ELSEVIER

Teaser Systemic diseases where foci are initially unrelated to the GI tract do in fact alter GI physiology and function. This ultimately affects the bioavailability of orally administered drugs.

Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption

Q1 **Grace B. Hatton**[‡], **Christine M. Madla**[‡], **Sarit C. Rabbie and Abdul W. Basit**

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

It was in 400 BC that Hippocrates reportedly stated that ''death sits in the colon''. The growth in our knowledge of the intestinal microbiome and the gut–brain axis, their function and imbalance, has distinctly uncovered the complex relationship between the gut to disease predisposition and development, heralding the problem and the solution to disease pathology. Human studies of new drug molecules are typically performed in healthy volunteers and their specific disease indication. Approved drugs, however, are used by patients with diverse disease backgrounds. Here, we review the current literature of the gastrointestinal tract reacting to systemic disease pathology that elicits physiological and functional changes that consequently affect oral drug product performance.

Introduction

Oral drug absorption in the gastrointestinal (GI) tract is a complex process with numerous factors contributing to low and erratic drug absorption. Such parameters include GI transit time, motility, pH, luminal contents and composition, permeation and transport systems, and the interactions between host and microbiome [1–7]. Interindividual differences in GI physiology are expected to acutely affect drug behaviour; however, some factors that might cause drug variability on one occasion might not elicit profound effects on another. This is further complicated when the GI environment is not only perturbed by GI diseases but also negatively 'reacts' to the potential impact of systemic diseases of various aetiologies that can concomitantly affect the GI Q2 tract and, thus, oral drug absorption.

Over 2000 years ago, the father of modern medicine, Hippocrates ascribed that ''death begins in the colon''. Although this is a case of oversimplification, Hippocrates forecasted the relationship between poor gut-health and the development of disease. The drug development process is required to optimise drug bioavailability for maximum therapeutic effect; however, the potential influence of disease is often neglected in the picture. Attempts have been made to elucidate the influence of GI diseases including irritable bowel syndrome, inflammatory bowel diseases (IBD), malabsorptive syndromes, microbial dysbiosis, GI infections and the impact of GI surgery on GI

Corresponding author: Basit, A.W. (a.basit@ucl.ac.uk)
[‡] These authors contributed equally towards this manuscript.

Grace B. Hatton is a London-based pharmacist and physician at the King's College London hospital with an expansive research background in clinical medicine and pharmaceutical science. Grace has a passion for research in the fields of hepatology and gastroenterology with a patient-oriented focus, and her work has involved leading and collaborating on several pioneering projects investigating drug delivery to the gastrointestinal tract. Grace is currently an author of several peer-reviewed papers covering the modern manufacture of pharmaceuticals using 3D printing, the microbiome and the use of faecal transplants in disease treatments.

Christine M. Madla received her BSc in pharmaceutical science from the University of Greenwich and her MSc in pharmaceutical formulation and entrepreneurship at the UCL School of Pharmacy. Christine is currently pursuing her PhD at the University College London funded by the Engineering and Physical Sciences Research Council (EPSRC) UK where she specialises in the effect of disease, sex differences and excipient formulation on drug absorption in the gastrointestinal tract. Christine has spearheaded a number of research publications spanning personalised medicines, modern pharmaceutical manufacturing and gastrointestinal drug delivery.

Abdul W. Basit is Professor of Pharmaceutics at the UCL School of Pharmacy, University College London, where his research sits at the interface between pharmaceutical science and gastroenterology. Abdul has invented a number of advanced drug delivery technologies that have been translated into the design of new drug products and improved disease treatments, of which many have been commercialised. Abdul's research further spans the personalisation of medicines where his group stands at the fore of developing modern pharmaceutical manufacturing techniques using 3D. In total, Abdul has attracted >£20 million in grant income. Abdul is also a serial entrepreneur who has filed multiple patents and founded three pharmaceutical companies. Abdul was also the recipient of the Young Investigator Award in Pharmaceutics and Pharmaceutical Technology from the American Association of Pharmaceutical Scientists and the recipient of the Academy of Pharmaceutical Sciences Award.

https://doi.org/10.1016/j.drudis.2018.11.009

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

physiology, function and, consequently, dosage form performance [8,9]. The impact of systemic disease, however, is scarcely appreciated.

Systemic disease can be defined as a disorder that affects the body in its entirety and, thus, is not limited to a single organ or body part. Although we speculate that a larger portfolio of systemic diseases can affect the GI tract and oral drug absorption, consequently limited data in the literature are available that investigate the complex relationship between disease–drug interactions. However, systemic diseases stemming from genetic mutations, neurodegenerative in origin, autoimmune and metabolic malfunction, infectious disease and nervous system injury including cystic fibrosis, Parkinson's disease, diabetes, human immunodeficiency virus (HIV) and pain were selected for review owing to available data in the literature. These disorders were chosen herein to raise awareness that diseases with no immediate association to the GI environment can, however, clinically manifest GI alterations with respect to physiology and function and, thus, influence formulation behaviour. In addition, whereas patients will take medicines specifically for the aforementioned diseases, little is understood on the outcome of drug bioavailability in patients with multiple and diverse disease backgrounds. This review, therefore, addresses the implications of the altered GI tract as a consequence of systemic disease and its impact on oral drug bioavailability.

Cystic fibrosis

Cystic fibrosis (CF) is a prominent example of a hereditary, severe, progressive and multisystemic disorder with varying worldwide prevalence. In North America, the frequency of CF is 1 in every 3500 individuals; but in Asia 1 in 100 000–350 000 individuals are affected. Prevalence of CF in Africa and South America are steadily increasing to 1 case in every 8000 people; however, studies have shown its regional dependence with the southern regions of both continents demonstrating an increasing incidence of CF [10]. CF involves the mutation of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene which affects the movement of salt and water in and out of cells. People diagnosed with CF experience a build-up of thick sticky mucus in the lungs and the digestive system, manifesting symptoms at multiple bodily sites. The most common of these are the respiratory tract and distinctive – and often detrimental – changes to GI physiology and function; the latter is characterised by gastro–oesophageal reflux disease, malabsorption and pancreatic insufficiency [11]. Fat and nutrient malabsorption in CF patients is also common and is further affected by altered intestinal pH, motility and mucosal abnormalities [12].

