models and 
the effects predicted. To verify an initially developed PBPK model and 
its assumptions, predictions should be confirmed with in vivo data from 
early clinical phases and in this context, a population PK (popPK) model 
which describes these data well, can be useful to refine a PBPK model 
(Kostewicz et al., 2014). In addition, when clinical data are available, 
verification of the special population-based PBPK model predictions can 
be performed (Suri et al., 2015). 

PopPK modelling is a statistical approach, typically applied to de-
scribe the sources of PK variability in in vivo data obtained in clinical 
studies in both healthy individuals and patients. Although popPK is 
usually considered a non-mechanistic approach, some physiological 
parameters can be incorporated in the models such as body size, age or 
organ function (Schlender et al., 2018). Furthermore, efforts are being 
undertaken to increase the physiological knowledge included in popPK 
models to describe the extent and rate of absorption. Due to ethical and 
practical considerations, patients representing special populations are 
often underrepresented in clinical trials. Nevertheless, a popPK ap-
proach can be applied to optimize study design to obtain optimal PK 
data. 

Several examples of simulations in special populations have been 
published. Perhaps the most studied is the paediatric population where 
reviews of the development and maturation of GI physiology have been 
published and implemented into commercial software platforms 
(Johnson et al., 2018; Samant et al., 2015). These paediatric absorption 
models provide an invaluable tool to guide formulation development in 
children although large gaps in understanding the underlying phy-
siology still exist and verification of the model performance is still 
limited (Kohlmann et al., 2017; Villiger et al., 2016). Other areas where 
oral absorption models are being applied is for modelling the influence 
of food (Tistaert et al., 2019) although effects of different diets is not 
well explored currently. The effect of changed GI pH on the absorption 
of ionisable drugs with pH dependent solubility is also studied and 
eexisting absorption models can account for these changes which could 
be relevant in elderly populations, as well as in those taking acid re-
ducing agents as co-medication (Cristofoletti et al., 2017), which is 
ofen the case for oncology patients. Within the commercial software 
tools, specific disease related PBPK models exist for hepatic and renal 
impairment (Hsueh et al., 2018; Wagner et al., 2017) and for different 
ethnicities (Barter et al., 2011), but these models include little to no 
information on differences in absorption between these populations. 
Publications have also reported PBPK models incorporating specific 
pathophysiological changes to capture drug-disease PK interactions 
(Rasool et al., 2015), but there is little done on diseases of the GI tract. 
For a more thorough review of applications of PBPK to enable perso-
nalized medicine a recent paper from Hartmanshenn is recommended 
(Hartmanshenn et al., 2016). 

PBPK and popPK modelling are complementary methods for char-
acterizing and predicting the impact of intrinsic and extrinsic factors on 
drug exposure. In order to describe and/or predict drug effects and 
inform special population-based drug dosing, the extension of popPK 
and PBPK models with a pharmacodynamic component is required 
(Fig. 4) (Kostewicz et al., 2014; Standing, 2017). 

7. How are special populations considered in regulatory 
guidance? 

Typical drug development requires clinical testing of medicines in a 
general population and can exclude special populations. For example, 
typical exclusion criteria in phase 1 and 2 trials include: adults aged 

Fig. 4. Schematic illustration of the role of physiologically based and popula-
tion pharmacokinetic/pharmacodynamics (PBPK/PD and popPK/PD) models 
towards guiding drug dosing in special populations.
| Regulatory guidelines that provide information on the inclusion of special populations in clinical testing. | Date of introduction | Body responsible | Title of guidance | Population included | Relevant content |
| --- | --- | --- | --- | --- | --- |
| General | 1997 | ICHE8 |  | | Obtaining pharmacokinetic information in sub-populations such as patients with impaired elimination (renal or hepatic failure), the elderly, sex, ethnic groups and children should be considered. Differences in population subgroups should be expected in pharmacokinetic and patient safety and efficacy factors. The population included in the final clinical trials will need to be representative of the population that will be later treated by the drug. Make reference to inclusion of women, pregnant women, special ethnic populations, pediatric populations. |
|  | 2003 | FDA | Prescription medicines - Study design, data analysis, and regulatory applications | | Refers to weight, excretory and metabolic functions, with specific attention to paediatric, elderly, sex, ethnic groups and children. |
|  | 2008 | FDA | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2008 | FDA | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2009 | ICH | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2010 | FDA | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2010 | FDA | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2011 | FDA | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2012 | Health Canada | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2013 | Health Canada | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2014 | FDA | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2015 | FDA | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2016 | FDA | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2017 | Health Canada | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2018 | Health Canada | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2019 | Health Canada | | | Refers to subpopulations with a specific paediatric decision tree |
|  | 2020 | Health Canada | | | Refers to subpopulations with a specific paediatric decision tree |
To determine whether the PK of a drug and its active metabolites are altered in patients with renal impairment to the extent that an adjustment to the dosage would be indicated, patients stratified by renal function based on GFR to determine the effect of decreased renal function on drug exposure and to guide dosing recommendations in patients who have impaired renal function.

