All disease begins in the gut: Influence of gastrointestinal disorders and surgery on oral drug performance

Grace B. Hatton[1], Christine M. Madla[1], Sarit C. Rabbie[1], Abdul W. Basit[1]*

[1]UCL School of Pharmacy, University College London, 29 – 39 Brunswick Square, London, WC1N 1AX

*Correspondence: a.basit@ucl.ac.uk

Contents

Abstract

The term “disease” conjures up a plethora of graphic imagery for many, and the use of drugs to combat symptoms and treat underlying pathology is at the core of modern medicine. However, the effects of the various gastrointestinal diseases, infections, co-morbidities and the impact of gastrointestinal surgery on the pharmacokinetic behaviour of drugs have been largely overlooked. The better elucidation of disease pathology and the role of underlying cellular and molecular mechanisms have increased our knowledge as far as diagnoses and prognoses are concerned. In addition, the recent advances in our understanding of the intestinal microbiome have linked the composition and function of gut microbiota to disease predisposition and development. However, this knowledge applies less so in the context of drug absorption and distribution mechanisms for orally administered dosage forms. Here, we revisit and re-evaluate the influence of a portfolio of gastrointestinal diseases and surgical effects on the functionality of the gastrointestinal tract, their implications for drug delivery and attempt to uncover significant links for clinical practice.

Keywords

Irritable bowel syndrome; Inflammatory bowel disease; Celiac disease; Antibiotics; Infections; Bariatric surgery

1.0 Introduction

"All disease begins in the gut" was the term reportedly coined by the father of modern medicine, Hippocrates, and though not strictly an all-encompassing truth, has important implications for the way in which our gut health is linked to disorders that can contribute to an early grave.

Peroral administration remains as the "holy grail" of drug delivery owing to matters of convenience and ease of administration. First-in-human studies and early clinical pharmacology studies are generally conducted in healthy adults, as are bioequivalence studies for generic drugs (Bai et al., 2016). However, in clinical practice, many drugs are frequently administered to individuals with underlying disease features that have the potential to alter drug pharmacokinetics and pharmacodynamics. Indeed, we know that drug absorption is specifically influenced by factors ranging from GI tract motility, luminal environment and the physical integrity of the gut including available surface area and mucosal permeability (Abuhelwa et al., 2016a, b; Hatton et al., 2015; Hens et al., 2017; Hurst et al., 2007; Sjogren et al., 2014; Smart et al., 2014; Trenfield et al., 2018). Given that both low and variable bioavailability of an orally-administered drug are undesirable, early characterisation of these features is vital to the drug development process (Jamei et al., 2009).

Efforts have been invested to increase the understanding of GI physiology and functional changes as a result of specific GI disease (Bai et al., 2016; Effinger et al., 2018; Grassi et al., 2011; Milovic, 2010). The influence of co-morbidities and gastrointestinal surgery on oral drug formulations, however, are still in its infancy. The presence and severity of disease is thought to be a central determinant for inter-individual and intra-individual variability with respect to oral drug delivery and subsequent formulation behaviour in the GI tract (Burcelin et al., 2013). As drug-drug interactions are considered in preclinical development, we believe that disease-drug interactions are of equal importance to understand the implications of GI disease and surgery on medicines administered for other indications but are yet absorbed in the GI environment. Although indirectly linked to the gut, the subject of systemic diseases including cystic fibrosis, Parkinson's disease and chronic pain do indeed present GI manifestations that result to clinical consequences is to be discussed in a subsequent review. In this review, however, we specifically focus on how GI diseases, infections and surgery all affect the physiology and function of the intestinal environment. The consideration of drug

pharmacokinetic and pharmacodynamic alterations in specific disease states is therefore necessary in order to appropriately evaluate disease effects on dosage form performance and consequent drug bioavailability.

2.0 Gastrointestinal diseases and its implications on oral drug delivery and absorption

It stands that any circumstance affecting normal gut function has the potential to alter drug pharmacokinetics and bioavailability, be that relative to physical injury or chemical influence. This also relates to the overlap and manipulation of physicochemical any physiological parameters, incorporating pH (Rabbie et al., 2015); fluid volumes (Chowdhury and Lobo, 2011) and composition (Fadda et al., 2010; Kalantzi et al., 2006; McConnell et al., 2008a); flow rate (Chowdhury and Lobo, 2011); transit time (Graff et al., 2001); surface tension (Kalantzi et al., 2006); mucus (Taherali et al., 2018; Varum et al., 2010) and the presence and activity of microbiota (El Rakaiby et al., 2014; Freire et al., 2011; Haiser et al., 2013; Merchant et al., 2016; Saad et al., 2012). In order to examine the influence of diseased states on the GI tract, we must first contextualise disease according to location.

"Local" GI diseases include irritable bowel syndrome, inflammatory bowel disease, malabsorptive syndromes, neurogastroenterological diseases, infections and disorders of transit and GI morphology, to name but a few, where the predominantly manifesting symptoms appear to be of GI origin (Duffield, 1996). A growing body of evidence has uncovered that disease development may be influenced by physiological and functional changes in the GI environment. This review highlights that the GI tract is, therefore, not merely a conduit for the absorption and digestion of food, but a carefully engineered environment to maintain overall health (Enright, 2016).

2.1 Irritable bowel syndrome

Irritable bowel syndrome (IBS) is the most extensively studied GI disorder and is a common reason for clinical referral. The mean prevalence among different regions ranges from 9.6% of the population in Asia, 8.1% in North America/Europe/Oceania, 17.5% in Latin America and 5.8% in the Middle East/Africa, all of which further exhibit a female predominance (Sperber et al., 2017). Exhibited symptoms range from intermittent and/or alternating episodes of alternating stool patterns (IBS-A), constipation (IBS-C), diarrhoea (IBS-D), abdominal pain and distension (Malagelada, 2006; Spiller, 2005), and at a more physiological level, reduced left colonic transit (Chey et al., 2001).

Conflicting differences in the gut and faecal microbiome composition and activity between affected patients and controls have been suggested (Bonfrate et al., 2013; Kassinen et al., 2007), though the notion of microbiota producing low-level immune activity in IBS has been linked to the predominance of diarrhoea as well as the initiation of IBS (Didari et al., 2015; Durban et al., 2013). Trials involving probiotic use to alleviate symptoms of IBS have to this end shown promising results (Bjarnason et al., 2012; Lee et al., 2013; Siew Chien et al., 2013), indicating a central role for microbiome composition influencing the onset and nature of IBS symptoms. In turn, studies involving female subjects have shown that the hormones oestrogen and progesterone may be associated with an increase in IBS symptom manifestation towards the end of each menstrual cycle with a concomitant decline in hormonal levels, indicating that the pathophysiology of IBS is also intricately related to endocrine function with the potential for regulation by hormonal contraceptive drugs and devices (Heitkemper and Chang, 2009; Rolston et al., 2018).

Gastric emptying time and small intestinal transit time were not significantly different in IBS patients when compared to controls measured with a SmartPill GI monitoring system (Lalezari, 2012). Differences, however, are exhibited between the IBS subtypes: IBS-D patients have a shorter small bowel transit time (3.3 ± 0.3 h) and total GI transit time (35 ± 5.0 h) than IBS-C patients (5.4 ± 0.3 h and 87 ± 13 h respectively) (Cann et al., 1983b). The implications for drug delivery to the gut in IBS are, therefore, differential affected due to variations in transit time. Indeed, drug bioavailability may be reduced by accelerated colonic transit where the time for dosage form disintegration, dissolution and drug absorption is also reduced by disease activity. Previous studies have demonstrated that food consumption correlates with the onset of ileal pain (Cann et al., 1983; Ragnarsson and Bodemar, 1998), and that food and fibre intake may also accelerate colonic transit in IBS patients (Bosaeus, 2004; Deiteren et al., 2010; Simren et al., 2001), thus, potentially reducing drug absorption and bioavailability further.

The role of bile acids (BAs) has also been underlined in IBS pathophysiology. Primary BAs undergo dehydroxylation by bacteria in the small intestine which facilitate lipid digestion and absorption (Hundt, 2018), forming secondary BAs. A significant increase in primary BAs was found in IBS–D and –C subtypes when compared with healthy subjects. Furthermore, a significant decrease in secondary BAs was demonstrated in IBS-D patients against healthy participants. Dior et al. have postulated that diarrhoea in IBS-D patients may be due to BA

malabsorption which is prevalent in 30 – 50% of patients (Dior et al., 2016). Given the decrease in BA biotransformation, the absorbed BA pool is enriched with primary BAs. These BAs are hydrophilic and active, absorbed through the apical sodium-dependent bile acid transporter. A modification in ileum conditions presented with an increased active absorption and a decrease in passive absorption, therefore, can especially affect the absorption of lipophilic drug compounds (Dior et al., 2016) which account for a considerable percentage of today's pipeline molecules that are both poorly soluble and poorly permeable (BCS Class IV) (Savla et al., 2017).

Intestinal barrier dysfunction has been found to play a pathogenic role in IBS (Brandtzaeg, 2011). There is increasing evidence that heightened intestinal permeability is related to low-grade inflammation, visceral hypersensitivity and pain in IBS. With the use of oral probe excretion assays, increased small bowel and colonic permeability was demonstrated in both paediatric and adult IBS patients regardless of IBS-subtypes when compared with healthy controls (Camilleri et al., 2012). In IBS-D patients particularly, electron microscopy studies shown enlarged intercellular spaces between epithelial cells, offering a morphological basis for increased intestinal permeability (Bischoff et al., 2014).

2.2 Inflammatory bowel diseases

Inflammatory bowel disease (IBD) is broadly recognised as chronic, relapsing idiopathic inflammatory conditions of the GI tract, leading to long-term damage to the gut structure and function (Hanauer, 2006; Yadav et al., 2016). Historically, IBD was described as a disease of those with a European descent who were raised in affluent Western countries such as the UK, North America and Australia with approximately 1.4 million people in the United States suffering from IBD, whilst 2.5 – 3.0 million patients are diagnosed with IBD in Europe (Kaplan, 2015). Population-based studies, however, revealed that the incidence of IBD in the West has shown a degree of stabilisation and decreasing incidence, although paediatric onset of IBD has steadily increased (Kaplan and Ng, 2017). In the last decade, epidemiological studies have shown that the diagnosis of IBD is not limited by socio-economic status, race or geographical borders (Sewell and Velayos, 2013). This discovery indicated that the disease is not driven by genetics, but rather manifests through environmental pressures prevalent in developing countries. Within Asia, the incidence of IBD was highest in Guanzhou in mainland China, followed by Hong Kong and Macau (Ng et al., 2013). Currently, it has been estimated

that over 120,000 patients are suffering from IBD in Japan, whilst India has an estimated disease burden of 1.1 million patients (Singh et al., 2017).

The two manifestations of IBD – ulcerative colitis and Crohn's disease – are distinct in their sites of inflammation.

2.2.1 Ulcerative Colitis

Ulcerative colitis is a chronic, idiopathic inflammatory disorder limited to the colonic and rectal mucosa; a distinguishing characteristic from Crohn's disease. It is typically qualified as either quiescent, mild, moderate or severe (Kaplan, 2015; Rizello et al., 2002), and is thought to result from a dysregulation of intestinal mucosal immune responses, characterised by intermittent and often unpredictable periods of remission and relapse along with high GI variability (Planell et al., 2013).

In contrast to IBS, IBD is largely associated with episodes of increased stool weight as a consequence of impaired colonic water absorption (Barrow et al., 1991) and reduced postprandial colonic contractility, specifically in active UC (Snape et al., 1980). Other symptoms range from fever to weight loss, abdominal pain, vomiting and loose stools featuring blood and/or mucous in contrast to the alternating constipation and diarrhoea, as seen in IBS (Jonefjäll, 2014). Currently, topically-active aminosalicylates form the mainstay of therapy for both mild to moderate active UC and in the maintenance of remission, and in both circumstances, these drugs are predominantly targeted at the colon for localised release (Feagan et al., 2013).

Patients with UC typically display a markedly lower colonic pH when compared with healthy individuals which has potential implications for the use of pH-sensitive polymer formulations – namely, that degradation and opening of pH-dependent coatings may be compromised (Basit et al., 2009; Bosworth, 2009; Ibekwe et al., 2008b; McConnell et al., 2009). Results obtained for pH values in the GI tract of UC patients are also highly variable, ranging from pH 2.4-3.4 in the proximal colon (Fallingborg et al., 1993) to pH 4.7-11.0 in the right colon (Nugent et al., 2001; Press et al., 1998; Raimundo et al., 1992). An additional study by Ewe et al (1999) measured the median rectal pH of UC patients to be pH 7.8 versus 7.2 in healthy volunteers.

Prior studies revealed that GI transit times for patients with active UC show high variability (Davis et al., 1986; Davis et al., 1991; Hardy et al., 1988; Hardy et al., 1987), though it is widely known that high GI variability is evident even in healthy subjects (Coupe et al., 1991; Degen and Phillips, 1996; Fadda et al., 2009; Karlstadt et al., 2004; McConnell et al., 2008a; Rabbie et al., 2015). Values also vary based on different reports from similar studies in UC patients, complicated by volunteers interchanging between active and inactive disease phases during the study period. Keller et al (2000) showed that gastric emptying time is prolonged in UC patients during both active and inactive disease phases, though again the involvement of individual variability in both healthy and diseased subjects in these investigations is complicating. The effect of the active and quiescent status of IBD on small intestinal transit time (SITT) was assessed by Fischer et al. (2017) without the interference from gastric residence times. Using a small-bowel video capsule endoscopy, the median SITT in non-UC participants was demonstrated to be 216 min when investigated in 125 non-UC participants, although inter-subject variability ranged from 39 to 512 minutes. UC patients, however, were found to have a longer SITT at an average of 264 mins (ranging from 216 to 326 min) when compared with healthy subjects (Fischer et al., 2017) (Figure 1), therefore suggesting a delay in the onset of action of orally administered drugs targeted to the distal gut.

Adding further to the complication of differing drug bioavailability is the distribution of drug in the colon. Hebden et al. reported that a marked asymmetry in the distribution of amberlite resin was identified in the large intestine of healthy volunteers with 69% disseminated in the proximal colon and 31% in the distal colon. In active left-sided UC, however, a distinct asymmetry of 91% of resin being found in the proximal colon when compared with 9% distributed in the distal colon. This was associated with a faster transit time of UC patients in the distal colon when compared with healthy subjects, thus, the distal colon is poorly exposed to administered drug and is further exacerbated in the diseased state. This would ultimately compromise the efficacy of modified-release dosage forms in active disease as UC is manifested in the distal colon whereas drug absorption largely occurs in the proximal region (Hebden et al., 2000).

As a consequence to varying pH, transit times and fluid volumes, pH sensitive systems targeted for colonic release often fail to disintegrate *in vivo* (Ibekwe et al., 2008a; Ibekwe et al., 2006; McConnell et al., 2008b; Safdi, 2005; Schroeder et al., 1987; Sinha et al., 2003). pH-responsive dosage forms, therefore, are suggested to be influenced by more than pH alone. Efforts have

been made to improve colonic drug release by designing alternative mechanisms that incorporate other parameters that drug release is further dependent upon (Kendall et al., 2009; Liu et al., 2009; Maroni et al., 2017; McConnell et al., 2009; Varum et al., 2013a), such as a microbial-trigger for example (D'Haens et al., 2017; Ibekwe et al., 2008b; Leong et al., 2002; McConnell et al., 2008b; McConnell et al., 2008c; Dodoo et al., 2017).

Studies have further identified physiological differences in the diseased UC gut when compared to healthy subjects in terms of the mucus barrier, expression of membrane transporters, metabolism and the composition of luminal contents. In terms of normal mucus barrier function, the protective phospholipid component of the GI mucosa, phosphatidylcholine, was strongly decreased in the colonic UC mucus barrier by approximately 70% (Ehehalt et al., 2004). The ascending UC colon fluid composition in the fasted state was shown to be significantly different when compared with healthy subjects where increased concentrations of soluble proteins was observed in the remission and relapse state (19.0 ± 10.8 mg/ml; 18.9 ± 8.1 mg/ml) than in the healthy colon (9.8 ± 4.6 mg/ml). In addition, the buffer capacity of the ascending colon fluid in both remission (hydrochloric acid: 37.7 mmol/l/ΔpH; sodium hydroxide solution: 16.7 mmol/l/ΔpH) and relapse (hydrochloric acid: 32.0 mmol/l/ΔpH; sodium hydroxide solution: 18.3 mmol/l/ΔpH) states were found to be higher when compared with the control (hydrochloric acid: 21.4 mmol/l/ΔpH; sodium hydroxide solution: 10.3 mmol/l/ΔpH), although volume and surface tension was found to be similar regardless of the healthy and diseased state (Vertzoni et al., 2010). In terms of membrane transporters, the expression of peptide transporter 1 (PepT1) is upregulated in the colon during chronic inflammation in subjects with UC and therefore, can negatively modulate the influx of peptidomimetics (Estudante et al., 2013). As a result, the increased expression of PepT1 can increase the drug absorption of peptidomimetic such as angiotensin-converting enzyme inhibitors and β-lactam antibiotics including penicillin an cephlasporins.