In terms of drug pharmacokinetics, increased plasma and renal clearance of dicloxacillin [13], as well as its increased volume of distribution and decreased half-life [14], have been reported in CF patients when compared with healthy subjects (Fig. 1). This is similarly true for cephalopsorins which have been shown to demonstrate higher total bodily clearance in CF [15]. Intestinal transit changes in CF patients are incompletely understood although factors such as mucosal inflammation [16] and small intestinal bacterial overgrowth (SIBO) [17] have been identified as contributing factors in animal models. Moreover, the inconsistency in data of changes to GI tract transit times have been widely reported. For instance, oral–colon transit time (OCTT) has been shown to be unchanged in terms of the migrating motor complex [18] or prolonged following the administration of a single-unit dosage form [19,20] at different regions of the GI tract in fasted CF patients, potentially contributing to wide variability in oral drug absorption and bioavailability. A study by Collins *et al.* demonstrated that gastric emptying (GE) is up to 30% faster in fed-state CF patients (average 53.0 min) when compared with healthy subjects (average 72.2 min), although marked discrepancies in gastric emptying time (GET) have also been observed including 58 min (range 6–107 min) and 41 min (range 4–125 min) noted within the same study [21].

In the small intestine, transit is significantly delayed in CF which is thought to be a consequence of abnormal intestinal mucous blocking normal transit. A study by Bali *et al.* [19] examined the small intestinal transit times (SITT) of ten CF patients (seven males and three females between 17 and 24 years of age) against 15 control subjects (nine males and six females between 18 and 26 years of age). SITT in CF patients ranged from 160 to 390 min, whereas the control group demonstrated a regular SITT of 50–150 min. However, it has also been observed that, whereas SITT is delayed in CF patients, duodenal and jejunal transit can also be abnormally fast in some subjects until the point of pH neutralisation in the intestine and activation of the 'ileal brake' [22].

In terms of pH, dysfunction of *CFTR* has been associated with reductions in pancreatic and duodenal – but not gastric – bicarbonate secretions [23], thereby lowering pre- and post-prandial duodenal pH by 1–2 units when compared with healthy controls (pH 5–7 versus pH 6, respectively). Low duodenal pH specifically in CF has been cited as the combined result of gastric hyperacidity and reduced pancreatic bicarbonate secretions [24]. Indeed, the efficacy of enteric-coated pancreatic enzyme preparations designed to dissolve above pH 5 for this purpose has been brought into question. Discrepancies in ranges observed for gastric pH have been noted according to different sources in fasted subjects with Youngberg *et al.* [25] citing between pH 0.9 and pH 1.8 in subjects with use of the Heidelberg Capsule and pH 1.3 according to Barraclough and Taylor [24]. However, sharp changes in pH from the terminal ileum (7.5) to the caecum (6.4) in CF patients when compared with the gradual increase in pH along the same length in healthy controls have been observed and, thus, could be responsible for aberrations in the delivery of pH-sensitive formulations [22].

A further study identified reduced oral drug bioavailability in CF patients following lung transplantation owing to impaired GI absorption. The absorption of tacrolimus, a highly lipophilic immunosuppressive drug often administered following allogeneic organ transplant to lower the risk of organ rejection, was studied in 11 subjects following lung grafts and 11 CF individuals after lung transplants. Knoop *et al.* identified that tacrolimus pharmacokinetics were highly variable in CF patients and non-CF individuals [26]. This is due to the AUC of tacrolimus in non-CF recipients of lung grafts being ~35 ng-h/ml/mg when compared with 17.3 ng-h/ml/mg for the 11 CF transplant recipients. The oral clearance of tacrolimus in the CF population, therefore, was ~50% owing to impaired drug absorption in the GI tract and pancreatic insufficiency, which can severely hamper fat absorption [27]. It is conse-