Table 1 continued

| Title of guidance | Population included | Relevant content |
|-------------------|---------------------|-----------------|
| Pharmacokinetics in patients with impaired renal function — study design, data analysis, and impact of co-administered drugs | Patients stratified by renal function based on estimated glomerular filtration rate (eGFR) or estimated creatinine clearance (CrCl) | To determine whether the PK of a drug and its active metabolites are altered in patients with renal impairment to the extent that an adjustment to the dosage would be indicated. |
| Pharmacokinetics in patients with impaired renal function — evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function | Patients stratified by renal function based on GFR | To determine the effect of decreased renal function on drug exposure and to guide dosing recommendations in patients who have impaired renal function. |
| Pharmacokinetics in pregnancy — study design, data analysis, and impact of co-administered drugs | Pregnant women | Study participants should be representative of a typical patient population for the drug to be studied, including race, ethnicity, and trimester of pregnancy. |
| Pharmacokinetics in lactating women | Lactating women | Study participants are lactating women who are planning to receive or are currently receiving study medication. |
| Pharmacokinetics in obese patients stratified by WHO classification of obesity | Obese patients stratified by WHO classification of obesity (linked to BMI) | Specific mention of issues in absorption, "first pass" metabolism, and renal function. |
| Pharmacokinetics in patients with impaired renal function — study design, data analysis, and impact of co-administered drugs | Study participants who are planning to receive or are currently receiving study medication. |
| Pharmacokinetics in patients with impaired renal function — evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function | Study participants should be representative of a typical patient population for the drug to be studied, including race, ethnicity, and trimester of pregnancy. |
| Pharmacokinetics in pregnancy — study design, data analysis, and impact of co-administered drugs | Study participants should be representative of a typical patient population for the drug to be studied, including race, ethnicity, and trimester of pregnancy. |
| Pharmacokinetics in lactating women | Study participants are lactating women who are planning to receive or are currently receiving study medication. |
| Pharmacokinetics in obese patients stratified by WHO classification of obesity | Obese patients stratified by WHO classification of obesity (linked to BMI) | Specific mention of issues in absorption, "first pass" metabolism, and renal function. |

8. Conclusions

The process of oral drug absorption is complex and influenced by many compound- and GI physiology-related factors. The present review evidences how different demographic and clinical conditions can influence the environment in the GI tract, and thus, modify the kinetics of drug release and absorption when compared to the situation in a healthy adult (Fig. 6). Consideration of these alterations in GI tract physiology is key to ensure safe and effective use of oral medications. Patient-specific PBPK models and biorelevant in vitro tests, which can account for these changes in GI tract physiology, are extremely useful to anticipate oral drug exposure in patient populations. Such predictive tools can support dose finding, formulation selection, as well as the design and conduct of clinical studies. If sufficient confidence in a compound-specific PBPK model is given, it may even be used to waive clinical studies, for example to show bioequivalence between different formulations.

Although multiple studies have already addressed some aspects of GI tract alterations in specific clinical conditions and have highlighted how these changes can impact oral exposure, there still exist significant knowledge gaps in this area. The relevant parameters for oral absorption, such as the volume and composition of GI fluids or the expression level of enzymes and transporters, are often insufficiently characterised, <18 or >65 years; a BMI greater than 30 kg/m²; pregnancy; hepatic dysfunction (Tamboli et al., 2010). Phase 3 trials can have broader recruitment with increased age; increased divergence in ethnicity and inclusion of patients with co-morbidities. Regulatory guidance on special populations has related to differences in PK broadly, yet there is limited focus on the GI and absorption parameters within this recognition. The importance of non-clinical safety studies to support clinical testing in special populations is detailed in the ICH M3 guidance document (ICH, 2008). Clinical testing in special populations is detailed in ICH E8 guidelines (ICH, 1997) and a recent review on special populations in clinical research (Grimsrud et al., 2015).

