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

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 oroecaecal 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 \((1.15 \pm 0.08 \text{ days})\) than healthy subjects \((1.95 \pm 0.25 \text{ days})\). The mean values for the total bile acid pool were exhibited to be \(1323.0 \pm 173.6 \text{ mg}\) in CD which were statistically significant \((p < 0.02)\) when compared with healthy subjects \((2290.9 \pm 327.3 \text{ mg})\). 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).
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 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).
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 MDRI 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, 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)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Gastric emptying $t^{1/2}$ (min)</th>
<th>Maximum plasma paracetamol concentration (µg/ml)</th>
<th>AUC$_{0 \text{ to } 1 \text{ hr}}$ (µg min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 13)</td>
<td>23.6 ± 10.3</td>
<td>20.2 ± 3.0</td>
<td>12.4 ± 3.2</td>
</tr>
<tr>
<td>Untreated celiac disease (n = 9)</td>
<td>35.1 ± 8.9</td>
<td>16.2 ± 2.5</td>
<td>9.0 ± 1.6</td>
</tr>
<tr>
<td>Treated celiac disease (n = 7)</td>
<td>45.2 ± 14.9</td>
<td>14.7 ± 1.9</td>
<td>8.2 ± 2.0</td>
</tr>
</tbody>
</table>
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 K₂-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 K₂ 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 (Brenchly 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 (An nibale 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](image.png)

**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 colonocyte 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 postsurgical 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 purposely) 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).

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

> indicates a significant increase in oral drug exposure (AUC) following surgery
– no statistical significance in oral drug exposure following surgery
* 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 $T_{\text{max}}$ 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 Almua, 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.

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