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

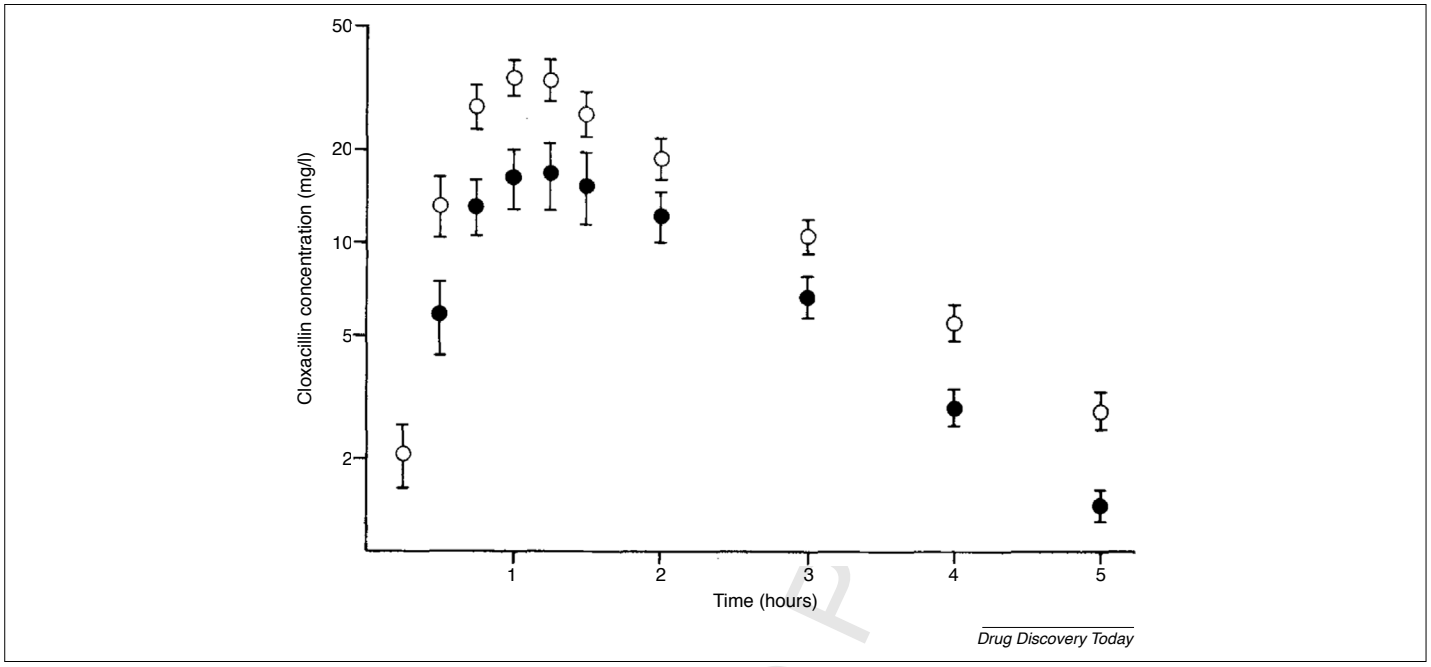

FIGURE 1

Q6 Mean cloxacillin serum concentrations following 25 mg/kg oral administration in 12 healthy subjects (○) and 12 cystic fibrosis patients (●). Reproduced, with permission, from Ref. [14].

quently often advised that tacrolimus should be delivered through an alternative drug delivery route to ensure effective therapeutic outcome for CF patients.

The intestinal microbiome of those with CF was found to be significantly less diverse when compared with non-CF controls. In particular, the relative abundance of Bacteroidetes was decreased whereas significant increases in Firmicutes were demonstrated in CF patients. Disease severity also contributed to microbial dysbiosis and individuals with severe lung dysfunction demonstrate a significantly reduced a diversity when compared with those with mild or moderate pulmonary impairment [28]. The slower SITT in CF patients can further lead to SIBO, characterised by the excessive concentrations of bacteria in the proximal small intestine. SIBO would be expected to enhance the translocation of intestinal bacterial products and harbour microbial-associated molecular patterns that are capable of stimulating Toll-like receptors, thus triggering inflammation and fibrogenic pathways [29]. It is suggested that, owing to SIBO, the synthesis of enterotoxic and unabsorbable metabolites could result in mucosal damage and interfere with digestion and absorption. In addition, the type of microbial flora present contributes to the manifestation of signs and symptoms or overgrowth. For example, a predominance of bacteria that metabolise bile salts to unconjugated or insoluble compounds could lead to fat malabsorption or bile acid diarrhoea [30]. The administration of the antibiotic ciprofloxacin, however, was shown to improve the digestion and absorption of fat CF patients with SIBO [30].

Parkinson's disease

Parkinson's disease (PD) is the second-most-common progressive and irreversible neurodegenerative disease with evolving layers of complexity. Its pathology involves extensive regions of the nervous system, an array of neurotransmitters and protein aggregates; but it is mainly characterised by the loss of dopaminergic neurons in the *substantia nigra*. The cause of PD remains unknown; however, is seems to result from a complicated interplay of genetic and environmental factors affecting fundamental cellular processes. Cardinal symptoms of PD include bradykinesia, tremor, restlessness and postural instability. In many cases, motor symptoms of PD are preceded by a series of milder prodromal symptoms such as fatigue and GI symptoms including constipation, dysphagia and defecatory dysfunction [31]. Epidemiological studies show that PD is predominant in mid-aged or older adults with a higher prevalence in males (61 cases in every 100 000) compared with females (38 cases in every 100 000) [32].

The appearance of early GI symptoms could also indicate that part of the pathological process originates in the gut given the abundance of enteric dopaminergic neurons collectively using ~50% of bodily dopamine [33], although GI symptoms are otherwise typically evident at all stages of PD. The gut–brain axis appears to dominate in PD because symptoms ranging from abdominal bloating, dyspepsia, nausea, vomiting and pain can be exacerbated by emotion [34]. Constipation is otherwise the most common GI symptom in PD reported by ~90% of patients and with the majority of cases associated with advanced disease progression [35].

Jost and Schimrigk [36] suggested that, in addition to impaired colonic motility, reduced tension of abdominal muscles and the diaphragm could contribute to the prolonged colon transit time in PD. Davies *et al*. administered oral mannitol to 15 PD patients as part of a study investigating intestinal permeability; in normal subjects, monosaccharides such as mannitol are absorbed by non-mediated diffusion through small channels in the enterocyte brush-border membrane. Disaccharides like lactulose, however,

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

are absorbed across tight junctions or between enterocytes. In PD, the percentage of mannitol absorption was reduced to 11.7% when compared with the healthy control group achieving 16.2% urinal mannitol recovery [37]. This suggested a reduction in the absorptive surface area of the small intestine owing to specific alterations in the enterocyte brush-border membrane in PD patients.

Abnormal GET has been described in 43–83% of PD patients [38] and is currently the most investigated parameter in relation to GI symptoms. Most antiparkinsonian drugs are delivered orally; therefore, altered gastric motility and GE rate might affect the bioavailability of medications and the rate of absorption from the GI tract is fundamental in achieving a beneficial therapeutic effect. In a study by Edwards *et al.* [39], 28 untreated patients with PD were assessed and found to have an average time to empty half of the gastric contents ($GET^1/_2$) of 59 min when compared with 44 min in a group of slightly younger healthy control individuals. An interesting association has also been made between delayed GET and the response fluctuations that develop after long-term levodopa therapy. Studies measuring gastric retention after 1 h showed GET to be increased but $GET^1/_2$ significantly delayed in patients with fluctuations when compared with those without fluctuations. This demonstrates that GET is more significant in those PD patients displaying response fluctuations [40]. Another possible outcome of GET is the prolonged exposure of drugs to gastric acid and digestive enzymes, as well as the binding of food components such as proteins in the stomach. In this instance, dopa-decarboxylase normally present in the gastric mucosa would be unable to metabolise protein-bound levodopa to the active dopamine, leading to absence of any therapeutic effect.