Regulatory guidance on biopharmaceutics classification system (BCS) based biowaivers do not mention any special populations or allude to any additional risk mitigation; this may cause particular risks for certain special populations (FDA, 2017). In addition, bioequivalence studies are likely to be undertaken in a small population of males aged 18–40 years of the same ethnicity (Western), with a BMI < 30 kg/m² and healthy volunteers (FDA, 2014). Despite regulations stating that a mixture of males and females should be included in bioequivalence studies, there are issues in identifying what proportion of women are involved in some key studies (McGregor et al., 2017). There are differences in the requirements for bioequivalence testing in Japan due to the lower gastric acidity reported in this population (Tamboli et al., 2010). Also the dose number, which is defined as the ratio of drug concentration in the administered volume to its saturation solubility in water, is calculated using a 150 mL volume in Japan rather than the 250 mL volume used in the rest of the world (Takagi et al., 2006). This lower volume accounts for the lower volume of co-administered water in Japanese bioequivalence studies (Kuribayashi et al., 2016).

The paediatric decision tree that was first presented within FDA Guidance on exposure-response relationships (FDA, 2003a) provides a decision tree that might be used also for other special populations in terms of extrapolation of PK data from a healthy adult population. Increasingly, the use of in vitro and in silico tools to mitigate risks in special populations has been highlighted for paediatric (Batchelor et al., 2013), elderly (Thompson et al., 2009), obese (Ghobadi et al., 2011) and pregnant (Dallmann et al., 2018) populations. These tools are increasingly supported by the regulators to support dose finding for trials or even replace clinical trials in special populations (FDA, 2018).

Table 1 describes the guidance available that mention the inclusion of special populations in clinical testing and the timeline for the introductions is shown in Fig. 5.
which is limiting, for example, the development of disease-specific PBPK models. Moreover, a clinical condition often implies a particular setting in terms of medication and diet, such as co-medications, crushing of tablets, or co-administration of fibre-rich nutrition in elderly patients, which increases the complexity for anticipating the impact on bioavailability.

Further research is therefore required using new methods and diagnostic tools to generate physiological reference data and improve biopharmaceutical tools to ensure safe and efficacious drug therapies in the targeted patient population.

---

**Fig. 5.** Timeline of regulations (listed in Table 1) introduced to provide guidance on special populations.

| Sex                        | FDA | Health Canada |
|---------------------------|-----|---------------|
| Ethnicity                 | ICH | EMA           |
| Elderly                   | FDA | EMA           |
| Pediatric                 | FDA | EMA           |
| Hepatic function          | FDA | EMA           |
| Renal function            | FDA | EMA           |
| Pregnancy                 | FDA | EMA           |
| Breastfeeding             | FDA | EMA           |
| Obesity                   | FDA | EMA           |

| Age                        | FDA | EMA |
|---------------------------|-----|-----|
| Elderly                   | FDA | EMA |
| Pediatric                 | FDA | EMA |

**Fig. 6.** Overview of the main GI parameters influencing oral drug absorption (black) and the corresponding disease and non-disease related conditions that are known to alter these physiological properties (blue) [RYGB: Roux-en-Y gastric bypass; H. pylori: Helicobacter pylori; PARKD: Parkinson’s disease; CF: Cystic fibrosis; CD: celiac disease; IBD: irritable bowel syndrome; HIV: human immunodeficiency virus].