2.2.2. Crohn's disease

As with UC, the development of Crohn's disease (CD) is linked to a disordered inflammatory and immune response within the GI tract, characterised by environmental influences superimposed on predisposing genetic factors (Danese et al., 2004; Hanauer, 2006; Podolsky, 2002). CD is recognised to peak between the ages of 15 and 25 in contrast to a peak incidence of between 25 – 35 years for UC (Molodecky et al., 2012), though again, the exact pathophysiology of CD is unknown. An increased risk of extra-intestinal disease has been

recently linked to the effects of smoking in CD (Ott et al., 2014), and both UC and CD also carry a higher proportional risk of malignancy as compared to the general population (Eaden et al., 2001), with CD thought to reduce overall survival more so than UC (Wolters et al., 2006).

CD is predominantly characterised by transmural inflammation and a non-caseating granuloma found along the full length of the gut. The main considerations which sets CD apart from UC as oral drug therapy is concerned are associated with ulcerations, fistulations and so-called "skip lesions" that characterised by alternating regions of inflammation and tissue oedema. It can manifest at any membranous location along the GI tract (Baumgart and Sandborn, 2012), though a population-based study carried out in Montreal revealed that the most common site of CD is in the terminal ileum (45%), followed by the colon (32%), ileo-colon (19%) and upper GI tract (4%) (Baumgart and Sandborn, 2012; Peyrin-Biroulet et al., 2010). Symptomatic manifestations of the disease also vary according to the site of origin; colonic CD being largely characterised by diarrhoea, whereas ileal CD is typically more associated with symptoms resembling acute appendicitis (Selby, 2000), extending to include symptoms of the upper GI tract in 0.5-13% of cases (Luetke et al., 2000).

Given that CD affects the full length of the GI tract, this is known to affect circumstances ranging from delayed orocaecal transit time (OCTT) (Tursi et al., 2003) to luminal pH changes (Nugent et al., 2001; Nugent et al., 2000; Press et al., 1998), enzyme activity (Carrette et al., 1995); bile acid malabsorption and enterohepatic recirculation (Vitek, 2015) and mucin expression (Dorofeyev et al., 2013). A study by Nishida et al. investigated the steady-state kinetics of enterohepatic circulation of bile acids in patients with CD using ^{2}H-labelled bile acid (Nishida et al., 1982). The mean value for biological half-life of the ^{2}H-labelled bile acid was significantly ($p < 0.01$) shorter (1.15 ± 0.08 days) than healthy subjects (1.95 ± 0.25 days). The mean values for the total bile acid pool were exhibited to be 1323.0 ± 173.6 mg in CD which were statistically significant ($p < 0.02$) when compared with healthy subjects (2290.9 ± 327.3 mg). It is known that conjugated bile acids are absorbed mainly at the ileum. Therefore, the diminished bile acid pool size in CD is attributed to the impaired absorption at the ileum (Nishida, 1982).

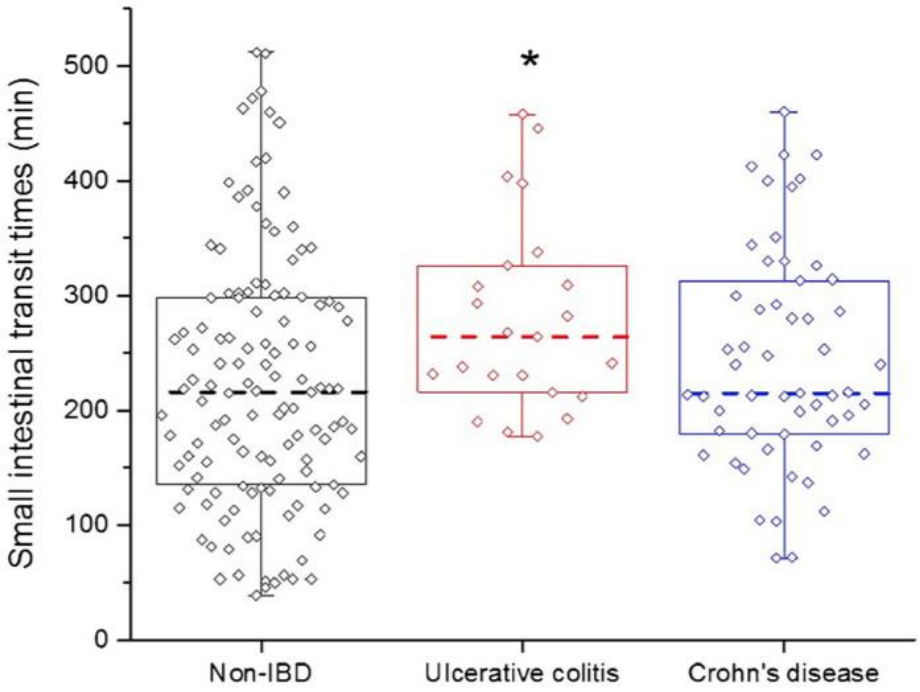

Figure 1. SITT in non-IBD subjects (n = 125), ulcerative colitis (n = 23) and Crohn's disease (n = 55). * denotes significant to non-IBD transit times (p = 0.010) (reproduced with permission from Fischer et al., 2017).

Other orally-administered treatment for induction of remission in CD (albeit not in maintenance therapy) is that of the corticosteroids – namely, prednisolone and budesonide; the latter of which is typically included in formulations targeted to the ileum and shown to be the most effective treatment in inducing remission (Moja et al., 2015). Shaffer et al. investigated the absorption of prednisolone in both healthy subjects and CD patients (Shaffer et al., 1983) (Figure 2). It was identified that plasma concentrations of prednisolone in healthy and CD patients exhibited a high degree of inter-subject variability following oral ingestion suggesting different severities and hence, different implications on absorption. CD, therefore, may benefit from the personalisation of therapies to maximise therapeutic effect and limit unwarranted adverse drug reactions. The reason for apparent malabsorption in Crohn's patients is unclear. Prednisolone is lipid-soluble, ergo should be readily absorbed by passive diffusion. The reduced surface area of diseased intestine, rapid transit, dispersion in unabsorbed luminal contents or changes in mucosal drug metabolising enzymes may all influence malabsorption (Matsuoka, 2018). Variable absorption mechanisms, therefore, should be taken into account when assessing drug responses in patients with CD.

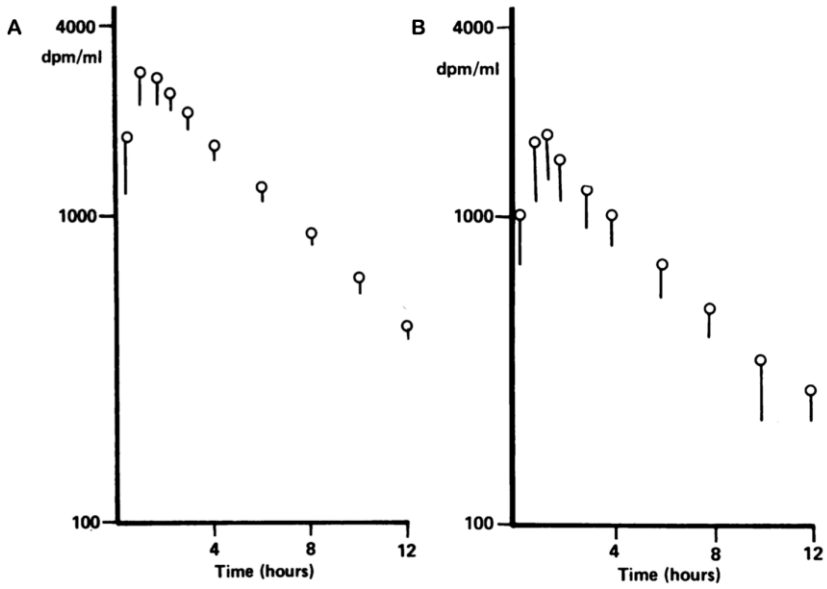

Figure 2. Plasma concentration-time curves for tritium in A) healthy subjects and B) CD patients after administration of 6,7-^{3}H-prednisolone by oral ingestion. Mean data with standard deviation shown (reproduced with permission from Shaffer, 1983).

Physiologically, it has been shown that the colonic pH of CD patients during both the inactive and active disease phases is much more acidic than that of healthy individuals – including those with resections (Fallingborg et al., 1998) – measured as 5.3 ± 0.3 (CD) versus 6.8 ± 0.2 (control) in the right colon, and 5.3 ± 0.7 (CD) versus 7.2 ± 0.3 (control) in the left colon by radiotelometry (Sasaki et al., 1997). These changes inevitably have implications for the delivery of colon-specific and pH-sensitive formulations. It should be noted, however, that ileo-colonic resection of the gut in CD may, as mentioned, unintentionally raise caecal pH from around 6.2 in the active disease (Ewe et al., 1999) to approximately 6.7 post-surgical (Fallingborg et al., 1998).

Similar to IBS, the disturbance of the integrity of the intestinal epithelial barrier contributes to the development of mucosal inflammation (Podolsky, 1999). Many proteins expressed by epithelial cells play a role in maintaining the protective barrier, facilitating transepithelial transportation and the efflux of potentially toxic compounds. P-glycoprotein (P-gp) is a transmembrane protein of the ATP-binding cassette transporter family (Borst and Elferink, 2002) that is highly expressed in the apical side of the intestinal epithelium, functioning to efflux compounds from the mucosa to the gut lumen. Increasing evidence has demonstrated that changes in MDR1 function and expression (a target gene of P-gp) contribute to the

pathogenesis of IBD (Blokzijl et al., 2007). Blokzijl et al. aimed to identify the intestinal MDR1 mRNA and protein expression in the uninflamed and inflamed intestinal epithelial of patients with IBD when compared with healthy controls. A slight decrease in the ileum and slight increase of MDR1 mRNA in the uninflamed colon of CD patients was identified, whereas a significant decrease of MDR1 expression was found in the inflamed ileum epithelia of the same patients (Blokzijl et al., 2007). The observed increase in MDR1 expression in the uninflamed colon could be an adaptive mechanism to consolidate for the decrease expression in inflamed tissue. The distinct significant effects were demonstrated in MDR1 expression in inflamed versus uninflamed intestinal tissue from individual patients where P-gp was strongly decrease in inflamed tissue of patients with CD and UC. As the main function of MDR1 is to export drugs out of cells, reduced P-gp expression in the diseased state can therefore increase the bioavailability of drugs used to treat IBD patients such as glucocorticoids and immunosuppressants.

Further physiological factors implicated in the diseased state have demonstrated to affect the effectiveness of medicine. Holt et al. investigated the gastric emptying, absorption and metabolism of paracetamol in 12 CD patients against 13 healthy controls (Holt, 1981). Gastric emptying and mean plasma concentrations were found to be lower and occurred later in CD patients when compared with control subjects, suggesting slow or impaired absorption of paracetamol (Figure 3).

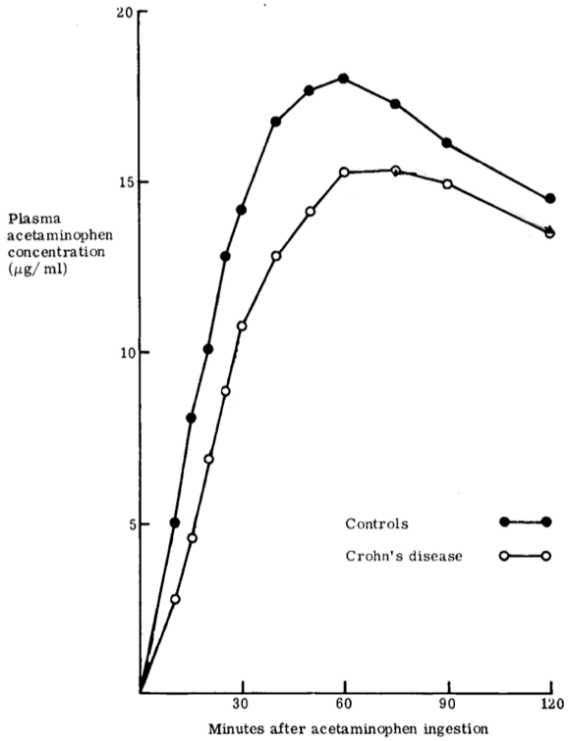

Figure 3. Mean plasma concentration of paracetamol (acetaminophen) in Crohn's disease when compared with healthy control subjects (reproduced with permission from Holt, 1981).

2.3 Malabsorption syndromes

Malabsorption is a central influence on oral drug delivery and bioavailability, defined as defective mucosal absorption occurring normally as a result of surgical complications, inflammatory and/or autoimmune disorders. Maldigestion – a term wholly distinct from that of malabsorption, which refers to an inability to digest food rather than the inability to absorb nutrients – are often present in conjunction with other disorders of the GI tract, including gastritis and pancreatitis. Here, the impaired absorption of ingested micronutrients and nanoparticles in the gut may lead to problems with drug permeation into the GI mucosa, such as that due to villous atrophy in celiac disease (Samsel and Seneff, 2013).

Overall, malabsorption syndromes can pertain to those which can affect the absorption of drugs and nutrients, may be drug-induced, or both. The main GI factors recognised for their involvement in drug malabsorption are numerous, ranging from available anatomical surface area to enzyme activity (Poka et al., 1968); changes to microbiota (Mortimer et al., 1964); food presence (Varum et al., 2013b); motility; intestinal and gallbladder obstruction (Collins et al., 1978; Parsons, 1977); pancreatitis (Dimagno et al., 1973); post-surgical causes and inflammatory disorders (Vitek, 2015). Drug and nutrient malabsorption is also a common

consequence of surgical procedures and/or resections involving the stomach and small intestine, associated with anatomical changes including reduced surface area, peristalsis, transit time and gut wall metabolism (Titus et al., 2013), and will be discussed later in the review.

Certain drugs known to result in nutrient malabsorption range from the bile acid sequestrant cholestyramine to anti-diabetic agents such as metformin, antacids, laxatives and a number of aminoglycoside antibiotics (namely neomycin), though by and large such phenomena are observed only with administration of high oral doses (Festi et al., 2006). These properties in the case of neomycin and cholestyramine have also been exploited for therapeutic means through inhibition of bile acid reabsorption in the treatment of hypercholesterolaemia and related lipid disorders. However, in patients presenting with pre-existing cholestasis or ileal disease, their use may lead to a much more pronounced malabsorption of lipid-soluble vitamins; namely D and K (Green and Tall, 1979). The impact of these drugs on other formulations where given concomitantly – specifically, those with lipid-based formulations – has yet to be comprehensively assessed, however, though cholestyramine is known to result in malabsorption of other drugs given concomitantly, including non-steroidal anti-inflammatory drugs (NSAIDs) and oral hypoglycaemic agents (Young et al., 1998).

2.3.1 Celiac disease

Celiac disease is a chronic autoimmune disorder common to Western nations such as Europe and the USA and estimated to affect up to 0.7% of these populations (Unalp-Arida, 2017), though has more recently seen to be on the increase in newer regions from 0.5% in Turkey, 0.6% in India and 0.7% in Israel (Singh, 2016). This implication is characterised by a hereditary sensitivity to the cereal protein gluten, abundant in many foodstuffs such as cereals and breads (Green, 2009). Incidence is high in elderly patients, though the disease is generally characterised by symptoms of lower severity when compared with the young (Holt, 2007), and is treated most successfully through lifelong abstinence from gluten-containing products.

Nutrient absorption in celiac disease is impaired due to atrophy of the upper intestinal villi, whereas the majority of celiac patients will present with symptoms of primarily GI manifestation, there is also known to be an association with extra-intestinal disorders considered useful to diagnosis (Krupa-Kozak, 2014). However, the adaptive immune response against gluten is enhanced and intestinal permeability is increased (Lammers et al., 2008). This characteristic gluten sensitivity has also been identified in other autoimmune disorders. For

instance, prolonged gluten exposure in undiagnosed celiac disease is seen to increase the incidence of autoimmune diseases such as diabetes and autoimmune thyroiditis (Ludvigsson et al., 2015).

The changes that occur along the length of the GI tract in celiac disease are also seen to correlate with disease severity and can impair normal patterns of drug absorption. Disease presentation at the proximal jejunum is typically characterised by seemingly mild symptoms such as weight loss and diarrhoea, whereas that which manifests in the ileum is otherwise characterised by morphological changes in the GI mucosa (Sergi et al., 2017). Freeman postulated that these changes in disease severity between the proximal and distal small intestine may potentially reflect changes in localised concentrations of dietary gluten, inducing gut hypersensitivity and inflammation (2008). Equally, and within a separate study by the group, it was further suggested that months or years of gluten abstinence in patients may be necessary in order to confirm normalisation of proximal duodenal mucosa function (Freeman and Whittaker, 1994). Whereas most patients will be diagnosed typically within a much shorter period, drug therapy may be initiated before normalisation of the gastric mucosa is established, with considerable implications for variability in dosage form performance and subsequent drug absorption (Freeman, 2012).