The short half-life of levodopa, its erratic absorption from the proximal part of the small intestine, the minimal absorption from the stomach, its peripheral metabolism and competition with large neutral amino acids from the intestinal barrier are crucial factors that can all hinder the cerebral availability of levodopa. Patients 1–3 (Fig. 2) demonstrate the unpredictable treatment and fluctuations to drug responses but experience a fourfold increase in mean T_{max} following duodenal absorption when compared with oral administration [41]. This, therefore, suggests a delayed and incomplete absorption caused by slower GE of levodopa in PD patients.

Gastroparesis, the reduced motility of the stomach, can be present in early and advanced PD. Few attempts have been achieved to overcome gastroparesis in PD patients by either adjusting dietary requirements when administrating drugs or with the use of prokinetic agents such as cisapride, domperidone and metoclopramide to normalise GE [42]. Different formulation approaches have also been employed to prolong drug transit in the upper GI tract to maximise the opportunity for absorption. For example, in one study, the difference between solid and liquid emptying time in PD patients was exploited as a method of optimising drug delivery with results showing that dispersible or liquid formulations of levodopa can, in fact, decrease T_{max} [43]. However, levodopa absorption takes place primarily in the intestine and not the colon, rendering targeting difficult. In addition, it appears that these formulations are still dependent on erratic GET, to which end Nyholm [44] suggested administering a levodopa gel solution directly into the duodenum or jejunum. This gel-formulation approach was shown to achieve consistent plasma levodopa levels in treated patients with the effective management of motor complications.

Most PD patients will present comorbidities and will often be prescribed cardiovascular and respiratory agents. Algeri *et al.* observed that the co-administration of the anticholinergic drug trihexyphenidyl reduced peak plasma levels of levodopa when compared with levodopa alone (from 2.29 ± 0.36 mg/ml to 1.90 ± 0.49 mg/ml). Trihexyphenidyl further decreased maximum peak levels and the AUC of levodopa (Fig. 3) as a consequence of increased gastric metabolism of the drug from delayed GE in PD patients. When levodopa was administered parentally, total levodopa plasma concentrations and half-life were not modified by the presence of trihexyphenidyl. The combined parkinsonian therapy to anticholinergic agents, therefore, can result in decreased bioavailability [45].

Emerging evidence has revealed the presence of an intense dialogue between the brain and the GI system, hence the term: gut–brain axis. It is becoming appreciated that a third player that is the intestinal microbiome can influence the bidirectional crosstalk between the gut and brain regarding the pathogenesis of PD. GI manifestations appear ~20 years before motor impairments; however, it is still unclear which condition comes first and what role the gut and the gut microbiome have on the progression of PD.

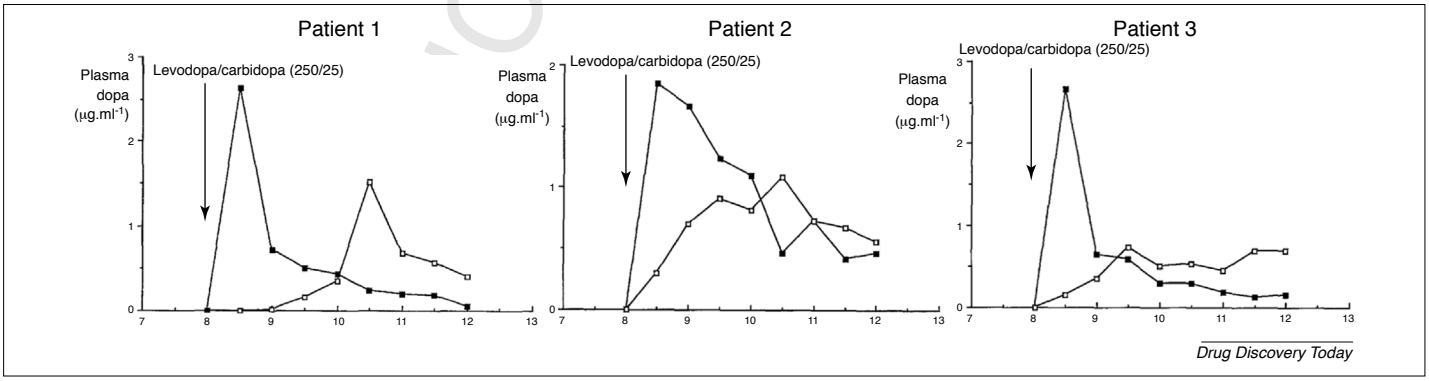

FIGURE 2

Levodopa plasma concentrations after (○) oral administration and (●) duodenal delivery of a single dose of levodopa in Parkinson's disease subjects. Reproduced, with permission, from Ref. [41].