---
信用作者陈述

所有作者均对本评论作出贡献。

在 addition, Cordula Stillhart 和 Anette Müllertz 负责为

将个人部分放在一起并修订手稿。

声明竞争利益

没有。

承认

这基于本工作使用来自 COST Action UNGAP (CA16205)，支持由欧洲研究委员会在科学和技术方面。

参考文献

Abdeljilali, K., Furness, P., Johnson, T.N., Rostami-Hodjegan, A., Soltani, H., 2012. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. Clin. Pharmacokinet. 51, 365–396.
Abdussalam, A., Al-Agili, M., Al Nebahy, H.M., Mayo, P.R., Gahr, R.Q., Brocks, D.R., 2018. Dietary-induced obesity and changes in the biodistribution and metabolism of amiodarone in the rat. J. Pharm. Sci. 107, 2938–2945.
Adamska, A., Falasca, M., 2018. ATP-binding cassette transporters in progression and clinical outcome of pancreatic cancer: What is the way forward? World J. Gastroenterol. 24, 3222–3238.
Aebischer, T., Fischer, A., Walduck, A., Schlotterburg, C., Lindig, M., Schreiber, S., Meyer, T., Bereswill, S., Göbel, U., 2006. Vaccination prevents Helicobacter pylori-induced alterations of the gastric flora in mice. FEMS Immunol. Med. Microbiol. 46, 221–229.
Afonso-Pereira, F., Du, L., Trenfield, S.J., Madla, C.M., Murdan, S., Sousa, J., Veiga, F., Basit, A.W., 2018. Sex differences in the gastrointestinal tract of rats and the implications for oral drug delivery. Eur. J. Pharm. Sci. 115, 339–344.
Agoram, B., Wolotzky, W.S., Bolger, M.B., 2001. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. Adv. Drug Deliv. Rev. 50 (1), 541–567 Suppl.
Aitken, A.E., Richardson, T.A., Morgan, E.T., 2006. Regulation of drug-metabolizing enyzmes and transporters in inflammation. Annu. Rev. Pharmacol. Toxicol. 46, 123–149.
Amidon, S., Brown, J.E., Dave, V.S., 2015. Colon-targeted oral drug delivery systems: design trends and approaches. AAPS PharmSciTech 16, 731–741.
Ashik, M., Gunes, F., Binnetoglu, E., Eroglu, M., Bozkurt, N., Sen, H., Akbal, E., Bakar, C., 2018. Comparison of total and compartmental gastric emptying and antral motility by healthy men and women. Eur. J. Nucl. Med. 25, 1293–1299.
Berggren, S., Gall, C., Wolinitz, N., Kielund, M., Karlbohm, U., Hoogstijkstra, J., Schrénk, D., Lennernäs, H., 2007. Grosi et al. Protein expression of P-glycoprotein, MRP1, MRP2, and CYP3A4 in the small and large human intestine. Mol. Pharm. 4 (2), 252–257.
Bergstrom, C.A., Holm, R., Jorgensen, S.A., Anderson, Á.S., Artursson, P., Base, S., Borde, A., Box, K., Brewer, M., Dressman, J., Flegl, K.I., Halbert, G.K., Kontewicz, E., MacIntyre, M., Muenster, U., Thines, J., Taylor, R., Mullertz, A., 2014. Early pharmacological profiling to predict oral drug absorption: current status and unmet needs. Eur. J. Pharm. Sci. 57, 173–199.
Beringer, P.M., Owens, H., Nguyen, A., Benitez, D., Rau, A., D’Argenio, D.Z., 2012. Pharmacokinetics of docusamine in adults with cystic fibrosis. Antimicrob. Agents Chemother. 56, 70–74.
Bezerra, J.J., Vajjah, P., Abduljalil, K., Jamei, M., Rostami-Hodjegan, A., Tucker, G.T., Johnson, T.N., 2015. Does age affect gastric emptying time? A model-based meta-analysis of data from premature neonates through to adults. Biopharm. Drug Dispos 36, 245–257.
Bower, L., Ball, J., 2015. The basic science of cystic fibrosis. J. Paediatr. Child Health 25, 159–164.
Brandi, L., 2013. The prevalence and growth of obesity and obesity related illnesses in Europe. European Center for International Political Economy, Geneva.
Brazier, J., Targan, S.R., Snapper, S.B., 2016. Therapeutic targets in inflammatory bowel disease: current and future. Am. J. Gastroenterol. 3, 27 Supplements.
Blake, M.J., Abdel-Rahman, S.M., Pearce, R.E., Leeder, J.S., Kearns, G.L., 2006. Effect of oral drug absorption in human subjects. Pediatr. Res. 60, 717–723.
Bolme, P., Margareta, E., 1975. Influence of diarrhea on the oral absorption of penicillin V and ampicillin in children. Scand. J. Infect. Dis. 7, 141–145.
Bonner, J.J., Vajjah, P., Abduljalil, K., Jamei, M., Rostami-Hodjegan, A., Tucker, G.T., Johnson, T.N., 2015. Does age affect gastric emptying time? A model-based meta-analysis of data from premature neonates through to adults. Biopharm. Drug Dispos 36, 245–257.
Bowen, J., Ball, J., 2015. The basic science of cystic fibrosis. J. Paediatr. Child Health 25, 159–164.
Brant LJ, E.F., 2013. The prevalence and growth of obesity and obesity related illnesses in Europe. European Center for International Political Economy, Geneva.
Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 68, 394–424.
Brenchley, J.M., Douek, D.C., 2008. HIV infection and the gastrointestinal immune system. Mucosal Immunol. 1, 23–30.
Broe, A., Pottegard, A., Lamont, R.F., Jorgensen, J.S., Knibbe, C.A., 2014. Comparison of oral and enteral feedings: does evidence support an interaction? Annu. Pharmacoth. 34, 896–905.
Brooke, A., Ferrara, R., Bruce, R., Buscher, M., Landers, E., Catalano, F., 1999. Influence of aging on gastrointestinal transit time. An ultrasonicographic and radiologic study. Invest. Radiol. 34, 357–359.
Brouwer, K.R.R., Alexioues, L.M., Brandys, B., Giacosa, G.P., Knipp, G., Lukaiovic, V., Mielck, B., Nigam, S.M., Rieder, M., Wildt, S.D., 2015. Human ontogeny of drug transporters: review and recommendations of the pediatric transporter working group. Clin. Pharmacol. Ther. 98, 266–287.
Bruze, J.M., Yu, H., Krekels, E.H.L., de Roo, R., Brill, M.J.E., van den Anker, J.N., Rostami-Hodjegan, A., de Wildt, S.N., Knibbe, C.A., 2018a. First-pass CYP3A-mediated metabolism of midazolam in the gut wall and liver in preterm neonates. CPT Pharmacometrics Syst. Pharmacol. 7, 374–383.
Bruze, J.M., Yu, H., Krekels, E.H.L., de Roo, R., Brill, M.J.E., van den Anker, J.N., Rostami-Hodjegan, A., de Wildt, S.N., Knibbe, C.A., 2018b. Characterization of intestinal and hepatic CYP3A-mediated metabolism of midazolam in children using a physiological population pharmacokinetic model. Pharm. Res. 35, 182.
Buchholz, V., Berkenstadt, H., Gostein, D., Dickman, R., Berstein, H., Rubin, I., 2013. Gastric emptying is not prolonged in obese patients. Surg. Obes. Relat. Dis. 9, 714–717.
Budzynski, J., Klopocka, M., 2014. Brain-gut axis in the pathogenesis of Helicobacter pylori infection. World J. Gastroenterol. 20, 5212–5225.
Buggins, T.R., Dickinson, P.A., Taylor, G. 2007. The effects of pharmaceutical excipients on drug disposition. Adv. Drug Deliv. Rev. 59, 1482–1503.