Untreated celiac disease can on the other hand increases the absorption of numerous orally-delivered drugs, including antibiotics (Mattila et al., 1973), aspirin (Parsons et al., 1977), methyldopa (Renwick et al., 1983), simvastatin (Moron et al., 2013), β-blockers (Kitis et al., 1982a) and levothyroxine (Collins et al., 2012) but decreases digoxin absorption (Heizer et al., 1989). The specific mechanisms underlying these effects on drug malabsorption in celiac disease are more extensively reviewed by Wang et al (2014), though briefly are thought to include rapid gastric emptying (Moberg and Carlberg.G, 1974), changes to intraluminal pH (Kitis et al., 1982a), abnormal mucosal permeability (Parsons, 1977), and enzyme deficiencies that may be associated with villous atrophy and reduced first-pass metabolic effects (Lang et al., 1996). Lang et al (1996) identified that small intestinal CYP3A enzyme levels involved in drug metabolism increase, however, with exclusion of gluten from the diet, potentially leading to an increase in oral drug bioavailability with initiation of a gluten-free diet.

A study by Holt et al. investigated the gastric emptying time and absorption of paracetamol in patients with untreated and treat celiac disease (Holt et al., 1981). The results showed that when

compared with the controls (n = 13), gastric emptying was slower in subjects with celiac disease (Table 1). In this study, it was determined that the slower paracetamol absorption rate in patients with celiac disease was not associated to the delayed or impaired absorption from the intestine, but rather attributed to the slow gastric emptying observed in this condition (Holt, 1981).

Collins et al. demonstrated that hypothyroid patients with underlying celiac disease required a higher dose of levothyroxine of at least 125 µg or 1.5 µg/kg to maintain a euthyroid state than patients without celiac disease (Collins et al., 2012). A significant reduction of levothyroxine dosing post-dietary treatment of celiac disease was further observed which supports that levothyroxine is malabsorbed by atrophied villi. In addition, the significant decrease of CYP3A enzymes expressed in duodenal biopsies of celiac disease patients would have implications specifically for CYP3A4 drug substrates such as midazolam, cyclosporine, carbamazepine and propranolol (Figure 4) where bioavailability is increased (Kitis et al., 1982b, Johnson et al., 2001). A variety of pharmaceuticals often prescribed to celiac disease patients, such as PPIs, are known to inhibit the absorption of levothyroxine due to the reduction in gastric acid secretion, chelation and obstructed intestinal transport (Liwanpo and Hershman, 2009).

Table 1. Gastric emptying and paracetamol absorption (reproduced with permission from Holt et al., 1981)

Subjects	Gastric emptying $t\,^1/_2$ (min)	Maximum plasma paracetamol concentration (µg/ml)	$AUC_{0\text{ to }1\text{ hr}}$ (µg min/ml)
Controls (n = 13)	23.6 ± 10.3	20.2 ± 3.0	12.4 ± 3.2
Untreated celiac disease (n = 9)	35.1 ± 8.9	16.2 ± 2.5	9.0 ± 1.6
Treated celiac disease (n = 7)	45.2 ± 14.9	14.7 ± 1.9	8.2 ± 2.0

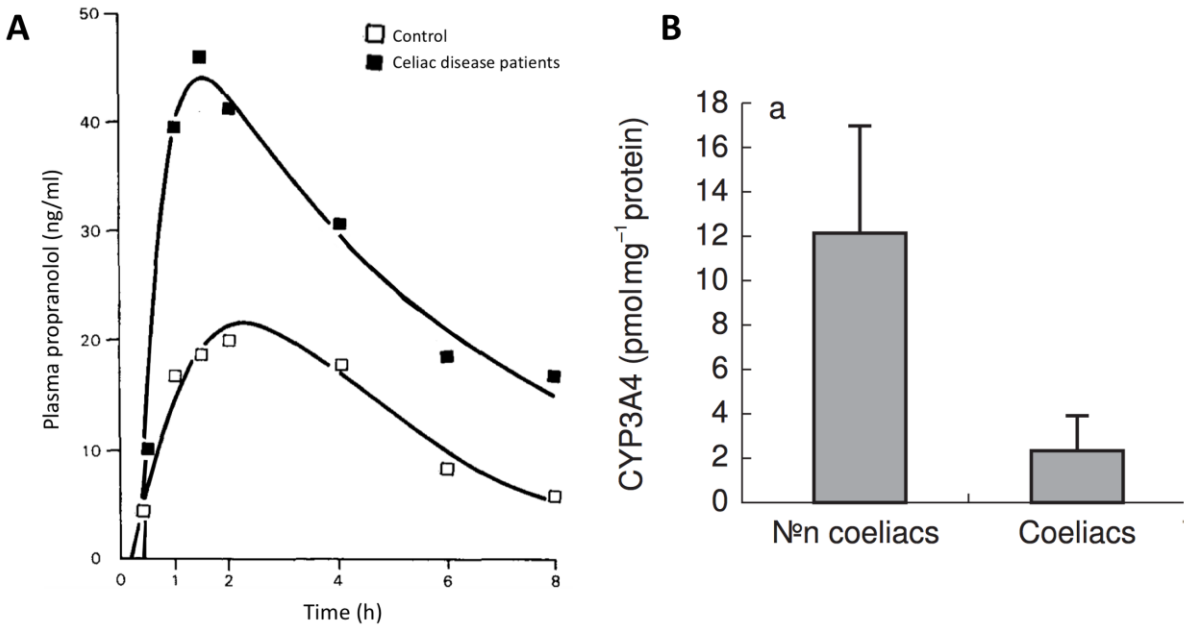

Figure 4. A) Increase in propranolol absorption in celiac disease patients when compared with the control may be attributed to B) the reduction in CYP3A4 enzyme oh which propranolol is a drug substrate. (reproduced with permission from Johnson et al., 2001; Kitis et al., 1982).

2.4 Microbial dysbiosis

The human gut harbours trillions of bacteria, fungi and viruses which symbiotically function with the host superorganism. (Enright, 2016). Although microbiomes regularly show a large degree of interpersonal diversity, even in the absence of disease, healthy gut microbiomes are consistently dominated by Bacteroidetes and Firmicutes (Human Microbiome Project, 2012; Qin et al., 2010). The realisation that imbalances in the microbiome can influence the onset of both local and systemic diseases, however, has altered the concept of a pharmaceutical-microbiome relationship. The microbiome now represents an intermediate, capable of metabolising and altering drug pharmacokinetics to consequently enhance or inhibit clinical response (Basit et al., 2002; Enright, 2016; Koppel et al., 2017; Sousa et al., 2008; Sousa et al., 2014; Spanogiannopoulos et al., 2016; Swanson, 2015; Walsh et al., 2018; Wilson and Nicholson, 2017; Yadav et al., 2013; Yoo et al., 2016; Vertzoni et al., 2011).

Small intestinal bacterial overgrowth (SIBO) is characterised by the excessive number of bacteria in the proximal small intestine (Muraki et al., 2014), and several studies have emphasised the association between SIBO and the prevalence of IBD. A study by Rana et al. (2013) demonstrated that SIBO was significantly higher in CD patients (45.2%) than UC

(17.8%), albeit both markedly higher when compared with controls (0.86%). Further to this, the development of SIBO has been linked to delayed oro-caecal transit time (OCTT) in UC patients associated with inflammatory changes, increased levels of pro-inflammatory cytokines and enhanced oxidative stress (Rana et al., 2014). In addition, a study reported that celiac disease has been hypothesised to be a risk factor of SIBO (Losurdo et al., 2017).

Antibiotics have been well-described on their impact on the intestinal microbiome with long-standing effects, such as further demonstrated with chemotherapy, causing dysbiosis (Papanicolas et al., 2017). More recent research has identified that the gut microbiome can be severely altered following prescription drug use (Figure 5). The most frequently prescribed non-antibiotic therapeutic classes were analgesics, antihyperlipidemic agents, antidepressants and antidiabetic agents (Prevention, 2013). Although many drugs present GI side effects, the role of the gut microbiota is rarely considered in early drug development (Wilson and Nicholson, 2017).

A correlation between arterial thromboembolic disease and vitamin K_2-producing intestinal bacteria is inferred by different evidence from the literature. Vitamin K antagonists (VKA) such as warfarin have been the mainstay therapy for venous thromboembolic disease of heart prosthetic valves as oral anticoagulants. Vitamin K, a co-factor for the formation of prothrombin, obtained entirely from the diet or produced by certain intestinal bacterial flora where vitamin K_2 contributes to the maintenance of coagulation homeostasis. Giuliano et al. (Giuliano et al., 2010) have demonstrated that flora-produced vitamin K interferes with the anticoagulant effect of warfarin by requiring higher doses at >70 mg/wk. As the microbiome presents high inter-subject variability in both the healthy and diseased states (even at different times of the day), the interference of flora producing vitamin K may be a critical consideration towards the personalised dosing for a narrow therapeutic drug such as warfarin to limit the risk of over or under-coagulation.

Another drug class that has demonstrated anti-commensal effects to the gut microbiome are proton pump inhibitors (PPIs). PPIs are prescribed for the prevention and treatment of gastroesophageal reflux and peptic ulcer disease. Meta-analysis has demonstrated that the use of PPIs is associated with the increase prevalence of *Clostridium difficile* infection (Kwok et al., 2012). The reduced gastric acidity induced by PPIs may be a contributing factor to the dysbiosis of the gut microbiome as fewer bacteria are destroyed when stomach acidity is

increased. A less acidic environment, therefore, may provide a favourable environment for the oral microbiome to colonise the intestinal microbiome of PPI users. This is supported by the findings of Imhann et al. (Imhann et al., 2016), who demonstrated that taxa associated with the oral cavity was found in faeces of patients of PPI therapy.

Likewise, metformin, one of the most widely prescribed medications for type 2 diabetes patients, has been reported to induce adverse abdominal pain and diarrhoea. A study by de la Cuesta-Zuluaga (de la Cuesta-Zuluaga et al., 2017) demonstrated that metformin is associated with a higher relative abundance mucinphilia and several short-chain fatty acid-producing microbiota in the gut. The metformin-induced gut dysbiosis could be an inhibition of the reabsorption of bile acids due to the altered function of the sodium-dependent intestinal bile acid transporter (Le Bastard et al., 2018). Morphine, often the drug of choice to be administered in cases of moderate to severe pain, has further demonstrated to cause gut barrier dysfunction (Brenchley and Douek, 2012). Opioid use for severe constipation may be implicated due to a disrupted gut environment following dysbiosis in the form of SIBO and microbial translocations as suggested in murine models (Banerjee et al., 2016).

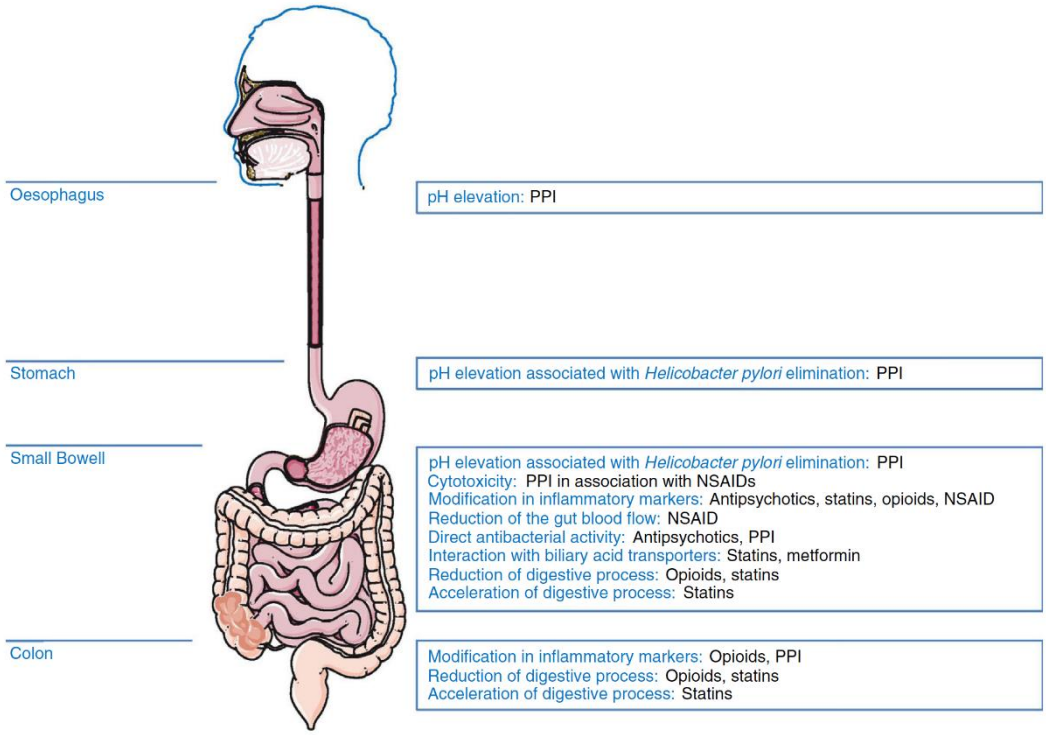

Figure 5. Proposed mechanism of non-antibiotics drugs demonstrating antibiotic-like activity in the human gut microbiome (reproduced with permission from Le Bastard et al., 2018).

3.0 Infections of the intestine and its implications on oral drug delivery and absorption

Bacterial, viral and parasitic infections of the intestine cause disease by the destruction of intestinal epithelial cells or toxin production. In the United States, an estimated 76 million cases of food or water contaminated with pathogens account for the 352,000 hospitalisation admissions and 5000 deaths per year (Yamada, 2013).

3.1 *Helicobacter pylori* infection

Infection of the gastric milieu by the gram-negative spiral bacterium, *Helicobacter pylori* (*H. pylori*), is one of the most common causes worldwide of stomach ulceration and malignancy (Kuipers, 1997; Marshall, 1994). An increased risk of development is also associated with the ageing process, potentially augmenting age-related barriers to drug absorption (Newton, 2004; Pilotto, 2004; Pilotto et al., 2002). The inflammatory response produced, however, can lead to chronic impairment of gastric function characterised by altered motility, gastric acid secretion and gastric emptying (McColl et al., 2000; Miyaji et al., 1999; Thor et al., 1996).

It is broadly accepted that eradication of the bacterium alleviates symptoms, promotes healing and protects against recurrence of ulceration, including recovery of drug absorption (Annibale et al., 2002; Lahner et al., 2014). However, contention remains as to whether this eradication also facilitates normalisation of gastric functions including motility, secretion and fluid pH. Whether *H. pylori* infection affects gastric pH has extensively been studied in the literature (Haruma et al., 2000; Labenz et al.; Testerman and Morris, 2014). Rácz et al. (2001) demonstrated through an *in vivo* pH study that gastric acidity remains largely unaltered for at least three months in spite of treatment for *H. pylori* infected patients, and that most patients will continue to present with dyspeptic symptoms in this time-frame, thereby necessitating continuation of anti-secretory therapy.

Other sources have inferred the likelihood of reflux symptoms developing in the duodenum following infection eradication (Bagnolo et al., 2001; Manes et al., 2001). One explanation for this relates to observations of decreased basal gastric output and abolition of buffer production following antibiotic therapy (Elomar et al., 1995; Verhulst et al., 1995), leading to enhanced gastric acidity. However, a study by Manes et al (2000) stated that there was no statistical difference between gastric and oesophageal pH values in human test subjects with and without gastritis associated with *H. pylori*; instead, highlighting that gastric pH is higher in patients

suffering from infective gastritis than those with non-infective gastritis. Conversely, Verdu et al (1995), when investigating the effects of *H. pylori* on oral omeprazole performance as part of a 24-hour study, indicated that it was possible for the bacterium to alter net gastric acidity, thus reducing drug efficacy even following eradication of the infection.

Prescott et al (1974) have postulated that a reduction in gastric acid secretion due to *H. pylori*-related gastritis may influence drug ionisation and solubility, thereby impairing absorption and subsequent bioavailability. A number of studies have since highlighted that *H. pylori* infection impairs the absorption of pH-sensitive drugs including levodopa (Pierantozzi et al., 2006; Pierantozzi et al., 2001), thyroxine (Figure 5) (Centanni et al., 2006) and delavirdine (Shelton et al., 2000), and the main mechanism underlying this absorption appears to be reduced gastric acid secretion (Lahner et al., 2014).