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

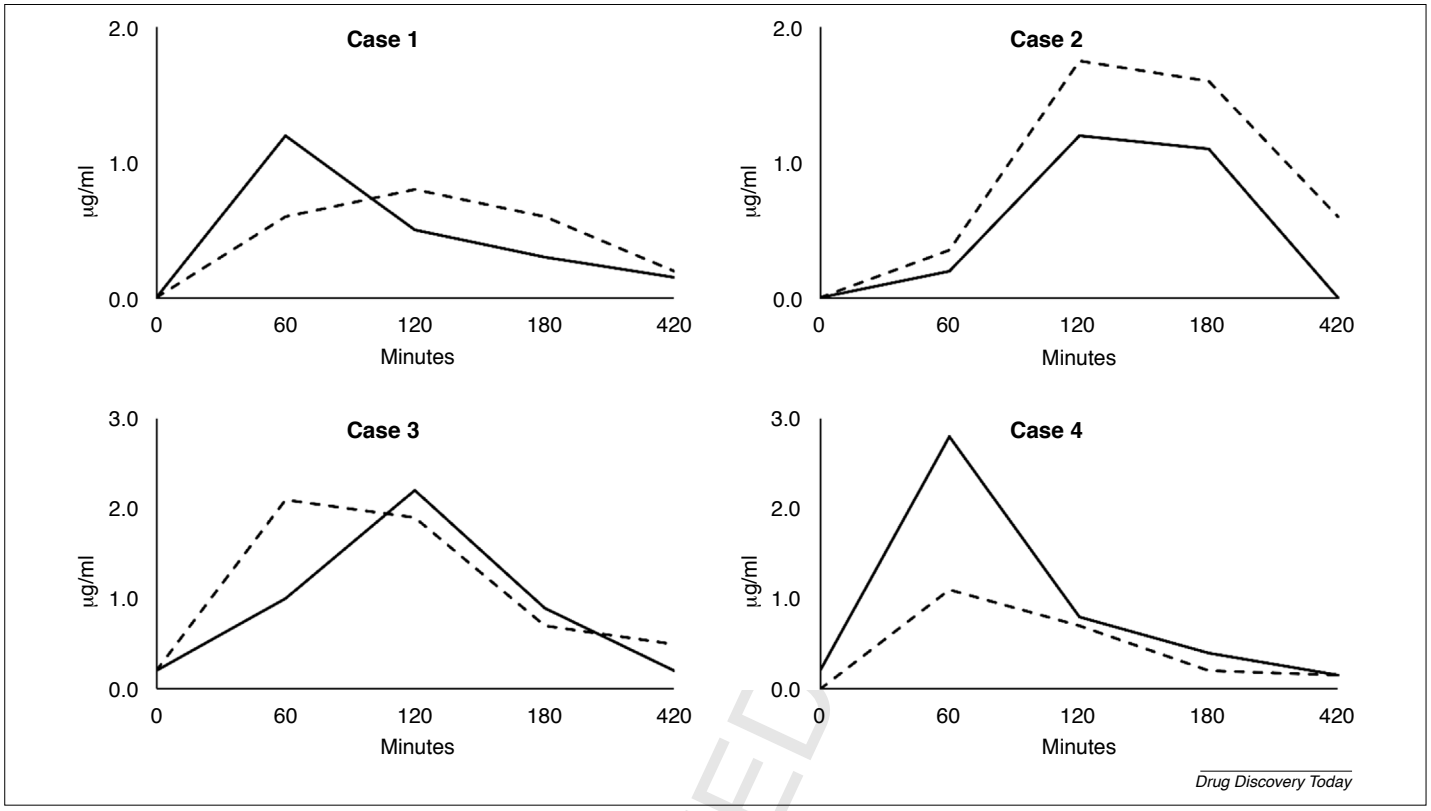

FIGURE 3

Q8 Plasma concentrations (mg/ml) of levodopa (—) and trihexyphenidyl + levodopa (. . .) in Parkinson's disease patients. Adapted, with permission, from Ref. [45].

Bacteria more commonly associated with anti-inflammatory properties such as butyrate-producing bacteria including *Blautia* and *Coprococcus* were significantly lower in PD patients when compared with healthy individuals, whereas an increase in abundance of the genus *Ralstonia* was found in the mucosa of PD patients [46]. Like CF patients, a significant proportion of PD patients demonstrate SIBO or the colonisation of *Helicobacter pylori* [47] where the eradication of these result in improvements of GI manifestations and motor fluctuations. In particular, the antibiotic treatment for *H. pylori* has been shown to improve levodopa absorption and bioavailability [48].

Diabetes

There are two manifestations of diabetes mellitus (DM) including type 1 DM (T1DM) and type 2 DM (T2DM). T1DM is an autoimmune disorder caused by the immune-mediated destruction of insulin-producing pancreatic b cells with a multifactorial interplay between genetic, environmental and immune factors. This results in the inability of the pancreas to create insulin, which consequently increases glucose levels in the bloodstream. Hyperglycaemia in T2DM, however, results from absolute or relative insulin deficiency which is attributed to the inability to compensate for insulin resistance. Similar to T1DM, the aetiology of insulin resistance in T2DM is theorised to be a combination of genetic and metabolic factors, although central obesity notably contributes to T2DM development. Both DM manifestations, however, feature significant links to impaired GI tract function [49]. The incidence of DM has at least quadrupled in the past three decades and is the ninth major cause of death. Epidemiology studies have shown that approximately one in 11 adults worldwide are diagnosed with DM with 90% of those being T2DM individuals. Asia is a major area of the rapidly emerging DM global epidemic, with China and India being the top two epicentres. Although genetic predisposition partly contributes to individual susceptibility, an unhealthy diet and sedentary lifestyle are important drivers for the prevalence of T2DM specifically [50].

There is ample evidence to suggest that diabetes and the GI tract are inextricably linked. The interaction between the upper GI tract and the endocrine system is important in the regulation of metabolism; the GI tract has a heterogenous cellular content and comprises a variety of cells that influence paracrine and endocrine mediators that collectively form the entero-endocrine system [51]. Some studies have shown that pronounced hyperglycaemia (>250 mg/dl) affects the motility of the oesophagus, stomach, small intestine and colon in T1DM and T2DM individuals [52]. Diabetes is further believed to affect the morphology and function of the GI tract (Table 1), which can consequently influence oral drug performance [53]. An inverse relationship has also been demonstrated whereupon alterations to the GI environment and particularly intestinal permeability, including immune responses and gut microbiota composition, have been seen to affect diabetes pathogenesis [54].