Calcagno, A.M., Ludvig, J.A., Fostel, J.M., Gottesman, M.M., Ambulkar, S.V., 2006. Comparison of drug transporter levels in normal colon, colon cancer, and Caco-2 cells: impact on drug absorption and disposition. Mol. Pharm. 3, 87–93.

Camilleri, M., Mahli, H., Acosta, A., 2017. Gastrointestinal complications of obesity. Gastroenterology 152, 1656–1670.

Health Canada, 2013. Guidance document: consideration for inclusion of women in clinical trials and analysis of sex differences. http://www.canada.ca/en/health-canada/services/drugs-health-products/products/applications-submissions/guidance-documents/clinical-trials-considerations-inclusion-women-clinical-trials-analysis-data-sex-differences.html (accessed 11 September 2019).

Carrion, S., Clevé, P., 2017. Gastrointestinal disease in the older population. In: Michel, J.P., Beattie, B.L., Martin, F.C., Walston, J. (Eds.), Oxford Textbook of Geriatric Medicine, 3rd ed. Oxford University Press, Oxford, United Kingdom, pp. 1110–1116.

Carrwood, K.A., Ving, H., Rau, A.P., Sherwood, R.R., Amiel, S.A., Patel, A.G., Je Rœx, C.W., 2014. The effect of bariatric surgery on intestinal absorption and transit time. Obes. Surg. 24, 796–805.

Cascorbi, I., 2006. Role of pharmacogenomics of ATP-binding cassette transporters in the pharmacokinetics of drugs. Pharmacol. Therapeut. 112, 457–473.

Cellini, M., Santaguida, M.G., Gato, L., Virili, C., Da Duca, S.C., Brusca, N., Caprirello, S., Garzoni, S., Gargano, L., Centanni, M., 2014. Systematic appraisal of lactose intolerance as cause of increased need for oral thyroxine. J. Clin. Endocrinol. Metab. 99, E1454–E1458.