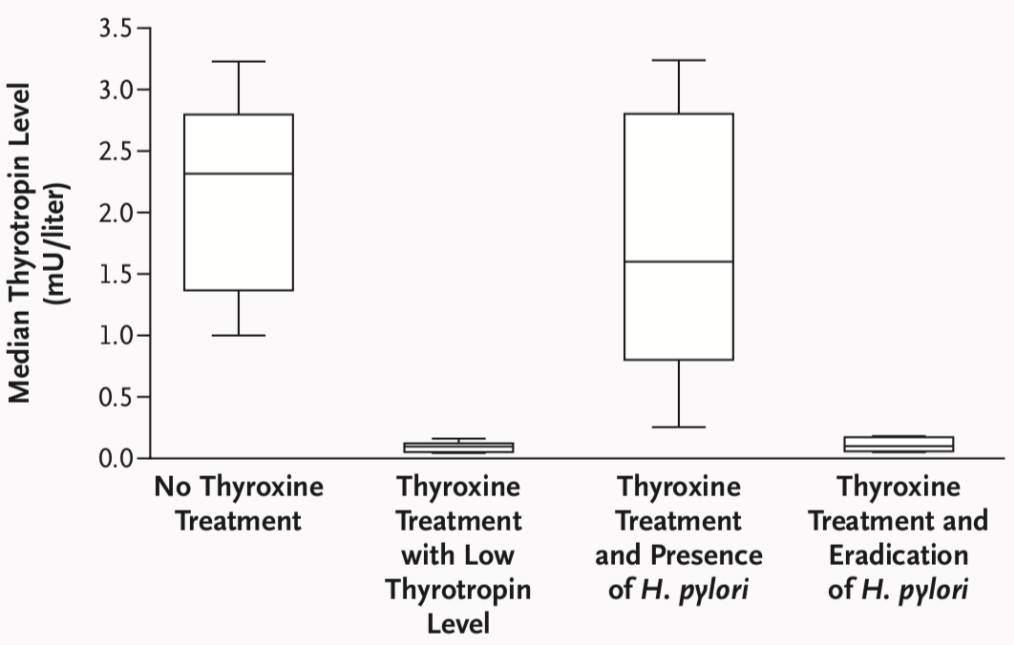

Figure 5. The effect of newly diagnosed *Helicobacter pylori* infection on thyrotropin levels in patients with multinodular goiter, treated with thyroxine (1.56 µg/kg/day) (reproduced with permission from Centanni, 2006).

Knowledge of bacterium-induced alterations in gastric pH during and following infection by *H. pylori* in the context of drug delivery may therefore necessitate the use of pH-sensitive formulations to achieve optimal clinical responsiveness; overcoming possible residual alterations in gastric acidity and secretion following apparent curation of the infection.

3.2 Traveller's diarrhoea

In 2017, approximately over 1300 million people travelled internationally (UNWTO, 2018) with an increasing number of tourists travelling to and from malaria endemic regions. In addition, over a quarter of travellers have sought medical treatment following GI symptoms (Freedman et al., 2006). Intestinal infections caused by bacterial, viral and parasitic pathogens can result in fluid loss, dehydration and diarrhoea. On initiation, diarrhoea occurs due to the inhibition of sodium ions and the absorption of chloride and bicarbonate ions which are secreted across the gut epithelium. Organisms that cause inflammatory diarrhoea particularly target the distal ileum and colon by secreting noxious cytotoxins or invade the epithelium and consequently alter the intestinal epithelial barrier function through the loss of epithelial cells and from disruption of tight junctions (Hoque et al., 2012).

In countries where the risk of malaria is high, much reliance is invested on chemoprophylaxis for malaria prevention. Although the kinetic profiles and bioavailability of proguanil and chloroquine have been well described, the presence of traveller's diarrhoea may compromise the absorption of drugs which may result in potential adverse effects. A clinical study administered proguanil and chloroquine to 12 travellers with diarrhoea and 12 asymptomatic subjects respectively (Behrens et al., 1994). Plasma concentrations demonstrated that patients with underlying traveller's diarrhoea administered with proguanil revealed that its maximum concentration and absorption coefficient was significantly lower and its time to reach maximum concentration was 16% longer when compared with their asymptomatic counterparts. This suggests that subjects with traveller's diarrhoea are more likely to have lower plasma concentrations of proguanil and thus, may be at a greater risk of contracting malaria. Chloroquine pharmacokinetics, however, were similar in both groups and did not require dose alterations in traveller's diarrhoea.

3.3 *Clostridium difficile* infection

In a healthy environment, the gut microbiota aids in preventing infection by competing against newly introduced and potentially harmful bacteria, releasing antimicrobial compounds or stimulating immune defences (Hattori and Taylor, 2009). However, widespread antibiotic use has led to a reduction in colonisation resistance. *Clostridium difficile* (*C. diff*) is a gram-positive bacterium which causes infection as a consequence of antibiotic therapy, presenting symptoms such as mild diarrhoea to severe pseudomembranous colitis (Schlenker and Surawicz, 2009). Exponential epidemics in the West and Japan have reached historic highs in the last decade

with increasing mortality rates reported as a result of *C. diff* infection (CDI) (McCollum and Rodriguez, 2012). Immunosuppressed patients and those diagnosed with IBD appear to be at increased risk (Nguyen and Steinhart, 2008). Ironically, antibiotics such as vancomycin are used as the mainstay therapy for CDI, although treatment with fidaxomicin, a structurally similar antibiotic, has proven to reduce the impairment of the intestinal microbiome during treatment (Louie et al., 2011). However, the success of faecal microbial transplantation demonstrates superiority for the treatment of recurrent CDI than vancomycin by curing 90% of cases when compared with 30% patients administered with vancomycin (van Nood et al., 2013).

The relative efficacy and safety of PPIs have contributed to their significant overutilization. Meta-analyses, however, have identified that the use of PPIs was associated with the rise in prevalence of CDI potentially due to their direct effect on stomach acid. The main structural changes following CDI is due to the increased expression Enterobacteriaceae and Enterococcaceae in the intestinal microbiome (Janarthanan et al., 2012). As gastric acidity is one of the main form of defence against the influx of bacteria, PPIs reduce the acidity and thus, allow more bacteria to survive (Theriot and Young, 2014). The decrease in acid levels, however, may affect toxin expression. Stewart et al. (Stewart and Hegarty, 2013) demonstrated that the expression of toxin genes and their regulators were different following PPI administration in some *C. diff* ribotypes. Another *in vitro* study identified that PPIs decreased the expression of coloncyte genes leading to the reduced production of proteins associated with the protection of intestinal epithelium and loss of maintenance of cell junctions (Hegarty et al., 2014). CDI is a growing concern, particularly as resistance to treatments increases. The use of PPIs is a modifiable risk factor for CDIs, therefore, clinicians should take this into consideration when treating at-risk patients.

As *C. diff* actively modulates the microbial environment, it can therefore be postulated that drug absorption may be attenuated due to the manifestation of gastrointestinal infections similar to the impact of *H. pylori* and Traveller's diarrhoea. More research in disease-drug interactions, however, should be invested to identify the potential consequence of CDI on the performance of oral dosage forms.

4.0 Impact of gastrointestinal and bariatric surgery on oral drug delivery and absorption

Over the last decade, the prevalence of obesity has exponentially increased in the Western world with approximately 30% of North Americans being obese (Myers et al., 2015). Drug and nutrient malabsorption is a common consequence of surgical procedures and/or resections involving the stomach and small intestine, associated with anatomical changes including reduced surface area, peristalsis, transit time and gut wall metabolism. Bariatric surgery has proven to be successful in treating morbid obesity. Several bariatric surgical methods coexist in healthcare, including; the adjustable gastric band (AGBD); sleeve gastrectomy (SG); biliopancreatic diversion (BPD); biliopancreatic diversion with duodenal switch (BPD-DS) and Roux-en-Y gastric bypass (RYGB) (Darwich et al., 2012). Other procedures such as jejunoileal bypass (JIB) have been gradually phased out due to the higher probability of post-surgical complications (Singh, 2009).

Bariatric surgery is another circumstance which is known to result in nutrient – and by implication, drug – malabsorption as a consequence of accelerated transit time due to modification of gastric emptying feedback controls. These changes result in reduced time for the performance of normal digestive functions, ergo subsequent nutrient absorption at the level of the small intestine (McKelvey, 1970). The effect of the loss of surface area should be measured on a drug-by-drug basis, established on factors such as molecular size, polarity, acid-base status, acid dissociated constant and lipid solubility (Greenblatt, 2015).

The structure of the GI tract may be routinely altered by surgical interventions, but the physiological consequences and effects on oral drug delivery are often dependent on the extent of this physical change as well as the location: In the intestine, for instance, the impact of a minor resection or anastomoses may have minimal influence on broader intestinal function and motility, whereas a gastric bypass may considerably (and purposefully) impair total oro-caecal transit time (OCTT) (Association, 2003; Titus et al., 2013). Trends in the oral drug exposure of cardiovascular, PPIs, anti-diabetics, immunosuppressants and antidepressants following bariatric surgery are summarised in Table 2.

Table 2. Controlled trials examining the trend in oral drug exposure following bariatric surgery. (adapted from Darwich et al., 2012).

	Drug	Surgery	Pre- to post-surgery oral drug exposure ratio	Patients (n)	Ref
>	Atorvastatin acid 20 – 80 mg	BPD-DS	1.85 (0.81, 4.27)†	10	(Skottheim et al., 2010)
	Ranitidine 300 mg	BPD	1.43 (1.12, 1.81)*	11	(Cossu et al., 1999)
	Metformin 1000 mg	RYGB	1.20 (0.91, 1.58)†	16	(Padwal et al., 2011)
–	Atorvstatin acid 20 – 80 mg	RYGB	1.00 (0.29, 3.46)†	12	(Skottheim et al., 2009)
	Erythromycin 250 mg	GBP	0.61 (0.38, 0.99)†	7	(Prince et al., 1984)
	MMF 2 1000 mg	RYGB	0.66 (0.21, 2.06)*	2	(Rogers et al., 2008)
<	Sirolimus 8 mg	RYGB	0.54 (0.25, 1.17)*	4	(Brattstrom et al., 2000; Mathew et al., 2006; Rogers et al., 2008)
	Setraline 100 mg	RYGB	0.40 (0.19, 0.84)†	5	(Roerig et al., 2012)

> indicates a significant increase in oral drug exposure (AUC) following surgery

– no statistical significance in oral drug exposure following surgery

< indicates a significant reduction in oral drug exposure BPD-DS: bioliopancreatic d-diversion with a duodenal switch, BDP: biliopancreatic diversion, RYGB: Roux-en Y gastric bypass and GBP: gastric bypass.

* denotes a t-test performed at 5% significance level and † as the statistical outcome as reported in the referenced publication

4.1 Gastric resections and bypass

The extent of a gastric lesion or section may be proportionally classified as a wedge resection or as a distal, subtotal or total gastrectomy, whereas bariatric procedures are referred to as those

which are restrictive (such as SG), malabsorptive (JIB), or both (such as in the case of the more common RYGB). Inevitably, the GI environment is altered considerably by these procedures, and with high likelihood of nutritional and/or luminal complications such as stomal and marginal ulcerations occurring.

Though the vast majority of orally-administered drugs are minimally absorbed at the level of the stomach, the effects of surgery on transit time and gastric emptying may otherwise influence the pharmacokinetics and pharmacodynamics of a dosage form in addition to its removal, though can also potentially be exploited for more rapid absorption in the case of immediate-release (IR) preparations. Postoperative syndromes (such as those following gastric resection by Billroth II operation, vagotomy and Whipple's operation) commonly lead to both disorders of motility and functional digestion, with impaired hormonal stimulation of the exocrine pancreas (postprandial pancreaticobiliary asynchrony) (Jefferson et al., 1950; Milovic and Stein, 2010).The effects of these alterations on drug absorption are difficult to predict, however; a study by Darwich et al. (2012) revealed that no trends were observed as for the reduction or increase in post-surgical drug absorption and bioavailability, indicating that each case should be investigated separately. Indeed, the same drug may exhibit different absorption trends following GI surgery: The bioavailability of atorvastatin as one example following biliopancreatic diversion with duodenal switch was increased significantly and T_{max} increased from 1.3 h pre- surgery to 2.3 h post-surgery ($p = 0.03$)(Skottheim et al., 2010) (Figure 6).

A more common complication, however, is that of associated dose-dumping of the drug which is usually in conjunction with physiological manifestations such as diarrhoea and abdominal pain within 30 minutes of meal consumption (Titus et al., 2013). This also has particular implications for the administration of those medications to be taken concomitantly with food. Drug and dosing characteristics are thus equally crucial – BCS Class II (low solubility and high permeability) and III (high solubility and low permeability) biopharmaceuticals may be met with limitations on windows for absorption (both time and physical capacity or surface area) imposed by a resection in the stomach or small intestine, and BCS Class I drugs primarily absorbed at the level of the stomach will be inevitably affected by gastric bypass procedures due to a later absorption and thus, may decrease drug efficacy (Miller and Smith, 2006). However, the latter may also predispose to toxicity from drugs such as NSAIDs and bisphosphonates, where damage to the gastric mucosa impairs normal barrier function. Switching to an alternative formulation or drug entirely may thus be necessitated in the case of

those drugs with a narrow therapeutic index affected by GI resection where a sub-therapeutic or toxic effect is arguably inevitable (Edwards and Ensom, 2012), and the use of modified or extended-release formulations may be inappropriate. Salt forms of drugs can also affect, and be affected by, mechanisms of drug absorption in the gut – some are also more easily absorbed than others, such as calcium citrate versus calcium carbonate (Miller and Smith, 2006).

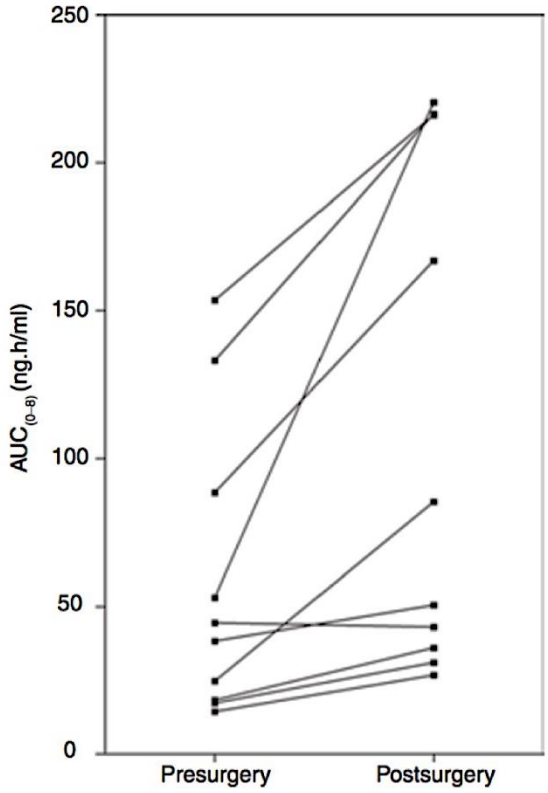

Figure 6. Individual atorvastatin acid AUC(ng•h/ml) changes between pre- and post-surgery. (reproduced with permission from Skottheim et al., 2010).

4.2 Small intestinal resections

The effects of surgery and gastric emptying have been well documented but less is known about the surgical effects on the small intestine due to congenital defects or the consequence of disease. Absorption, immunity and motility are fundamental components of small bowel physiology. Resection of less than half of the small intestine poses minimal difficulties for patient management and the resection of up to 8 feet of the proximal jejunum is often compensated for with the residual distal gut (Kvietys, 1999). However, when extended segments of bowel are bypassed or resected, fat malabsorption plays a role in GI dysfunction as indicated by significant steatorrhea (Gondolesi and Almau, 2012), predisposing patients to deficiencies of fat soluble vitamins (A, D, E and K) and drugs that interact with them (Mitchell

et al., 1977). Malabsorption of BCS Class III and notably fat-soluble drugs such as the androgen therapies may also be affected by the simultaneous impairment of fat absorption due to SI resection and a decrease in available intestinal surface area which again may warrant the selection of drug alternatives for affected patients, or an alternative route of delivery. Other lipophilic drugs such as hydrocortisone, oestrogen and cyclosporine become similarly malabsorbed (Hanker, 1990). In the case of oral antibiotics, however, cephalexin, trimethoprim and metronidazole are well absorbed in the short gut (Menardi and Guggenbichler, 1984).

The consequences of surgical intervention in the small intestine on oral drug delivery and dosage performance relate largely to those drugs which undergo enterohepatic recirculation, and which is almost always impaired in the case of SI anastomoses with increased excretion of recycled bile acids in faeces. Commonly-prescribed examples include the cardiovascular agents warfarin (Jahnchen et al., 1978), digoxin (Roberts et al., 2002), and the statins (Kim et al., 2011), to name but a few affected in this way. Loss of the duodenum or the terminal ileum implicate the effectiveness of absorption more than the resection of other parts of the small bowel as specific absorptive and regulatory functions cannot be compensated by other intestinal sites.