Diabetic patients exhibit significantly reduced gastric acid secretion [55], which is more pronounced in diabetic gastroparesis [56]. Furthermore, gastric pH is also increased in the fasted state of diabetic patients when compared with healthy individuals, lead-

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

TABLE 1

Diabetes-mellitus-induced physiological, motor and sensory changes in the small intestine and colon[a]

Changes	Small intestine	Colon
Mucosa	• Increased thickness • Damaged tight junctions • Decreased membrane fluidity • Enhanced transport of glucose, amino acids, bile salts, phosphate, fatty acids, fatty alcohols and cholesterol • Decreased protein synthesis • Increased expression of monosaccharide transporters	• Increased thickness • Increased thickness of subepithelial collagen layer • Increased expression of AGE and RAGE
Submucosa	• Increased thickness	• Increased thickness • Increased expression of AGE and RAGE
Wall	• Increased thickness • Increase expression of AGE and RAGE	• Increased thickness
Motor	• Highly variable transit time • Decreased muscle tone • Increased jejunal and ileal contractility in response to distension • Dysmotility	• Increased transit time • Highly variable contractility • Highly variable spontaneous contractility • Impaired contraction and relaxation of circular muscle strips
Sensory	• Decreased duodenal sensitivity in response to mechanical, thermal and electrical stimulations • Increased jejunal sensitivity in response to mechanical stimulation	• Increased colonic sensitivity to mechanical stimulation

Abbreviations: AGE, advanced glycation end-product; RAGE, advanced glycation of end-product receptor.
[a] Adapted, with permission, from Ref. [53].

ing to impaired absorption of basic drugs in the stomach [57]. Changes in aboral pH can also impair the disintegration and dissolution of coated dosage forms, particularly those incorporating pH-sensitive materials. Indeed, modern enteric coatings such as cellulose acetate phthalate, polyvinylacetate phthalate and the polymethacrylates are almost entirely insoluble at normal gastric pH but begin to dissolve rapidly above pH 5 [58]. Equally, diabetes has also been shown to delay GET [59] and total GI transit time [60], whereas diabetes-associated diarrhoea can also have clinical implications for drugs such as antiretrovirals that have not been readily absorbed before they are excreted [61].

A study investigated the pharmacokinetic activity of atorvastatin acid and its main metabolites in human liver microsomal fractions from nondiabetic and diabetic donors [62]. In diabetic patients, it was identified that the average dose-normalised concentrations of atorvastatin lactone and its *o*- and *p*-OH metabolites were significantly higher during the absorption phase (Fig. 4). Because atorvastatin lactone formation takes place at low pH levels, the prolonged gastric transit time observed in diabetic patients can promote the oral bioavailability of atorvastatin lactone in the GI tract. The altered drug response, therefore, should be taken into consideration when initiating atorvastatin acid treatment in patients with diabetes.

In addition, one of the major microvascular complications of DM includes a 60–70% reduction of gastric mucosal blood flow, which ultimately influences the rate of GE. It has been reported that 28–65% of diabetic patients experience delayed GE which causes a 300% longer gastric transit time in diabetic patients when compared with healthy subjects [63]. The significant changes in gastric motility and gastric transit time, therefore, can impact the extent of absorption in orally administered drugs. For example, lower serum concentrations of oral ampicillin were demonstrated in DM patients when compared with healthy controls despite unaltered elimination kinetics [64]. With regards to the microbial environment in diabetes, T1DM and T2DM diabetes subjects display key differences in gut dysbiosis. The imbalance of microbes related to mucosal barrier function is altered in diseases where *Lactobacilli*, *Bifidobacteria* and *Roseburia* are depleted, whereas *Clostridium perfringerns*, Bacteroides and *Prevotella* are enriched [65]. In T1DM, there is also a decrease in the number of Firmicutes in favour of Bacteroidetes; whereas in T2DM Firmicutes levels are elevated, contributing to the development of chronic inflammation and, in turn, obesity and insulin resistance [66]. In addition, evidence has indicated that metformin induces rapid changes in gut bacterial composition [67,68] that, although possibly improving glucose homeostasis, could have negative implications on the pharmacokinetics of concomitantly administered drugs such as organic cation transporter (OCT)-1 inhibitors [69] cimetidine and verapamil. Other factors such as the significant reduction in cytochrome (CYP)3A4 enzyme levels in DM have considerable potential to alter the bioavailability of CYP3A4 drug substrates such as atorvastatin, carbamazepine and budesonide [70].

HIV infection

HIV infection and AIDS is chronic and, to all intents and purposes, irreversible. HIV specifically attacks cluster T cells which aid the immune system to overcome infections. If HIV is untreated, HIV reduces the number of T cells in the body, which increases the likelihood of contracting other infections. The number of people living with HIV and AIDS has been steadily increasing and reached a total of 38.8 million in 2015. Mortality rates, however, have declined from 1.8 million deaths in 2005 to 1.2 million deaths a decade later. Sub-Saharan Africa demonstrates the highest concentration of HIV-infected individuals with ~1.8 million people being