Centanni, M., Gargano, L., Canettieri, G., Vicoccenti, N., Franchi, A., Deleve, F., Gobbi, A., Annibale, B., 2006. Thryroxine in goiter, Helicobacter pylori infection, and chronic gastritis. N. Engl. J. Med. 354, 1787–1795.

Chang, F.Y., Chen, C.Y., Lu, C.L., Luo, J.C., Jian, K.L., Lee, S.D., Wu, C.W., 2004. Undisturbed water gastric emptying in patients of stomach cancer. Hepato-Gastroenterology 51, 1219–1224.

Chang, J., Rayner, C.K., Jones, K.L., Horowitz, M., 2010. Diabetic gastroparesis and its impact on glycemia. Endocrinol Metabol. Clin. 39, 745–762.

Chen, L., Prasad, G.V.R., 2018. CYP3A5 polymorphisms in renal transplant recipients: influence on tacrolimus treatment. Pharmacogenomics Pers. Med. 11, 23–33.

Chen, M.L., 2006. Ethnic or racial differences revisited: impact of dosage regimen and dosage form on pharmacokinetics and pharmacodynamics. Clin. Pharmacokinet. 45, 927–964.

Cheung, K.W.K., Van Groen, B.D., Buckart, G.J., Zhang, L., de Wilde, S.N., Huang, S.M., 2019. Incorporating ontogeny in physiologically based pharmacokinetic modeling to improve pediatric drug development: What we know about developmental changes in drug disposition transporters. J. Pharm. Sci. 59, 526–560.

Chiorioni, G., Basotti, G., Germani, U., Battaglia, E., Bregantini, M.T., Morelli, A., Vaniti, L., 1997. Gluten-free diet normalizes mouth-to-cecum transit of a caloric meal in adult patients with celiac disease. Digest. Dis. Sci. 42, 2100–2105.

Chiolom, M., Darconza, G., Piccioli, E., De Carne, M., Clemente, C., Biezio, G., 2001. Gastric emptying and orocecal transit time in pregnancy. J. Gastroenterol. 36, 538–543.

Ciaccio, E.J., Bhagat, G., Lewis, S.K., Green, P.H., 2016. Recommendations to quantify the gastrointestinal tract of male and female rats is influenced differently by food. Mol. Pharm. 3, 87–93.

Cirino, T.A., Birmaher, B., Storch, A.D., 2010. Does exercise reduce suicidal ideation in youth with mood disorders and comorbid anxiety? J. Child Adolesc. Psychopharmacol. 20, 229–236.

Cristofoletti, R., Patel, N., Dressman, J.B., 2017. Assessment of bioequivalence of weak base solid dispersions by high-performance liquid chromatography in obes compared to non-obese subjects. Surg. Endosc. 32, 1755–1761.

Deleu, D., Ebinger, G., Michotey, Y., 1991. Clinical and pharmacokinetic comparison of oral and duodenal delivery of levodopa/carbidopa in patients with Parkinson's disease within Fibrasingar. Eur. J. Clin. Pharmacol. 41, 453–458.

Delijannidiad, K.M., Byant, N., Freeman, M.P., 2014. Pharmacotherapy for mood disorders in pregnancy: a review of pharmacokinetic changes and clinical recommendations for therapeutic drug monitoring. Clin. Pharmacokinet. 53, 705–717.

Deng, J., Zhou, X., Chen, Z.X., Zhuo, Y., Gao, W.H., Gao, C.Y., Shek, K.Y., Zou, Z., Lan, T.N., 2017. A review of food-drug interactions on oral drug absorption. Drugs 77, 1833–1855.

Derdzinski, H., Izadi, Z., Alasi, L., Lotfahadi, A., Saboury, A.A., Dinavaran, R., Divvalar, A., Seyedarabi, A., Barzegari, E., Emini, V., 2017. Colon cancer and specific ways to deliver drugs to the large intestine. Anticancer Agents Med. Chem. 17, 1317–1327.

Devriese, S., Van den Boshche, L., Van Welden, S., Holvoet, T., Pinheiro, J., Hindryckx, P., De Vos, M., Laukens, D., 2017. T84 monolayers are superior to Caco-2 as a model system of colonocytes. Histochim. Cell. Biol. 148, 85–93.

Di Cagno, R., De Angelis, M. De Pasquali, I., Ndagijimana, E., Vermonchi, P., Ricciuti, P., Goglio, F., Leghi, L., Fraioli, F., Guerzoni, M.E., Greco, F., Francescilli, D. 2011. Feasibility and microfluidic models of cell culture: molecular, phenotype and metabolome characterization. BMC Microbiol. 11, 219.