Total GI transit times are largely decreased in patients with severe short bowel syndrome averaging to 96.3 min (observed by using blue food colouring to appear in ostomy effluent of stool samples) and thus, can contribute to reduced nutrient and drug absorption (Compher et al., 2007). Another GI parameter that is deeply altered due to small bowel syndrome is the faecal and mucosal associated microbiome when compared to controls. *Lactobacillus mucosae*, a bacterial family not detected in controls, was specifically prevalent in subjects who underwent small intestinal resections (Ziegler et al., 2002). Decreased levels of *C. coccoides*, Bacteroidetes, *C. leptum*, Bifidovacterium and *Methanobrevibacter smithii* were also observed in patients with small bowel syndrome.

4.3 Colonic resections

The importance of the colon has gained increased significance in recent years as a target for both localised and systemic drug delivery via the oral and rectal routes. Exploitation of colonic pH and the gut microbiota provide major avenues for the delivery of modified-release formulations, in addition to acting as a “fail-safe” site for remnant absorption of drugs largely bypassing the stomach and small intestine, including a number of NSAIDs (Kennedy and Van

Riji, 1998). However, with colonic resection (e.g. ileal-pouch-anal anastomosis), the benefits and ease of colonic targeting are markedly impaired and often ablated entirely relative to the extent of the anastomosis, and almost always in the case of delayed-release products. This in turn leads to sub-therapeutic efficacy of the administered product(s) which have only been moderately managed through the use of increasingly complex polymer formulations (Berner and Cowles, 2006; Titus et al., 2013).

5.0 Conclusions

Drug release and availability at the site of action are the major factors determining clinical response for drugs administered for GI diseases. Drugs are extensively investigated regarding its pharmacokinetics, pharmacodynamics and toxicity in healthy patients by virtue of first-in-human studies and for its particular indication, however, drug development fails to assess the implication of co-morbidities on drug effectiveness. Indeed, there remain strikingly large gaps in our knowledge of the potential ramification of GI diseases such as IBS, IBD, UC, CD, celiac disease, microbial dysbiosis, infections, the impact of GI surgery and other disease indications despite the intestinal environment being the main site of absorption for orally administered drugs. In this review, we report that the influence of disease states on GI physiology and oral absorption are sporadic and often contradictory. Although, the overarching theme that resounds is that diseases of the GI tract can significantly affect motility, luminal environment, permeability, GI tract mucosa and perturb microbial symbiosis. Formulation development in this context is required to consider the highly variable nature of the GI tract in order to achieve dosage form optimisation. Given that drug pharmacokinetics already demonstrate high inter-individual variability in healthy adults which is further complicated in the presence of disease states, disease localisation and co-morbidities, drug development should test under conditions specific to the particular pathophysiology and consider the assessment of medications not directly prescribed for the treatment of GI disorders. This would improve the identification of potential differences in absorption between healthy and diseased states which should be the vision of improving dissolution models and thus, accelerate the translation of important new drugs to patients.

Acknowledgements

The authors would like to acknowledge the help of the members of the Basit Research Group for their helpful comments and suggestions towards this manuscript.

References

Abuhelwa, A.Y., Foster, D.J., Upton, R.N., 2016a. A Quantitative Review and Meta-Models of the Variability and Factors Affecting Oral Drug Absorption-Part I: Gastrointestinal pH. AAPS J 18, 1309-1321.

Abuhelwa, A.Y., Foster, D.J., Upton, R.N., 2016b. A Quantitative Review and Meta-models of the Variability and Factors Affecting Oral Drug Absorption-Part II: Gastrointestinal Transit Time. AAPS J 18, 1322-1333.

Annibale, B., Di Giulio, E., Caruana, P., Lahner, E., Capurso, G., Bordi, C., Delle Fave, G., 2002. The long-term effects of cure of Helicobacter pylori infection on patients with atrophic body gastritis. Alimentary Pharmacology & Therapeutics 16, 1723-1731.

American Gastroinestinal Association, 2003. American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. Gastroenterology 124, 1105-1110.

Bagnolo, F., Bonassi, U., Lella, F., Colombo, E., Testoni, P.A., 2001. In functional dyspepsia curing helicobacter pylori infection increases the risk of reflux esophagttis. Digestive and Liver Disease 33, Supplement 1, A52.

Bai, J.P.F., Burckart, G.J., Mulberg, A.E., 2016. Literature Review of Gastrointestinal Physiology in the Elderly, in Pediatric Patients, and in Patients with Gastrointestinal Diseases. J Pharm Sci 105, 476-483.

Banerjee, S., Sindberg, G., Wang, F., Meng, J., Sharma, U., Zhang, L., Dauer, P., Chen, C., Dalluge, J., Johnson, T., Roy, S., 2016. Opioid-induced gut microbial disruption and bile dysregulation leads to gut barrier compromise and sustained systemic inflammation. Mucosal Immunol 9, 1418-1428.

Barrow, L., Spiller, R.C., Wilson, C.G., 1991. Pathological influences on colonic motility: implications for drug delivery. Advanced Drug Delivery Reviews 7, 201-218.

Basit, A.W., Newton, J.M., Lacey, L.F., 2002. Susceptibility of the H2-receptor antagonists cimetidine, famotidine and nizatidine, to metabolism by the gastrointestinal microflora. Int J Pharm 237, 23-33.

Basit, A.W., Short, M.D., McConnell, E.L., 2009. Microbiota-triggered colonic delivery: robustness of the polysaccharide approach in the fed state in man. J Drug Target 17, 64-71.

Baumgart, D.C., Sandborn, W.J., 2012. Crohn's disease. Lancet 380, 1590-1605.

Behrens, R.H., Taylor, R.B., Low, A.S., Warburton, B., Pryce, D., 1994. Traveller's diarrhoea; a controlled study of its effect on chloroquine and proguanil absorption. Trans R Soc Trop Med Hyg 88, 86-88.

Berner, B., Cowles, V.E., 2006. Case studies in swelling polymeric gastric retentive tablets. Expert opinion on drug delivery 3, 541-548.

Bischoff, S.C., Barbara, G., Buurman, W., Ockhuizen, T., Schulzke, J.D., Serino, M., Tilg, H., Watson, A., Wells, J.M., 2014. Intestinal permeability--a new target for disease prevention and therapy. BMC Gastroenterol 14, 189.

Bjarnason, I., Sisson, G., Ayis, S., 2012. ASSESSMENT OF THE PROBIOTIC SYMPROVE IN PATIENTS WITH IBS: A RANDOMISED DOUBLE BLIND PLACEBO CONTROLLED TRIAL. Gut 61, A104-A104.

Blokzijl, H., Vander Borght, S., Bok, L.I., Libbrecht, L., Geuken, M., van den Heuvel, F.A., Dijkstra, G., Roskams, T.A., Moshage, H., Jansen, P.L., Faber, K.N., 2007. Decreased P-glycoprotein (P-gp/MDR1) expression in inflamed human intestinal epithelium is independent of PXR protein levels. Inflamm Bowel Dis 13, 710-720.

Bonfrate, L., Tack, J., Grattagliano, I., Cuomo, R., Portincasa, P., 2013. Microbiota in health and irritable bowel syndrome: current knowledge, perspectives and therapeutic options. Scandinavian Journal of Gastroenterology 48, 995-1009.

Borst, P., Elferink, R.O., 2002. Mammalian ABC transporters in health and disease. Annu Rev Biochem 71, 537-592.

Bosaeus, I., 2004. Fibre effects on intestinal functions (diarrhoea, constipation and irritable bowel syndrome). Clinical Nutrition, 33-38.

Bosworth, B.P., Cohen, M., Weine, D. M., Scherl, E. J., 2009. Colonic pH Is Lower in Patients with Mild Ulcerative Colitis Compared to Normal Controls. Gastroenterology 136, A682-A683.

Brandtzaeg, P., 2011. The gut as communicator between environment and host: immunological consequences. Eur J Pharmacol 668 Suppl 1, S16-32.

Brattstrom, C., Sawe, J., Jansson, B., Lonnebo, A., Nordin, J., Zimmerman, J.J., Burke, J.T., Groth, C.G., 2000. Pharmacokinetics and safety of single oral doses of sirolimus (rapamycin) in healthy male volunteers. Ther Drug Monit 22, 537-544.

Brenchley, J.M., Douek, D.C., 2012. Microbial translocation across the GI tract. Annu Rev Immunol 30, 149-173.

Burcelin, R., Serino, M., Chabo, C., Garidou, L., Pomie, C., Courtney, M., Amar, J., Bouloumie, A., 2013. Metagenome and metabolism: the tissue microbiota hypothesis. Diabetes Obesity & Metabolism 15, 61-70.

Camilleri, M., Lasch, K., Zhou, W., 2012. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 303, G775-785.

Cann, P.A., Read, N.W., Brown, C., Hobson, N., Holdsworth, C.D., 1983. Irritable bowel syndrome: relationship of disorders in the transit of a single solid meal to symptom patterns. Gut 24, 405-411.

Carrette, O., Favier, C., Mizon, C., Neut, C., Cortot, A., Colombel, J.F., Mizon, J., 1995. Bacterial enzymes used for colon-specific drug delivery are decreased in active Crohn's disease. Digestive Diseases and Sciences 40, 2641-2646.

Centanni, M., Gargano, L., Canettieri, G., Viceconti, N., Franchi, A., Delle Fave, G. and Annibale, B., 2006. Thyroxine in Goiter, *Helicobacter pylori* infection and chronic gastritis. The New England Journal of Medicine 354, 1787 - 1795.

Chey, W.Y., Jin, H.O., Lee, M.H., Sun, S.W., Lee, K.Y., 2001. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. The American Journal of Gastroenterology 96, 1499-1506.

Chowdhury, A.H., Lobo, D.N., 2011. Fluids and gastrointestinal function. Current Opinion in Clinical Nutrition and Metabolic Care 14, 469-476.

Collins, D., Wilcox, R., Nathan, M., Zubarik, R., 2012. Celiac Disease and Hypothyroidism. American Journal of Medicine 125, 278-282.

Collins, S.M., Hamilton, J.D., Lewis, T.D., Laufer, I., 1978. SMALL BOWEL MALABSORPTION AND GASTROINTESTINAL MALIGNANCY. Radiology 126, 603-609.

Compher, C., Rubesin, S., Kinosian, B., Madaras, J., Metz, D., 2007. Noninvasive measurement of transit time in short bowel syndrome. JPEN J Parenter Enteral Nutr 31, 240-245.

Cossu, M.L., Caccia, S., Coppola, M., Fais, E., Ruggiu, M., Fracasso, C., Nacca, A., Noya, G., 1999. Orally administered ranitidine plasma concentrations before and after biliopancreatic diversion in morbidly obese patients. Obes Surg 9, 36-39.

Coupe, A.J., Davis, S.S., Wilding, I.R., 1991. VARIATION IN GASTROINTESTINAL TRANSIT OF PHARMACEUTICAL DOSAGE FORMS IN HEALTHY-SUBJECTS. Pharmaceutical Research 8, 360-364.

Danese, S., Sans, M., Fiocchi, C., 2004. Inflammatory bowel disease: the role of environmental factors. Autoimmunity Reviews 3, 394-400.

Darwich, A.S., Henderson, K., Burgin, A., Ward, N., Whittam, J., Ammori, B.J., Ashcroft, D.M., Rostami-Hodjegan, A., 2012. Trends in oral drug bioavailability following bariatric surgery: examining the variable extent of impact on exposure of different drug classes. Br J Clin Pharmacol 74, 774-787.

Davis, S.S., Hardy, J.G., Fara, J.W., 1986. TRANSIT OF PHARMACEUTICAL DOSAGE FORMS THROUGH THE SMALL-INTESTINE. Gut 27, 886-892.

Davis, S.S., Robertson, C., Wilding, I.R., 1991. Gastrointestinal transit of a multiparticulate tablet formulation in patients with active ulcerative colitis. International Journal of Pharmaceutics 68, 199-204.

de la Cuesta-Zuluaga, J., Mueller, N.T., Corrales-Agudelo, V., Velasquez-Mejia, E.P., Carmona, J.A., Abad, J.M., Escobar, J.S., 2017. Metformin Is Associated With Higher Relative Abundance of Mucin-Degrading Akkermansia muciniphila and Several Short-Chain Fatty Acid-Producing Microbiota in the Gut. Diabetes Care 40, 54-62.

Degen, L.P., Phillips, S.F., 1996. Variability of gastrointestinal transit in healthy women and men. Gut 39, 299-305.

Deiteren, A., Camilleri, M., Burton, D., McKinzie, S., Rao, A., Zinsmeister, A.R., 2010. Effect of Meal Ingestion on Ileocolonic and Colonic Transit in Health and Irritable Bowel Syndrome. Digestive Diseases and Sciences 55, 384-391.

D'Haens G.R., Sandborn W.J., Zou, G., Stitt, L.W., Rutgeerts, P.J., Gilgen, D., Jairath, V., Hindryckx, P., Shackelton, L.M., Vandervoort, M.K., Parker, C.E., Muller, C., Pai, R.K., Levchenko, O., Marakhouski, Y., Horynski, M., Mikhailova, E., Kharchenko, N., Pimanov, S., Feagan, B.G., 2017. Randomised non-inferiority trial: 1600 mg versus 400 mg tablets of mesalazine for the treatment of mild-to-moderate ulcerative colitis. Randomised Clinical Trial 46, 292-302.

Didari, T., Mozaffari, S., Nikfar, S., Abdollahi, M., 2015. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. World Journal of Gastroenterology 21, 3072-3084.

Dimagno, E.P., Go, V.L.W., Summersk.Wh, 1973. RELATIONS BETWEEN PANCREATIC ENZYME OUTPUTS AND MALABSORPTION IN SEVERE PANCREATIC INSUFFICIENCY. New England Journal of Medicine 288, 813-815.

Dior, M., Delagreverie, H., Duboc, H., Jouet, P., Coffin, B., Brot, L., Humbert, L., Trugnan, G., Seksik, P., Sokol, H., Rainteau, D., Sabate, J.M., 2016. Interplay between bile acid

metabolism and microbiota in irritable bowel syndrome. Neurogastroenterol Motil 28, 1330-1340.

Dodoo, C.C., Wang, J., Basit, A.W., Stapleton, P., Gaisford, S., 2017. Targeted delivery of probiotics to enhance gastrointestinal stability and intestinal colonisation. Int J Pharm 530, 224-229.

Dorofeyev, A.E., Vasilenko, I.V., Rassokhina, O.A., Kondratiuk, R.B., 2013. Mucosal Barrier in Ulcerative Colitis and Crohn's Disease. Gastroenterology Research and Practice.

Duffield, R.A., 1996. Cystic fibrosis and the gastrointestinal tract. Journal of Pediatric Health Care 10, 51-57.

Durban, A., Abellan, J.J., Jimenez-Hernandez, N., Artacho, A., Garrigues, V., Ortiz, V., Ponce, J., Latorre, A., Moya, A., 2013. Instability of the faecal microbiota in diarrhoea-predominant irritable bowel syndrome. Fems Microbiology Ecology 86, 581-589.

Eaden, J.A., Abrams, K.R., Mayberry, J.F., 2001. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 48, 526-535.

Edwards, A., Ensom, M.H.H., 2012. Pharmacokinetic Effects of Bariatric Surgery. Annals of Pharmacotherapy 46, 130-136.

Effinger, A., O'Driscoll, C.M., McAllister, M., Fotaki, N., 2018. Impact of gastrointestinal disease states on oral drug absorption - implications for formulation design - a PEARRL review. J Pharm Pharmacol.

Ehehalt, R., Wagenblast, J., Erben, G., Lehmann, W.D., Hinz, U., Merle, U., Stremmel, W., 2004. Phosphatidylcholine and lysophosphatidylcholine in intestinal mucus of ulcerative colitis patients. A quantitative approach by nanoElectrospray-tandem mass spectrometry. Scand J Gastroenterol 39, 737-742.

Elomar, E., Penman, I., Ardill, J.E.S., McColl, K.E.L., 1995. A SUBSTANTIAL PROPORTION OF NONULCER DYSPEPSIA PATIENTS HAVE THE SAME ABNORMALITY OF ACID-SECRETION AS DUODENAL-ULCER PATIENTS. Gut 36.

El Rakaiby, M., Dutilh, B.E., Rizkallah, M.R., Boleij, A., Cole, J.N., Aziz, R.K., 2014. Pharmacomicrobiomics: The Impact of Human Microbiome Variations on Systems Pharmacology and Personalized Therapeutics. Omics-a Journal of Integrative Biology 18, 402-414.