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

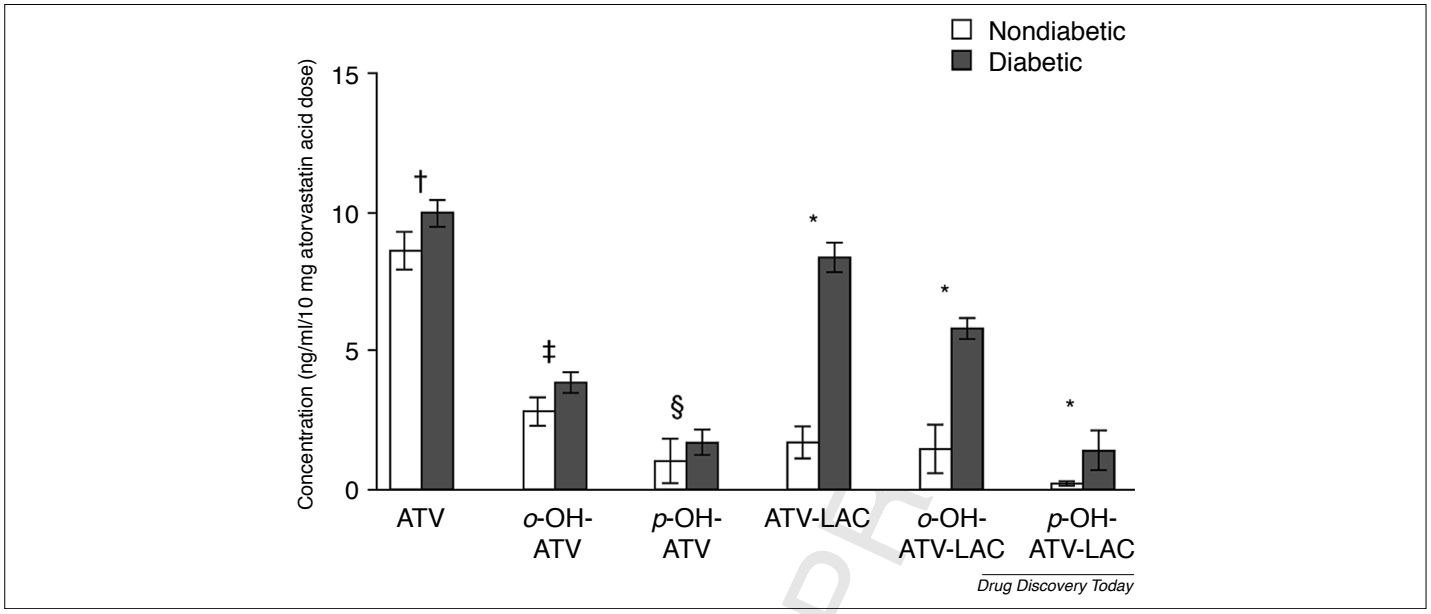

FIGURE 4

The dose-normalised concentration of atorvastatin acid (ATV), ortho-hydroxy atorvastatin acid (*o*-OH-ATV), para-hydroxy atorvastatin acid (*p*-OH-ATV), atorvastatin-lactone (ATV-LAC), ortho-hydroxy atorvastatin lactone (*o*-OH-ATV-LAC) and para-hydroxy atorvastatin lactone (*p*-OH-ATV-LAC) in the absorption phase (0.25–5 h post-dose administration) in nondiabetic and diabetic patients. *$P < 0.001$; †$P = 0.462$; ‡$P = 0.168$; §$P = 0.042$ [62].

diagnosed annually. Outside of sub-Saharan Africa, Southeast Asia accounted for 4.7% of global infections in 2015 with equal prevalence in both sexes. The highest estimated incidence rate in Europe was recorded in Russia with ~607 000 people diagnosed [71].

In vitro studies have postulated that there is a reduction in the number of enterocytes differentiating in HIV/AIDS patients, ultimately leading to morphological changes in the intestinal lining and compromising intestinal epithelial barrier function [72], thus not only predisposing to opportunistic infections and more-extensive cellular damage but also impairing the absorption of orally delivered drugs. Gastric hypochlorhydria and hypoacidity have also been observed in AIDS patients up to a pH value ~1.5–3-times higher than that of healthy individuals [73], which can lead to reduction in the absorption and subsequent bioavailability of basic drugs such as ketoconazole [74] and itraconazole [75]. An altered gastric pH owing to HIV/AIDS infection can also feature self-implicating knock-on effects; for example, the drugs indinavir and delavirdine used in infection treatment have been shown to be <50% absorbed at alkaline pH values [76]. Equally, up to 20% of patients with AIDS feature abnormal intestinal permeability [77]. As disease progresses, the functional and selective absorptive surface area of the intestine decreases, as evidenced by a study of mannitol permeability in HIV/AIDS patients with and without diarrhoea [78]. These changes can concomitantly influence the oral therapeutic efficacy of drugs for infections such as tuberculosis, which is seen to be the most common opportunistic infection in HIV/AIDS patients worldwide. For instance, Gurumurthy *et al.* [79] demonstrated that peak concentrations for rifampicin and isoniazid were reduced in HIV patients which followed an earlier study that revealed that rifampicin and ethambutol plasma concentrations were significantly low in HIV/AIDS patients [80].

Reduced drug bioavailability could also be caused by fat malabsorption syndromes prevalent in the majority of HIV patients [81]. Hyperlipidemia can have significant implications, therefore, on the pharmacokinetics of lipid-soluble drugs such as the antiretroviral drug zidovudine. Zidovudine pharmacokinetics were highly altered when administered to HIV-infected patients; C_{max} was reduced to 6.39 ± 3.39 mmol/l versus 11.51 ± 5.01 mmol/l and T_{max} was prolonged to 0.81 ± 0.51 h versus 0.40 ± 0.14 h in HIV-infected patients when compared with healthy subjects (Fig. 5). These data suggest a delayed absorption rather than an altered metabolism of zodivudine in AIDS-related small intestinal defect as a result of fat malabsorption [82]. Prominent fat malabsorption is further linked to the reduced bioavailability of rifampicin in the treatment of opportunistic tuberculosis in HIV-infected patients; rifampicin plasma concentrations were reduced by 32% in HIV patients when compared with the control owing to GI malabsorption. GI malfunction can further increase rifampicin clearance by reducing its reabsorption in the enterohepatic circulation which can explain why rifampicin is associated with a large decrease in total and peak exposure in HIV patients [83]. In addition to its reduced bioavailability, rifampicin can also negatively affect the absorption of the antiretroviral medication efavirenz. If co-administration is necessary for efavirenz and rifampicin, HIV patients would require an increased dose of 800 mg from 600 mg daily because AUC is reduced by 26% in the presence of the antibiotic (Fig. 5) [84].

A reduced microbial diversity has also been reported for HIV-infected patients. Specifically, a shift to Bacteroides and *Prevotella* predominance with a significant reduction in the Firmucutes phyla, when compared to uninfected individuals, contributes to a loss in immune regulatory and probiotic activity [85]. The effect of HIV on the gut mucosal barrier might be a direct result from microbial dysbiosis, which could induce a leak in gut mucosa and, thus, trigger systemic inflammation from the circulation of microbial elements in the blood [86]. Combination therapy is often