Dikablia, A., Verzoni, M., Goumas, K., Soderlin, E., Abrahamsson, B., Dressman, J., Segonzac, C., 2009. Characterization of the contents of ascending colon to which drugs are exposed after oral administration to healthy adults. Pharm. Res. 26, 2141–2151.

Díaz, A.T.M., Cordero, C., Rivas, C., 2015. Impact of breastfeeding on the microflora of female and male newborns. Acta Obstet. Gynecol. Scand. 94, 489–496.

Dolfini, K.M., Byatt, N., Freeman, M., 2014. Pharmacokinetics of drugs. Pharmacol.Therapeut. 112, 457–473.

Dow, L., Wang, Y., Prasad, G.V.R., 2018. CYP2D6 polymorphisms in renal transplant recipients: influence on tacrolimus treatment. Pharmacogenomics Pers. Med. 11, 23–33.

Elli, L., Bardella, M.T., 2005. Motility disorders in patients with celiac disease. Eur. J. Gastroenterol. Hepato-Bull. 17, 891–897.

El-Omar, E.M., 2006. Mechanisms of increased acid secretion after eradication of Helicobacter pylori infection. Gastroenterology 130, 1656–1670.

El-Omar, E.M., 2006. Mechanisms of increased acid secretion after eradication of Helicobacter pylori infection. Gut 55, 1446–1454.

El-Omar, E.M., 2006. Mechanisms of increased acid secretion after eradication of Helicobacter pylori infection. Gut 55, 1446–1454.