Enright, E.F., Gahan, C. G. M., Joyce, S. A. and Griffin, B. T., 2016. The Impact of the Gut Microbiota on Drug Metabolism and Clinical Outcome. Yale Journal of Biology and Medicine 89, 375 - 383.

Estudante, M., Morais, J.G., Soveral, G., Benet, L.Z., 2013. Intestinal drug transporters: an overview. Adv Drug Deliv Rev 65, 1340-1356.

Ewe, K., Schwartz, S., Petersen, S., Press, A.G., 1999. Inflammation does not decrease intraluminal pH in chronic inflammatory bowel disease. Digestive Diseases and Sciences 44.

Fadda, H.M., Sousa, T., Carlsson, A.S., Abrahamsson, B., Williams, J.G., Kumar, D., Basit, A.W., 2010. Drug solubility in luminal fluids from different regions of the small and large intestine of humans. Mol Pharm 7, 1527-1532.

Fadda, H.M., McConnell, E.L., Short, M.D., Basit, A.W., 2009. Meal-induced acceleration of tablet transit through the human small intestine. Pharm Res 26, 356-360.

Fallingborg, J., Christensen, L.A., Jacobsen, B.A., Rasmussen, S.N., 1993. VERY-LOW INTRALUMINAL COLONIC PH IN PATIENTS WITH ACTIVE ULCERATIVE-COLITIS. Digestive Diseases and Sciences 38, 1989-1993.

Fallingborg, J., Pedersen, F., Jacobsen, B.A., 1998. Small intestinal transit time and intraluminal pH in ileocecal resected patients with Crohn's disease. Digestive Diseases and Sciences 43.

Feagan, B.G., Chande, N., MacDonald, J.K., 2013. Are there any differences in the efficacy and safety of different formulations of Oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? evidence from cochrane reviews. Inflamm Bowel Dis 19, 2031-2040.

Festi, D., Vestito, A., Mazzella, G., Roda, E., Colecchia, A., 2006. Management of hepatic encephalopathy: focus on antibiotic therapy. Digestion 73 Suppl 1, 94-101.

Fischer, M., Siva, S., Wo, J.M., Fadda, H.M., 2017. Assessment of Small Intestinal Transit Times in Ulcerative Colitis and Crohn's Disease Patients with Different Disease Activity Using Video Capsule Endoscopy. AAPS PharmSciTech 18, 404-409.

Freedman, D.O., Weld, L.H., Kozarsky, P.E., Fisk, T., Robins, R., von Sonnenburg, F., Keystone, J.S., Pandey, P., Cetron, M.S., GeoSentinel Surveillance, N., 2006. Spectrum of disease and relation to place of exposure among ill returned travelers. N Engl J Med 354, 119-130.

Freeman, H.J., 2008. Pearls and pitfalls in the diagnosis of adult celiac disease. Canadian Journal of Gastroenterology 22.

Freeman, H.J., 2012. Celiac disease and selected long-term health issues. Maturitas 73, 206-211.

Freeman, H.J., Whittaker, J.S., 1994. NONALCOHOLIC CHRONIC-PANCREATITIS WITH PANCREATIC CALCIFICATION - PRESENTING MANIFESTATION OF OCCULT CELIAC-DISEASE. Canadian Journal of Gastroenterology 8.

Freire, A.C., Basit, A.W., Choudhary, R., Piong, C.W., Merchant, H.A., 2011. Does sex matter? The influence of gender on gastrointestinal physiology nd drug delivery. Int J Pharm 415, 15-28.

Giuliano, V., Bassotti, G., Mourvaki, E., Castellani, D., Filippucci, E., Sabatino, G., Gizzi, S., Palmerini, F., Galli, F., Morelli, O., Baldoni, M., Morelli, A., Iorio, A., 2010. Small intestinal bacterial overgrowth and warfarin dose requirement variability. Thromb Res 126, 12-17.

Gondolesi, G.E., Almau, H.M., 2012. Intestinal transplantation outcomes. Mt Sinai J Med 79, 246-255.

Graff, J., Brinch, K., Madsen, J.L., 2001. Gastrointestinal mean transit times in young and middle-aged healthy subjects. Clinical Physiology 21, 253-259.

Grassi, M., Petraccia, L., Mennuni, G., Fontana, M., Scarno, A., Sabetta, S., Fraioli, A., 2011. Changes, functional disorders, and diseases in the gastrointestinal tract of elderly. Nutr Hosp 26, 659-668.

Green, P.H.R., 2009. Mortality in Celiac Disease, Intestinal Inflammation, and Gluten Sensitivity. Jama-Journal of the American Medical Association 302, 1225-1226.

Green, P.H.R., Tall, A.R., 1979. DRUGS, ALCOHOL AND MALABSORPTION. American Journal of Medicine 67.

Greenblatt, H.K.a.G., D. J. , 2015. Altered Drug Disposition Following Bariatric Surgery: A Research Challenge. Clin Pharmacokinet 54, 573 - 579.

Haiser, H.J., Gootenberg, D.B., Chatman, K., Sirasani, G., Balskus, E.P., Turnbaugh, P.J., 2013. Predicting and Manipulating Cardiac Drug Inactivation by the Human Gut Bacterium Eggerthella lenta. Science 341, 295-298.

Hanauer, S.B., 2006. Inflammatory bowel disease: Epidemiology, pathogenesis, and therapeutic opportunities. Inflammatory Bowel Diseases 12, S3-S9.

Hanker, J.P., 1990. Gastrointestinal disease and oral contraception. Am J Obstet Gynecol 163, 2204-2207.

Hardy, J.G., Davis, S.S., Khosla, R., Robertson, C.S., 1988. GASTROINTESTINAL TRANSIT OF SMALL TABLETS IN PATIENTS WITH ULCERATIVE-COLITIS. International Journal of Pharmaceutics 48, 79-82.

Hardy, J.G., Healey, J.N.C., Reynolds, J.R., 1987. EVALUATION OF AN ENTERIC-COATED DELAYED-RELEASE 5 AMINOSALICYLIC ACID TABLET IN PATIENTS

WITH INFLAMMATORY BOWEL DISEASE. Alimentary Pharmacology and Therapeutics 1, 273-280.

Haruma, K., Kamada, T., Kawaguchi, H., Okamoto, S., Yoshihara, M., Sumii, K., Inoue, M., Kishimoto, S., Kajiyama, G., Miyoshi, A., 2000. Effect of age and Helicobacter pylori infection on gastric acid secretion. J Gastroenterol Hepatol 15, 277-283.

Hatton, G.B., Yadav, V., Basit, A.W., Merchant, H.A., 2015. Animal farm: considerations in animal gastrointestinal physiology and relevance to drug delivery in humans. J Pharm Sci 109, 2747-2776.

Hattori, M., Taylor, T.D., 2009. The human intestinal microbiome: a new frontier of human biology. DNA Res 16, 1-12.

Hebden, J.M., Blackshaw, P.E., Perkins, A.C., Wilson, C.G., Spiller, R.C., 2000. Limited exposure of the healthy distal colon to orally-dosed formulation is further exaggerated in active left-sided ulcerative colitis. Aliment Pharmacol Ther 14, 155-161.

Hegarty, J.P., Sangster, W., Harris, L.R., 3rd, Stewart, D.B., 2014. Proton pump inhibitors induce changes in colonocyte gene expression that may affect Clostridium difficile infection. Surgery 156, 972-978.

Heitkemper, M.M., Chang, L., 2009. Do fluctuations in ovarian hormones affect gastrointestinal symptoms in women with irritable bowel syndrome? Gender Medicine 6, Part 2, 152-167.

Heizer, W.D., Pittman, A.W., Hammond, J.E., Fitch, D.D., Bustrack, J.A., Hull, J.H., 1989. ABSORPTION OF DIGOXIN FROM TABLETS AND CAPSULES IN SUBJECTS WITH MALABSORPTION-SYNDROMES. Dicp-the Annals of Pharmacotherapy 23, 764-769.

Hens, B., Corsetti, M., Spiller, R., Marciani, L., Vanuytsel, T., Tack, J., Talattof, A., Amidon, G.L., Koziolek, M., Weitschies, W., Wilson, C.G., Bennink, R.J., Brouwers, J., Augustijns, P., 2017. Exploring gastrointestinal variables affecting drug and formulation behavior: Methodologies, challenges and opportunities. Int J Pharm 519, 79-97.

Holt, P.R., 2007. Intestinal malabsorption in the elderly. Digestive Diseases 25.

Holt, S., Heading, R. C., Clements, J. A., Tothill, P. and Prescott, L. F., 1981. Acetaminophen absorption and metablism in celiac disease and Crohn's disease. Clin Pharmacol Ther 30, 232 - 238.

Hoque, K.M., Chakraborty, S., Sheikh, I.A., Woodward, O.M., 2012. New advances in the pathophysiology of intestinal ion transport and barrier function in diarrhea and the impact on therapy. Expert Rev Anti Infect Ther 10, 687-699.

Human Microbiome Project, C., 2012. Structure, function and diversity of the healthy human microbiome. Nature 486, 207-214.

Hundt, M., John, S., 2018. Physiology, Bile Secretion. StatPearls Publishing, Treasure Island (FL).

Hurst, S., Loi, C.-M., Brodfuehrer, J., El-Kattan, A., 2007. Impact of physiological, and biopharmaceutical factors in absorption and metabolism mechanisms on the drug oral bioavailability of rats and humans. Expert Opinion on Drug Metabolism & Toxicology 3, 469-489.

Ibekwe, V.C., Fadda, H.M., McConnell, E.L., Khela, M.K., Evans, D.F., Basit, A.W., 2008a. Interplay between intestinal pH, transit time and feed status on the in vivo performance of pH responsive ileo-colonic release systems. Pharm Res 25, 1828-1835.

Ibekwe, V.C., Khela, M.K., Evans, D.F., Basit, A.W., 2008b. A new concept in colonic drug targeting: a combined pH-responsive and bacterially-triggered drug delivery technology. Aliment Pharmacol Ther 28, 911-916.

Ibekwe, V.C., Liu, F., Fadda, H.M., Khela, M.K., Evans, D.F., Parsons, G.E., Basit, A.W., 2006. An investigation into the in vivo performance variability of pH responsive polymers for ileo-colonic drug delivery using gamma scintigraphy in humans. J Pharm Sci 95, 2760-2766.

Imhann, F., Bonder, M.J., Vich Vila, A., Fu, J., Mujagic, Z., Vork, L., Tigchelaar, E.F., Jankipersadsing, S.A., Cenit, M.C., Harmsen, H.J., Dijkstra, G., Franke, L., Xavier, R.J., Jonkers, D., Wijmenga, C., Weersma, R.K., Zhernakova, A., 2016. Proton pump inhibitors affect the gut microbiome. Gut 65, 740-748.

Jahnchen, E., Meinertz, T., Gilfrich, H.J., Kersting, F., Groth, U., 1978. ENHANCED ELIMINATION OF WARFARIN DURING TREATMENT WITH CHOLESTYRAMINE. British Journal of Clinical Pharmacology 5, 437-440.

Jamei, M., Turner, D., Yang, J., Neuhoff, S., Polak, S., Rostami-Hodjegan, A., Tucker, G., 2009. Population-Based Mechanistic Prediction of Oral Drug Absorption. Aaps Journal 11, 225-237.

Janarthanan, S., Ditah, I., Adler, D.G., Ehrinpreis, M.N., 2012. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol 107, 1001-1010.

Jefferson, N.C., Phillips, C.W., Levine, R., Necheles, H., 1950. POSTGASTRECTOMY AND POSTVAGOTOMY SYNDROME. Journal of Applied Physiology 2, 469-476.

Johnson, T.N., Tanner, M.S., Taylor, C.J., Tucker, G.T., 2001. Enterocytic CYP3A4 in a paediatric population: developmental changes and the effect of coeliac disease and cystic fibrosis. Br J Clin Pharmacol 51, 451-460.

Jonefjäll, B., Strid, H., Ohman, L., Svedlund, J., Bergstedt, A., Simren, M., 2014. The Severity of Abdominal Pain At Onset of Ulcerative Colitis Is Associated With IBS-Like Symptoms During Clinical Remission. Gastroenterology 146, S448.

Kalantzi, L., Goumas, K., Kalioras, V., Abrahamsson, B., Dressman, J.B., Reppas, C., 2006. Characterization of the human upper gastrointestinal contents under conditions simulating bioavailability/bioequivalence studies. Pharmaceutical Research 23, 165-176.

Kaplan, G.G., 2015. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol 12, 720-727.

Kaplan, G.G., Ng, S.C., 2017. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. Gastroenterology 152, 313-321 e312.

Karlstadt, R.G., Hogan, D.L., Foxx-Orenstein, A., 2004. 36 - Normal Physiology of the Gastrointestinal Tract and Gender Differences, in: Marianne, J.L., Mda2 - Marianne J. Legato, M.D. (Eds.), Principles of Gender-Specific Medicine. Academic Press, San Diego, pp. 377-396.

Kassinen, A., Krogius-Kurikka, L., Makivuokko, H., Rinttila, T., Paulin, L., Corander, J., Malinen, E., Apajalahti, J., Palva, A., 2007. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. Gastroenterology 133, 24-33.

Keller, J., Melle, U., Schneider, M., Hoene, K., Henniges, U., Groeger, G., Layer, P., 2000. Delayed gastric emptying of solids in Crohn's disease and ulcerative colitis. Gastroenterology 118, A1180.

Kendall, R.A., Alhan, M.A., Nilkumhang, S., Mudan, S., Basit, A.W., 2009. Fabrication an in vivo evaluation of highly pH-responsive acrylic microparticles for targeted gastrointestinal delivery. Eur J Pharm Sci 37, 284-290.

Kennedy, J.M., Van Riji, A.M., 1998. Effects of surgery on the pharmacokinetic parameters of drugs. Clinical Pharmacokinetics 35, 293-312.

Kim, K., Yoon, I., Chun, I., Lee, N., Kim, T., Gwak, H.S., 2011. Effects of bile salts on the lovastatin pharmacokinetics following oral administration to rats. Drug Delivery 18, 79-83.

Kitis, G., Lucas, M.L., Bishop, H., Sargent, A., Schneider, R.E., Blair, J.A., Allan, R.N., 1982a. ALTERED JEJUNAL SURFACE PH IN CELIAC-DISEASE - ITS EFFECT ON PROPRANOLOL AND FOLIC-ACID ABSORPTION. Clinical Science 63, 373-380.

Kitis, G., Lucas, M.L., Bishop, H., Sargent, A., Schneider, R.E., Blair, J.A., Allan, R.N., 1982b. Altered jejunal surface pH in coeliac disease: its effect on propranolol and folic acid absorption. Clin Sci (Lond) 63, 373-380.

Koppel, N., Maini Rekdal, V., Balskus, E.P., 2017. Chemical transformation of xenobiotics by the human gut microbiota. Science 356.

Krupa-Kozak, U., 2014. Pathologic bone alterations in celiac disease: etiology, epidemiology, and treatment. Nutrition 30, 16-24.

Kuipers, E.J., 1997. Helicobacter pylori and the risk and management of associated diseases: Gastritis, ulcer disease, atrophic gastritis and gastric cancer. Alimentary Pharmacology & Therapeutics 11.

Kvietys, P.R., 1999. Intestinal physiology relevant to short-bowel syndrome. Eur J Pediatr Surg 9, 196-199.

Kwok, C.S., Arthur, A.K., Anibueze, C.I., Singh, S., Cavallazzi, R., Loke, Y.K., 2012. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. Am J Gastroenterol 107, 1011-1019.

Labenz, J., Tillenburg, B., Peitz, U., Idstrom, J.P., Verdu, E.F., Stolte, M., Borsch, G., Blum, A.L., Helicobacter pylori augments the pH-increasing effect of omeprazole in patients with duodenal ulcer. Gastroenterology 110, 725-732.

Lahner, E., Virili, C., Santaguida, M.G., Annibale, B., Centanni, M., 2014. Helicobacter pylori infection and drugs malabsorption. World Journal of Gastroenterology 20, 10331-10337.

Lalezari, D., 2012. Gastrointestinal pH profile in subjects with irritable bowel syndrome. Ann Gastroenterol 25, 333-337.

Lammers, K.M., Lu, R., Brownley, J., Lu, B., Gerard, C., Thomas, K., Rallabhandi, P., Shea-Donohue, T., Tamiz, A., Alkan, S., Netzel-Arnett, S., Antalis, T., Vogel, S.N., Fasano, A., 2008. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. Gastroenterology 135, 194-204 e193.

Lang, C.C., Brown, R.M., Kinirons, M.T., Deathridge, M.A., Guengerich, F.P., Kelleher, D., Obriain, D.S., Ghishan, F.K., Wood, A.J.J., 1996. Decreased intestinal CYP3A in celiac disease: Reversal after successful gluten-free diet: A potential source of interindividual variability in first-pass drug metabolism. Clinical Pharmacology & Therapeutics 59.

Le Bastard, Q., Al-Ghalith, G.A., Gregoire, M., Chapelet, G., Javaudin, F., Dailly, E., Batard, E., Knights, D., Montassier, E., 2018. Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications. Aliment Pharmacol Ther 47, 332-345.

Lee, J., Rheem, S., Yun, B., Ahn, Y., Joung, J., Lee, S.J., Oh, S., Chun, T., Rheem, I., Yea, H.S., Lim, K.S., Cha, J.M., Kim, S., 2013. Effects of probiotic yoghurt on symptoms and intestinal microbiota in patients with irritable bowel syndrome. International Journal of Dairy Technology 66, 243-255.

Leong, C.W., Newton, J.M., Basit, A.W., Podczeck, F., Cummings, J.H., Ring, S.G., 2002. The formation of colonic digestible films of amylose and ethylcellulose from aqueous dispersions at temperatures below 37 degrees C. Eur J Pharm Biopharm 54, 291-297.

Liu, F., Lizio, R., Meier, C., Petereit, H.U., Blakey, P., Basit, A.W., 2009. A novel concept in enteric coating: a double-coating system providing rapid drug release in the proximal small intestine. J Control Release 133, 119-124.

Liwanpo, L., Hershman, J.M., 2009. Conditions and drugs interfering with thyroxine absorption. Best Pract Res Clin Endocrinol Metab 23, 781-792.

Losurdo, G., Marra, A., Shahini, E., Girardi, B., Giorgio, F., Amoruso, A., Pisani, A., Piscitelli, D., Barone, M., Principi, M., Di Leo, A., Ierardi, E., 2017. Small intestinal bacterial overgrowth and celiac disease: A systematic review with pooled-data analysis. Neurogastroenterology & Motility 29, e13028-n/a.

Louie, T.J., Miller, M.A., Mullane, K.M., Weiss, K., Lentnek, A., Golan, Y., Gorbach, S., Sears, P., Shue, Y.K., Group, O.P.T.C.S., 2011. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 364, 422-431.

Ludvigsson, J.F., Card, T.R., Kaukinen, K., Bai, J., Zingone, F., Sanders, D.S., Murray, J.A., 2015. Screening for celiac disease in the general population and in high-risk groups. United European Gastroenterology Journal 3, 106-120.

Luetke, A., Weismueller, J., Kuller-Luetke, G., Practice, G., 2000. Crohn's disease of the upper gastrointestinal tract. Gastroenterology 118, A1355.

Malagelada, J.R., 2006. A symptom-based approach to making a positive diagnosis of irritable bowel syndrome with constipation. International Journal of Clinical Practice 60, 57-63.

Manes, G., Esposito, P., Lioniello, M., Bove, A., Mosca, S., Balzano, A., 2000. Manometric and pH-metric features in gastro-oesophageal reflux disease patients with and without Helicobacter pylori infection. Digestive and Liver Disease 32, 372-377.

Manes, G., Mosca, S., de Nucci, C., Lombardi, G., Lioniello, M., Salzano, A., 2001. High prevalence of reflux symptoms in duodenal ulcer patients who develop gastro-oesophageal reflux disease after curing Helicobacter pylori infection. Digestive and Liver Disease 33, 665-670.

Maroni, A., Moutaharrik, S., Zema, L., Gazzaniga, A., 2017. Enteric coatings for colonic drug delivery: state of the art. Expert Opin Drug Deliv 14, 1027-1029.

Marshall, B.J., 1994. HELICOBACTER-PYLORI. American Journal of Gastroenterology 89.

Mathew, T.H., Van Buren, C., Kahan, B.D., Butt, K., Hariharan, S., Zimmerman, J.J., 2006. A comparative study of sirolimus tablet versus oral solution for prophylaxis of acute renal allograft rejection. J Clin Pharmacol 46, 76-87.

Matsuoka, K., Kobayashi, T., Ueno, F., Matsui, T., Hirai, F., Inoue, N., Kato, J., Kobayashi, K., Kobayashi, K., Koganei, K., Kunisaki, R., Motoya, S., Nagahori, M., Nakase, H., Omata, F., Saruta, M., Watanabe, T., Tanaka, T., Kanai, T., Noguchi, Y., Takahashi, K., Watanabe, K., Hibi, T., Suzuki, Y., Watanabe, M., Sugano, K., Shimosegawa, T., 2018. Evidence-based clinical practice guidelines for inflammatory bowel disease. J Gastroenterol 53, 305 - 353.

Mattila, M.J., Jussila, J., Takki, S., 1973. DRUG ABSORPTION IN PATIENTS WITH INTESTINAL VILLOUS ATROPHY. Arzneimittel-Forschung/Drug Research 23.

McColl, K.E.L., El-Omar, E., Gillen, D., 2000. Helicobacter pylori gastritis and gastric physiology. Gastroenterology Clinics of North America 29, 687-+.

McCollum, D.L., Rodriguez, J.M., 2012. Detection, treatment, and prevention of Clostridium difficile infection. Clin Gastroenterol Hepatol 10, 581-592.

McConnell, E.L., Fadda, H.M., Basit, A.W., 2008a. Gut instincts: explorations in intestinal physiology and drug delivery. Int J Pharm 364, 213-226.

McConnell, E.L., Liu, F., Basit, A.W., 2009. Colonic treatments and targets: issues and opportunities. J Drug Target 17, 335-363.

McConnell, E.L., Short, M.D., Basit, A.W., 2008b. An in vivo comparison of intestinal pH and bacteria as physiological trigger mechanisms for colonic targeting in man. J Control Release 130, 154-160.

McConnell, E.L., Murdan, S., Basit, A.W., 2008c. An investigation into the digestion of chitosan (noncrosslinked and crosslinked) by human colonic bacteria. J Pharm Sci 97, 3820-3829.

McKelvey, S.T., 1970. GASTRIC INCONTINENCE AND POST-VAGOTOMY DIARRHOEA. British Journal of Surgery 57.

Menardi, G., Guggenbichler, J.P., 1984. Bioavailability of oral antibiotics in children with short-bowel syndrome. J Pediatr Surg 19, 84-86.

Merchant, H.A., Liu, F., Gul, M. O., Basit, A.W., 2016. Age-mediated changes in the gastrointestinal tract. Int J Pharm 512, 382-395.

Miller, A.D., Smith, K.M., 2006. Medication and nutrient administration considerations after bariatric surgery. American Journal of Health-System Pharmacy 63, 1852-1857.

Milovic, V., Stein, J., 2010. Gastrointestinal disease and dosage form performance, in: Dressman, J.B., Reppas, C. (Eds.), Oral Drug Absorption: Prediction and Assessment, 2nd ed. Informa Healthcare, USA, pp. 133-136.

Milovic, V.a.S., J., 2010. Gastrointestinal Disease and Dosage Form Performance, in: Dressman, J.B.a.R., C. (Ed.), Oral Drug Absorption. CRC Press, Taylor and Francis Group, Florisa, pp. 127 - 135.

Mitchell, J.F., Maas, L.C., Barger, R.C., Geizayd, E.A., 1977. Successful oral anticoagulant therapy in a patient with short bowel syndrome. Am J Hosp Pharm 34, 171-172.

Miyaji, H., Azuma, T., Ito, S., Abe, Y., Ono, H., Suto, H., Ito, Y., Yamazaki, Y., Kohli, Y., Kuriyama, M., 1999. The effect of Helicobacter pylori eradication therapy on gastric antral myoelectrical activity and gastric emptying in patients with non-ulcer dyspepsia. Alimentary Pharmacology & Therapeutics 13, 1473-1480.

Moberg, S., Carlberg.G, 1974. GASTRIC-EMPTYING IN HEALTHY SUBJECTS AND IN PATIENTS WITH VARIOUS MALABSORPTIVE STATES. Scandinavian Journal of Gastroenterology 9, 17-21.

Moja, L., Danese, S., Fiorino, G., Del Giovane, C., Bonovas, S., 2015. Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine (mesalamine) for Crohn's disease. Alimentary pharmacology & therapeutics 41, 1055-1065.

Molodecky, N.A., Soon, I.S., Rabi, D.M., Ghali, W.A., Ferris, M., Chernoff, G., Benchimol, E.I., Panaccione, R., Ghosh, S., Barkema, H.W., Kaplan, G.G., 2012. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review. Gastroenterology 142, 46-54.

Moron, B., Verma, A.K., Das, P., Taavela, J., Dafik, L., DiRaimondo, T.R., Albertelli, M.A., Kraemer, T., Maki, M., Khosla, C., Rogler, G., Makharia, G.K., 2013. CYP3A4-Catalyzed Simvastatin Metabolism as a Non-Invasive Marker of Small Intestinal Health in Celiac Disease. American Journal of Gastroenterology 108, 1344-1351.

Mortimer, D.C., Finlay, J.M., Vidinli, M., Reed, P.I., 1964. ROLE OF UPPER GASTROINTESTINAL FLORA IN MALABSORPTION SYNDROME. Canadian Medical Association Journal 90, 559-&.

Muraki, M., Fujiwara, Y., Machida, H., Okazaki, H., Sogawa, M., Yamagami, H., Tanigawa, T., Shiba, M., Watanabe, K., Tominaga, K., Watanabe, T., Arakawa, T., 2014. Role of small

intestinal bacterial overgrowth in severe small intestinal damage in chronic non-steroidal anti-inflammatory drug users. Scand J Gastroenterol 49, 267-273.

Myers, C.A., Slack, T., Martin, C.K., Broyles, S.T., Heymsfield, S.B., 2015. Regional disparities in obesity prevalence in the United States: A spatial regime analysis. Obesity (Silver Spring) 23, 481-487.

Newton, J.L., 2004. Changes in upper gastrointestinal physiology with age. Mechanisms of Ageing and Development 125, 867-870.

Ng, S.C., Tang, W., Ching, J.Y., Wong, M., Chow, C.M., Hui, A.J., Wong, T.C., Leung, V.K., Tsang, S.W., Yu, H.H., Li, M.F., Ng, K.K., Kamm, M.A., Studd, C., Bell, S., Leong, R., de Silva, H.J., Kasturiratne, A., Mufeena, M.N., Ling, K.L., Ooi, C.J., Tan, P.S., Ong, D., Goh, K.L., Hilmi, I., Pisespongsa, P., Manatsathit, S., Rerknimitr, R., Aniwan, S., Wang, Y.F., Ouyang, Q., Zeng, Z., Zhu, Z., Chen, M.H., Hu, P.J., Wu, K., Wang, X., Simadibrata, M., Abdullah, M., Wu, J.C., Sung, J.J., Chan, F.K., Asia-Pacific, C.s., Colitis Epidemiologic Study Study, G., 2013. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. Gastroenterology 145, 158-165 e152.

Nguyen, G.C., Steinhart, A.H., 2008. Nationwide patterns of hospitalizations to centers with high volume of admissions for inflammatory bowel disease and their impact on mortality. Inflamm Bowel Dis 14, 1688-1694.

Nishida, T., Miwa, H., Yamamoto, M., Koga, T. and Yao, T., 1982. Bile acid absorption kinetics in Crohn's disease on elemental diet after oral administration of stable-isotope tracer with chenodeoxycholic-11, 12-d2 acid. Gut 23, 751 - 757.

Nugent, S.G., Kumar, D., Rampton, D.S., Evans, D.F., 2001. Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs. Gut 48, 571-577.

Nugent, S.G., Rampton, D.S., Evans, D.F., Yazaki, E., Kumar, D., 2000. Small intestinal luminal pH in Crohn's disease. Gut 46, A9-A9.

Ott, C., Takses, A., Obermeier, F., Schnoy, E., Mueller, M., 2014. Smoking increases the risk of extraintestinal manifestations in Crohn's disease. World Journal of Gastroenterology 20, 12269-12276.

Padwal, R.S., Gabr, R.Q., Sharma, A.M., Langkaas, L.A., Birch, D.W., Karmali, S., Brocks, D.R., 2011. Effect of gastric bypass surgery on the absorption and bioavailability of metformin. Diabetes Care 34, 1295-1300.

Papanicolas, L.E., Gordon, D.L., Wesselingh, S.L., Rogers, G.B., 2017. Not Just Antibiotics: Is Cancer Chemotherapy Driving Antimicrobial Resistance? Trends Microbiol.

Parsons, R.L., 1977. DRUG ABSORPTION IN GASTROINTESTINAL-DISEASE WITH PARTICULAR REFERENCE TO MALABSORPTION-SYNDROMES. Clinical Pharmacokinetics 2, 45-60.

Parsons, R.L., Kaye, C.M., Raymond, K., 1977. PHARMACOKINETICS OF SALICYLATE AND INDOMETHACIN IN CELIAC-DISEASE. European Journal of Clinical Pharmacology 11, 473-477.

Peyrin-Biroulet, L., Loftus, E.V., Jr., Colombel, J.-F., Sandborn, W.J., 2010. The Natural History of Adult Crohn's Disease in Population-Based Cohorts. American Journal of Gastroenterology 105, 289-297.

Pierantozzi, M., Pietroiusti, A., Brusa, L., Galati, S., Stefani, A., Lunardi, G., Fedele, E., Sancesario, G., Bernardi, G., Bergamaschi, A., Magrini, A., Stanzione, P., Galante, A., 2006. Helicobacter pylori eradication and L-dopa absorption in patients with PD and motor fluctuations. Neurology 66, 1824-1829.

Pierantozzi, M., Pietroiusti, A., Sancesario, G., Lunardi, G., Fedele, E., Giacomini, P., Frasca, S., Galante, A., Marciani, M.G., Stanzione, P., 2001. Reduced L-dopa absorption and increased clinical fluctuations in Helicobacter pylori-infected Parkinson's disease patients. Neurological Sciences 22, 89-91.

Pilotto, A., 2004. Aging and upper gastrointestinal disorders. Best Practice & Research Clinical Gastroenterology 18, Supplement, 73-81.

Pilotto, A., Franceschi, M., Leandro, G., Rassu, M., Bozzola, L., Valerio, G., Di Mario, F., 2002. Influence of Helicobacter pylori infection on severity of oesophagitis and response to therapy in the elderly. Digestive and Liver Disease 34, 328-331.

Planell, N., Lozano, J.J., Mora-Buch, R., Masamunt, M.C., Jimeno, M., Ordas, I., Esteller, M., Ricart, E., Pique, J.M., Panes, J., Salas, A., 2013. Transcriptional analysis of the intestinal mucosa of patients with ulcerative colitis in remission reveals lasting epithelial cell alterations. Gut 62, 967-976.

Podolsky, D.K., 1999. Mucosal immunity and inflammation. V. Innate mechanisms of mucosal defense and repair: the best offense is a good defense. Am J Physiol 277, G495-499.

Podolsky, D.K., 2002. Inflammatory bowel disease. New England Journal of Medicine 347, 417-429.

Poka, L., Czirbusz, G., Foldi, E., Farkas, A., Kerner, J., Bartek, I., 1968. CHANGES OF STRUCTURE AND ENZYME ACTIVITY IN MALABSORPTION DURING GASTROINTESTINAL PARESIS. Digestion 1, 33-&.

Prescott, L.F., 1974. GASTROINTESTINAL ABSORPTION OF DRUGS. Medical Clinics of North America 58, 907-916.

Press, A.G., Hauptmann, I.A., Hauptmann, L., Fuchs, B., Fuchs, M., Ewe, K., Ramadori, G., 1998. Gastrointestinal pH profiles in patients with inflammatory bowel disease. Alimentary Pharmacology & Therapeutics 12, 673-678.

Prevention, C.f.D.C.a., 2013. National Ambulatory Medical Care Survery: 2013 State and National Summary Tables.

Prince, R.A., Pincheira, J.C., Mason, E.E., Printen, K.J., 1984. Influence of bariatric surgery on erythromycin absorption. J Clin Pharmacol 24, 523-527.

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K.S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., Mende, D.R., Li, J., Xu, J., Li, S., Li, D., Cao, J., Wang, B., Liang, H., Zheng, H., Xie, Y., Tap, J., Lepage, P., Bertalan, M., Batto, J.M., Hansen, T., Le Paslier, D., Linneberg, A., Nielsen, H.B., Pelletier, E., Renault, P., Sicheritz-Ponten, T., Turner, K., Zhu, H., Yu, C., Li, S., Jian, M., Zhou, Y., Li, Y., Zhang, X., Li, S., Qin, N., Yang, H., Wang, J., Brunak, S., Dore, J., Guarner, F., Kristiansen, K., Pedersen, O., Parkhill, J., Weissenbach, J., Meta, H.I.T.C., Bork, P., Ehrlich, S.D., Wang, J., 2010. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464, 59-65.

Rabbie, S.C., Flanagan, T., Martin, P.D., Basit, A.W., 2015. Inter-subject variability in intestinal drug solubility. International Journal of Pharmaceutics 485, 229-234.