El-Omar, E.M., 2006. Mechanisms of increased acid secretion after eradication of Helicobacter pylori infection. Gut 55, 1446–1454.
Primary care 44, 673–692.
Samant, T.S., Mangal, N., Lukacova, V., Schmidt, S., 2015. Quantitative clinical pharmacology for size and age scaling in pediatric drug development: A systematic review. J. Clin. Pharmacol. 55, 1207–1217.
Silver, C., Seneff, S., 2013. Adult-onset, pathways to modern diseases II: Celiac sprue and gluten intolerance. Interdiscip. Toxicol. 6, 159–184.
Santamaría, M.M., Villafranca, J.A., Abilés, J., López, A.F., Rosas, L.V., Goitia, B.T., Navarro, P.U., 2018. Systematic review of drug bioavailability following gastro-intestinal surgery. Eur. J. Clin. Pharmacol. 74, 1531–1545.
Sanz, Y., De Pama, G., Laparra, M., 2011. Unraveling the ties between celiac disease and intestinal microbiota. Int. Rev. Immunol. 30, 207–218.
Sarosiek, I., Sevor, K.H., Katz, L.A., Semler, J.R., Wilding, G.E., Lackner, J.M., Sitrin, M.D., Russ, B., Chey, W.D., Hainer, W.L., Koch, K.L., Parkman, H.P., Sarosiek, J., McCalm, R.W., 2010. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. Aliment. Pharmacol. Ther. 31, 313–322.
Scarpello, J.H., Greaves, M., Sladen, G.E., 1976. Small intestinal transit in diabetics. BMJ 2, 1225–1226.
Schiller, C., Frohlich, C.P., Giessmann, T., Siegmund, W., Monnikes, H., Hosten, N., Weitschies, W., 2005. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. Aliment. Pharmacol. Ther. 22, 971–979.
Schiller, L., 1999. Secretory diarrhea. Curr. Gastroenterol. Rep 1, 389–397.
Schleider, J.F., Vozmediano, V., Golden, A.G., Rodriguez, M., Samant, T.S., Laghiibetti, C.V., Eising, T., Schmidt, S., 2018. Current strategies to streamline pharmacotherapy for older adults. Eur. J. Clin. Pharmacol. 71, 412–442.
Seaman, J.S., Bowers, S.P., Dixon, P., Schindler, L., 2015. Dissolution of common psychiatric medications in a Roux-en-Y gastric bypass model. Psychosomatics 46, 45–49.
Sekirov, I., Finlay, B.B., 2009. The role of the intestinal microbiota in enteric infection. The J. Physiol. 587, 4159–4167.
Sharpstone, D., Neild, P., Crane, R., Taylor, C., Hodgson, C., Sherwood, R., Gazzard, B., Bignell, J., 1999. Regional intestinal transit, absorptions, and permeability in patients with AIDS with and without diarrhoea. Gut 45, 70–76.
Shelton, M.J., Akbari, B., Hewitt, R.G., Adams, J.M., Morse, G.D., 2000. Eradication of Helicobacter pylori is associated with increased exposure to delavirdine in hypercholesterolaemic HIV-positive patients. J. Acquir. Immune Defic. Syndr. 24, 79–82.
Shelton, M.J., Hewitt, R.G., Adams, J.M., Cox, S.R., Chambers, J.H., Morse, G.D., 2003. Delavirdine malabsorption in HIV-infected subjects with spontaneous gastric hypochlorhydria. J. Clin. Pharmacol. 43, 171–179.
Sheppard, J.J., Muntaner, A., Lennon, H., Abrahamsson, B., 2009. Toward an increased understanding of the barriers to colonic drug absorption in humans: implications for early controlled release candidate assessment. Mol. Pharm. 6, 60–73.
Sistrunk, M., Ishii, H., Okuda, S., 2014. Gastric emptying in patients with fundal gastric and gastric cancer. Gut 31, 767–769.
Thais, C.A., Levy, M., Groshova, I., Zheng, D., Soffer, E., Blacher, E., Braverman, S., Tengeler, A.C., Barak, O., Elazar, M., Ben-Zeév, R., Lebav-Regev, D., Katz, M.N., Pevsner-Fischer, M., Gertler, A., Halfpern, Z., Harmelin, A., Aamar, S., Serradas, P., Grofeld, A., Shapiro, H., Geiger, B., Elia, E., 2018. Hyperglycaemias drives intestinal barrier dysfunction and risk for enteric infection. Science 359, 1376–1383.
Thakkar, N., Salerno, S., Hornik, C.P., Gonzalez, D., 2017. Clinical Pharmacology Studies for Pediatric All II Children. J. Clin. Pharmacol. 57, 7–24.
Thompson, C.M., Johnson, D.O., Sawonana, B., Barton, H.A., Hattis, D., Tardif, R., Krishnan, K., 2009. Database for physiologically based pharmacokinetic (PBPK) modeling: physiological data for healthy and health-impaired elderly. J. Toxicol. Environ. Heal. B 8, 129–144.
Thompson, T., Lee, M.G., Clarke, T., Mills, W., Wharfe, G., Walters, S., 2012. Prevalence of gastrointestinal symptoms among ambulatory HIV patients and a control population. Ann. Gastroenterol. 25, 234–248.
Tofte, I., Taiminen, T., Konturek, S., Konturek, J.W., 1996. Dysfunction in gastric myoelectric and motor activity in Helicobacter pylori positive gastritis patients with non-ulcer dyspepsia. J. Pharmacol. 47, 469–476.
Tilg, H., Moschen, A.R., 2014. Microbiota and diabetes: an evolving relationship. Gut 63, 1513–2012.
Tistaert, C., Heimbach, T., Xia, B., Parrott, N., Samant, T.S., Keisigou, F., 2019. Food effect projections via physiologically based pharmacokinetic modeling: predictive pharmacology for size and age scaling in pediatric drug development. Br. J. Clin. Pharmacol. 87, 592–602.
Tosti, G., Goriandelli, R., Santin, F., Pasquali, R., Corbelli, C., Zoccoll, G., Di Febo, G., Montesi, N., Barbata, I., 1996. Gastric emptying of solids in morbid obesity. Int. J. Obes. Relat. Metab. Disord. 20, 200–205.
Touw, D., Mouton, J., Vinks, A., Horroverts, A., Heijman, R., 2000. Antibiotic treatment in cystic fibrosis: Part I: Drug interactions. Clin. Pharmacokinet. 38, 479–492.
Usai-Satta, P., Oppia, F., Lai, M., Cabrelli, C., 2018. Motility disorders in celiac disease and non-celiac gluten sensitivity: the impact of a gluten-free diet. Nutrients 10, 1189–1200.
Vaarala, O., Atkinson, M.A., Neu, J., 2008. The ‘perfect storm’ for type 1 diabetes: the complex interplay between intestinal microbiota, gut permeability, and mucosal immunity. Diabetes 57, 2555–2562.
Van Den Abeele, J., Rayman, M., Hofman, I., Van de Vijver, E., Ziu, W., Augustijns, P., 2010. Gastric fluid composition in a paediatric population: Age-dependent changes relevant for gastrointestinal drug disposition. Eur. J. Pharm. Sci. 43, 301–311.