Rácz, I., Szabó, A., Csöndes, M., Pécsi, G., Goda, M., 2001. Eradication of Helicobacter pylori has no effect on gastric acidity in duodenal ulcer patients—evaluation of 24-h pH monitoring. Journal of Physiology-Paris 95, 469-475.

Ragnarsson, G., Bodemar, G., 1998. Pain is temporally related to eating but not to defaecation in the irritable bowel syndrome (IBS). Patients' description of diarrhoea, constipation and symptom variation during a prospective 6-week study. European Journal of Gastroenterology & Hepatology 10, 415-421.

Raimundo, A.H., Evans, D.F., Rogers, J., Silk, D.B.A., 1992. GASTROINTESTINAL PH PROFILES IN ULCERATIVE COLITIS. Gastroenterology 102, A681-A681.

Rana, S.V., Sharma, S., Kaur, J., Prasad, K.K., Sinha, S.K., Kochhar, R., Malik, A., Morya, R.K., 2014. Relationship of cytokines, oxidative stress and GI motility with bacterial overgrowth in ulcerative colitis patients. Journal of Crohns & Colitis 8, 859-865.

Rana, S.V., Sharma, S., Malik, A., Kaur, J., Prasad, K.K., Sinha, S.K., Singh, K., 2013. Small Intestinal Bacterial Overgrowth and Orocecal Transit Time in Patients of Inflammatory Bowel Disease. Digestive Diseases and Sciences 58, 2594-2598.

Renwick, A.G., Higgins, V., Powers, K., Smith, C.L., George, C.F., 1983. THE ABSORPTION AND CONJUGATION OF METHYLDOPA IN PATIENTS WITH CELIAC AND CROHNS DISEASES DURING TREATMENT. British Journal of Clinical Pharmacology 16, 77-83.

Rizello, Gionchetti P., Venturi A., Amandini R., Romangnoli R., Campieri M., 2002. Review article: monitoring activity in ulcerative colitis. Alimentary Pharmacology & Therapeutics 16, 3-6.

Roberts, M.S., Magnusson, B.M., Burczynski, F.J., Weiss, M., 2002. Enterohepatic circulation - Physiological, pharmacokinetic and clinical implications. Clinical Pharmacokinetics 41, 751-790.

Roerig, J.L., Steffen, K., Zimmerman, C., Mitchell, J.E., Crosby, R.D., Cao, L., 2012. Preliminary comparison of sertraline levels in postbariatric surgery patients versus matched nonsurgical cohort. Surg Obes Relat Dis 8, 62-66.

Rogers, C.C., Alloway, R.R., Alexander, J.W., Cardi, M., Trofe, J., Vinks, A.A., 2008. Pharmacokinetics of mycophenolic acid, tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients: a pilot study. Clin Transplant 22, 281-291.

Rolston, V.S., Boroujerdi, L., Long, M.D., McGovern, D.P.B., Chen, W., Martin, C.F., Sandler, R.S., Carmichael, J.D., Dubinsky, M., Melmed, G.Y., 2018. The Influence of Hormonal Fluctuation on Inflammatory Bowel Disease Symptom Severity-A Cross-Sectional Cohort Study. Inflamm Bowel Dis 24, 387-393.

Saad, R., Rizkallah, M.R., Aziz, R.K., 2012. Gut Pharmacomicrobiomics: the tip of an iceberg of complex interactions between drugs and gut-associated microbes. Gut Pathogens 4.

Safdi, A. V., 2005. Determination of mesalazine in whole or partial mesalamine delayed-release tablets recovered from fecal samples of healthy volunteers. Am J Gastroenterol 100, S159.

Samsel, A., Seneff, S., 2013. Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. Interdiscip Toxicol 6, 159-184.

Sasaki, Y., Hada, R., Nakajima, H., Fukuda, S., Munakata, A., 1997. Improved localizing method of radiopill in measurement of entire gastrointestinal pH profiles: Colonic luminal pH in normal subjects and patients with Crohn's disease. American Journal of Gastroenterology 92, 114-118.

Savla, R., Browne, J., Plassat, V., Wasan, K.M., Wasan, E.K., 2017. Review and analysis of FDA approved drugs using lipid-based formulations. Drug Dev Ind Pharm 43, 1743-1758.

Schlenker, C., Surawicz, C.M., 2009. Emerging infections of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 23, 89-99.

Schroeder, K.W., Tremaine, W.J., Ilstrup, D.M., 1987. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 317, 1625-1629.

Selby, W., 2000. Pathogenesis and therapeutic aspects of Crohn's disease. Veterinary Microbiology 77, 505-511.

Sergi, C., Shen, F., Bouma, G., 2017. Intraepithelial lymphocytes, scores, mimickers and challenges in diagnosing gluten-sensitive enteropathy (celiac disease). World J Gastroenterol 23, 573-589.

Sewell, J.L., Velayos, F.S., 2013. Systematic review: The role of race and socioeconomic factors on IBD healthcare delivery and effectiveness. Inflamm Bowel Dis 19, 627-643.

Shaffer, J.A., Williams, S. E., Turnberg, L. A., Houston, J. B. and Rowland, M., 1983. Absorption of prednisolone in patients with Crohn's disease. Gut 24, 182 - 186.

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 hypochlorhydric HIV-positive patients. Journal of Acquired Immune Deficiency Syndromes 24, 79-82.

Siew Chien, N., Lam, E.F.C., Lam, T.T.Y., Chan, Y., Law, W., Tse, P.C.H., Kamm, M.A., Sung, J.J.Y., Chan, F.K.L., Wu, J.C.Y., 2013. Effect of probiotic bacteria on the intestinal microbiota in irritable bowel syndrome. Journal of Gastroenterology and Hepatology 28, 1624-1631.

Simren, M., Mansson, A., Langkilde, A.M., Svedlund, J., Abrahamsson, H., Bengtsson, U., Bjornsson, E.S., 2001. Food-related gastrointestinal symptoms in the irritable bowel syndrome. Digestion 63, 108-115.

Singh, D., Laya, A. S., Clarkston, W. K. and Allen, M. J., 2009. Jejunoileal bypass: A surgery of the past and a review of its complications. World J Gastroenterol 15, 2277 - 2279.

Singh, P., Ananthakrishnan, A., Ahuja, V., 2017. Pivot to Asia: inflammatory bowel disease burden. Intest Res 15, 138-141.

Singh, P., Arora, S., Singh, A., Strand, T. A., Makharia, G. K., 2016. Prevalence of Celiac Disease in Asia: A Sustemic Review and Meta-Analysis. Gastroenterology 150, S487.

Sinha, A., Nightingale, J., West, K.P., Berlanga-Acosta, J., Playford, R.J., 2003. Epidermal growth factor enemas with oral mesalamine for mild-to-moderate left-sided ulcerative colitis or proctitis. N Engl J Med 349, 350-357.

Sjogren, E., Abrahamsson, B., Augustijns, P., Becker, D., Bolger, M.B., Brewster, M., Brouwers, J., Flanagan, T., Harwood, M., Heinen, C., Holm, R., Juretschke, H.P., Kubbinga, M., Lindahl, A., Lukacova, V., Munster, U., Neuhoff, S., Nguyen, M.A., Peer, A., Reppas, C., Hodjegan, A.R., Tannergren, C., Weitschies, W., Wilson, C., Zane, P., Lennernas, H., Langguth, P., 2014. In vivo methods for drug absorption - comparative physiologies, model selection, correlations with in vitro methods (IVIVC), and applications for formulation/API/excipient characterization including food effects. Eur J Pharm Sci 57, 99-151. version With Duodenal Switch. Clinical Pharmacology & Therapeutics 87, 699-705.

Skottheim, I.B., Jakobsen, G.S., Stormark, K., Christensen, H., Hjelmesaeth, J., Jenssen, T., Asberg, A., Sandbu, R., 2010. Significant increase in systemic exposure of atorvastatin after biliopancreatic diversion with duodenal switch. Clin Pharmacol Ther 87, 699-705.

Skottheim, I.B., Stormark, K., Christensen, H., Jakobsen, G.S., Hjelmesaeth, J., Jenssen, T., Reubsaet, J.L., Sandbu, R., Asberg, A., 2009. Significantly altered systemic exposure to atorvastatin acid following gastric bypass surgery in morbidly obese patients. Clin Pharmacol Ther 86, 311-318.

Smart, A.L., Gaisford, S., Basit, A.W., 2014. Oral peptide and protein delivery: intestinal obstacles and commercial prospects. J Pharm Sci 11, 1323-1335.

Snape, W.J., Matarazzo, S.A., Cohen, S., 1980. ABNORMAL GASTROCOLONIC RESPONSE IN PATIENTS WITH ULCERATIVE-COLITIS. Gut 21, 392-396.

Sousa, T., Paterson, R., Moore, V., Carlsson, A., Abrahamsson, B., Basit, A.W., 2008. The gastrointestinal microbiota as a site for the biotransformation of drugs. Int J Pharm 363, 1-25.

Sousa, T., Yadav, V., Zann, V., Borde, A., Abrahamsson, B., Basit, A.W., 2014. On the colonic bacterial metabolism of azo-bonded prodrugsof 5-aminosalicylic acid. J Pharm Sci 103, 3171-3175.

Spanogiannopoulos, P., Bess, E.N., Carmody, R.N., Turnbaugh, P.J., 2016. The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. Nat Rev Microbiol 14, 273-287.

Sperber, A.D., Dumitrascu, D., Fukudo, S., Gerson, C., Ghoshal, U.C., Gwee, K.A., Hungin, A.P.S., Kang, J.Y., Minhu, C., Schmulson, M., Bolotin, A., Friger, M., Freud, T., Whitehead, W., 2017. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut 66, 1075-1082.

Spiller, R.C., 2005. Irritable bowel syndrome. British Medical Bulletin 72, 15-29.

Stewart, D.B., Hegarty, J.P., 2013. Correlation between virulence gene expression and proton pump inhibitors and ambient pH in Clostridium difficile: results of an in vitro study. J Med Microbiol 62, 1517-1523.

Swanson, H.I., 2015. Drug Metabolism by the Host and Gut Microbiota: A Partnership or Rivalry? Drug Metab Dispos 43, 1499-1504.

Taherali, F., Varum, F., Basit, A.W., 2018. A slippery slope: On the origin, role and physiology of mucus. Advanced Drug Delivery Reviews 124, 16-33.

Testerman, T.L., Morris, J., 2014. Beyond the stomach: An updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. World Journal of Gastroenterology : WJG 20, 12781-12808.

Theriot, C.M., Young, V.B., 2014. Microbial and metabolic interactions between the gastrointestinal tract and Clostridium difficile infection. Gut Microbes 5, 86-95.

Thor, P., Lorens, K., Tabor, S., Herman, R., Konturek, J.W., Konturek, S.J., 1996. Dysfunction in gastric myoelectric and motor activity in Helicobacter pylori positive gastritis patients with non-ulcer dyspesia. Journal of Physiology and Pharmacology 47, 469-476.

Titus, R., Kastenmeier, A., Otterson, M.F., 2013. Consequences of Gastrointestinal Surgery on Drug Absorption. Nutrition in Clinical Practice 28, 429-436.

Tursi, A., Brandimarte, G., Giorgetti, G., Nasi, G., 2003. Assessment of orocaecal transit time in different localization of Crohn's disease and its possible influence on clinical response to therapy. European Journal of Gastroenterology & Hepatology 15, 69-74.

Unalp-Arida, A., Ruhl, C. E., Choung, R. S., Brantner, T. L., Murray, J. A., 2017. Lower Prevalence of Celiac Disease and Gluten-Relared Disorders in Persons Living in Southern vs. Northern Latitudes of the United States. Gastroenterology 152, 1922 - 1932.

UNWTO, W.T.O., 2018. 2017 International Tourism Results: The Highest in Seven Years. Specialized Agency of the United Nations.

van Nood, E., Vrieze, A., Nieuwdorp, M., Fuentes, S., Zoetendal, E.G., de Vos, W.M., Visser, C.E., Kuijper, E.J., Bartelsman, J.F., Tijssen, J.G., Speelman, P., Dijkgraaf, M.G., Keller, J.J., 2013. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 368, 407-415.

Varum, F.J., Hatton, G.B., Freire, A.C., Basit, A.W., 2013a. A novel coating concept for ileo-colonic drug targeting: proof of concept in humans using scintigraphy. Eur J Pharm Biopharm 84, 573-577.

Varum, F.J.O., Hatton, G.B., Basit, A.W., 2013b. Food, physiology and drug delivery. International Journal of Pharmaceutics 457, 446-460.

Varum, F.J.O., Veiga, F., Sousa, J.S., Basit, A.W., 2010. An investigation into the role of mucus thickness on mucoadhesion in the gastrointestinal tract of pig. Eur J Pharm Sci 40, 335-341.

Verdu, E.F., Armstrong, D., Idstrom, J.P., Labenz, J., Stolte, M., Dorta, G., Borsch, G., Blum, A.L., 1995. EFFECT OF CURING HELICOBACTER-PYLORI INFECTION ON INTRAGASTRIC PH DURING TREATMENT WITH OMEPRAZOLE. Gut 37.

Verhulst, M.L., Hopman, W.P.M., Tangerman, A., Jansen, J., 1995. ERADICATION OF HELICOBACTER-PYLORI INFECTION IN PATIENTS WITH NONULCER DYSPEPSIA - EFFECTS ON BASAL AND BOMBESIN-STIMULATED SERUM GASTRIN AND GASTRIC-ACID SECRETION. Scandinavian Journal of Gastroenterology 30.

Vertzoni, M., Carlsson, A., Abraamsson, B., Goumas, K., Reppas, C., 2011. Degradation kinetics of metronidazole and olsalazine by bacteria in ascending colon and in feces of healthy adults. Int J Pharm 413, 81-86.

Vertzoni, M., Goumas, K., Soderlind, E., Abrahamsson, B., Dressman, J.B., Poulou, A., Reppas, C., 2010. Characterization of the ascending colon fluids in ulcerative colitis. Pharm Res 27, 1620-1626.

Trenfield, S.J., Awad, A., Goyanes, A., Gaisford, S., Basit, A.W., 2018. 3D printing pharmaceuticals: drug development to frontline care. Trends Pharmacol Sci 39, 440-451.

Vitek, L., 2015. Bile acid malabsorption in inflammatory bowel disease. Inflamm Bowel Dis 21, 476-483.

Walsh, J., Griffin, B.T., Clarke, G., Hyland, N.P., 2018. Drug-Gut Microbiota Interactions: Implications for Neuropharmacology. Br J Pharmacol.

Wang, I., Hopper, I., 2014. Celiac Disease and Drug Absorption: Implications for Cardiovascular Therapeutics. Cardiovascular Therapeutics 32, 253-256.

Wilson, I.D., Nicholson, J.K., 2017. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Transl Res 179, 204-222.

Wolters, F.L., Russel, M.G., Sijbrandij, J., Schouten, L.J., Odes, S., Riis, L., Munkholm, P., Bodini, P., O'Morain, C., Mouzas, I.A., Tsianos, E., Vermeire, S., Monteiro, E., Limonard, C., Vatn, M., Fornaciari, G., Pereira, S., Moum, B., Stockbrugger, R.W., Grp, E.-I., 2006. Crohn's disease: increased mortality 10 years after diagnosis in a Europe-wide population based cohort. Gut 55, 510-518.

Yadav, V., Gaisford, S., Merchant, H.A., Basit, A.W., 2013. Colonic bacterial metabolism of corticosteroids. Int J Pharm 457, 268-274.

Yadav, V., Varum, F., Bravo, R., Furrer, E., Bojic, D., Basit, A.W., 2016. Inflammatory bowel disease: exploring gut pathophysiology for novel therapeutic targets. Transl Res 176, 38-68.
Yamada, T.a.I., J. M., 2013. Infections of the Gastrointestinal Tract, in: Yamada, T.a.I., J. M. (Ed.), Yamada's Handbook of Gastroenterology. John Wiley & Sons, Ltd., pp. 451-470.
Yoo, H.H., Kim, I.S., Yoo, D.H., Kim, D.H., 2016. Effects of orally administered antibiotics on the bioavailability of amlodipine: gut microbiota-mediated drug interaction. J Hypertens 34, 156-162.
Young, M.A., Lettis, S., Eastmond, R., 1998. Concomitant administration of cholestyramine influences the absorption of troglitazone. British Journal of Clinical Pharmacology 45, 37-40.
Ziegler, T.R., Fernandez-Estivariz, C., Gu, L.H., Bazargan, N., Umeakunne, K., Wallace, T.M., Diaz, E.E., Rosado, K.E., Pascal, R.R., Galloway, J.R., Wilcox, J.N., Leader, L.M., 2002. Distribution of the H+/peptide transporter PepT1 in human intestine: up-regulated expression in the colonic mucosa of patients with short-bowel syndrome. Am J Clin Nutr 75, 922-930.