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

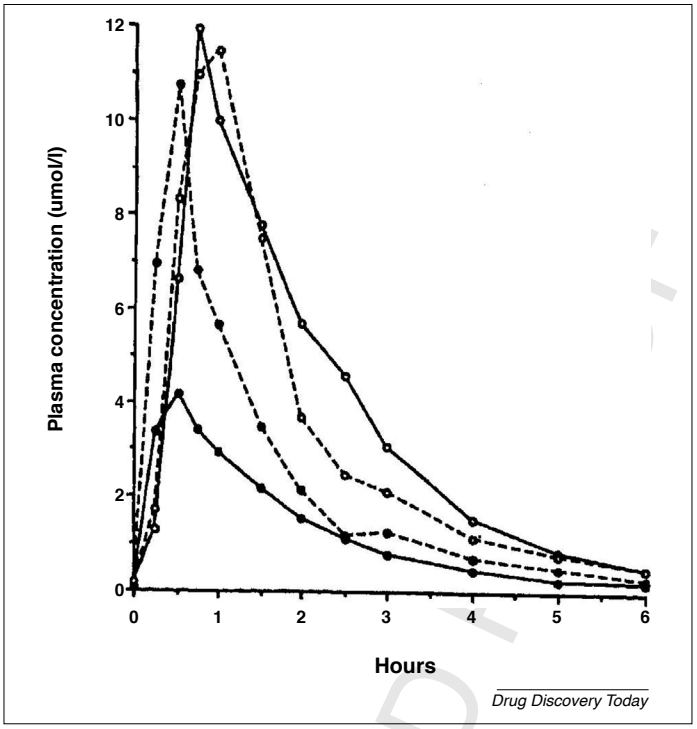

FIGURE 5

Comparison of zidovudine and zidovudine glucuronide plasma concentration (mmol/l) versus time (h) profiles following the oral administration of zidovudine in patients with normal fat absorption when compared with impaired fat absorption in the HIV-infected group. –●– denotes zidovudine in AIDS patients with impaired fat absorption; . . . ● . . . denotes zidovudine in AIDS patients with normal fat absorption; –○– denotes glucuronide zidovudine in AIDS patients with impaired fat absorption and . . . ○ . . . denotes glucuronide zidovudine in AIDS patients with normal fat absorption. Reproduced, with permission, from Ref. [82].

used to control the rapid replication rate of HIV in plasma [87]. For example, BILR355, a non-nucleotide reverse transcriptase inhibitor, is co-administered with ritonavir. The drug combination acts to interfere with the reproductive cycle of HIV and boosts BILR 355 efficacy by inhibiting its metabolism by CYP3A4-mediated catabolism [88]. A metabolite of BILR 355, however, is unusually increased to toxic levels when the drug is concomitantly administered. It is now recognised that ritonavir triggers BILR 344 metabolism which is reduced to an intermediate by the gut microbiota in patients with HIV, followed by further oxidation to the metabolite BILR 516 which exceeds the concentration of the administered drug [89]. This demonstrates how the gut microbiome can induce the biotransformation of drugs to create an alternative metabolic pathway that could result in adverse effects [90].

Pain

Pain is a phenomenon separate from nociception in that it refers to higher conscious perception of an unpleasant feeling, rather than the process of neuronal transmission of noxious stimuli. The global burden of chronic pain is projected to be large and growing in parallel to noncommunicable disease burden with chronic pain affecting at least 20% of the European population with a higher prevalence in women, the same being true in the geriatric population [91]. Heightened pain perception can occur as a result of a combination of central and peripheral sensitisation. The hypothalamic-pituitary-adrenal axis is activated by stress, which results in the secretion of corticotropin-releasing hormone into the hypophyseal portal system. This activates the anterior pituitary and subsequent release of adrenocorticotropic hormone (ACTH) into the systemic circulation. In response to ACTH, the adrenal cortex releases cortisol, which can directly activate resident immune cells and extrinsic primary afferents within the GI tract to promote peripheral sensitisation [92]. GI physiology can consequently be altered by pain owing to the gut–brain axis in terms of motility, visceral perception, secretion, intestinal permeability, reduced regenerative capacity of GI mucosa and mucosal blood flow and negative effects on the intestinal microbiome [93]. For example, in paediatric studies, correlating episodes of functional abdominal pain with GE revealed an inverse relationship where higher pain scores were demonstrated in subjects with low GE and antral motility [94]. In this study, 13 out of 31 patients featured delayed GE where the mean abdominal pain score was significantly higher ($P < 0.05$) than for those with normal GE. Sixteen out of 31 also featured abnormal gastric myoelectrical activity.

Jamali and Kunz-Dober [95] identified that the absorption of orally administered analgesics can be impaired following dental surgery. Plasma concentrations of ibuprofen were measured before and after the removal of wisdom teeth in 14 patients. A marked decrease in the AUC (0–2 h) was observed post-surgery in 13 patients, along with inhibition of the chiral inversion of the serum ibuprofen enantiomer concentrations, which delay the onset of analgesia. The exact mechanisms responsible for this observation were not fully understood, although postoperative fatigue was proposed as one that can temporarily reduce nutritional intake and therefore delay T_{max} [96]; stress-induced decreases in GE and

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

blood flow to the GI tract [97] potentially contribute to reduced drug absorption and GI motility by the depression of the vagus nerve. This indicates that higher drug doses are required to achieve the same analgesic effect as pre-surgery in patients suffering from pain.

It is common that chronic pain patients such as those diagnosed with rheumatoid arthritis (RA) can present co-morbidities. Because chronic pain is capable of altering the healthy GI environment, the oral administration of drugs prescribed for other disease indications can be compromised, such as the case of verapamil for the treatment of high blood pressure, angina and supraventricular tachycardia. Inflammation increases plasma concentrations of a1-acid glycoprotein (AAG), potentially leading to a reduction in drug clearance where much of the drug remains bound to these glycoproteins. Mayo *et al*. [98] showed that RA causes a significant rise in the serum concentration of R-verapamil (AUC of 125 ± 34 mg/ml/min) and S-verapamil (AUC of 33.6 ± 6.8 mg/ml/min) enantiomers when compared with the controls (AUC 39.1 ± 4.6 mg/ml/min for R-verapamil; 8.1 ± 1.2 mg/ml/min for S-verapamil) (Fig. 6). However, this did not otherwise increase patient response but instead decreased verapamil activity, probably because of the increase in drug–protein binding. This suggests that, unlike in conditions dominated by pain symptoms that can necessitate an increase in drug dosing to achieve therapeutic concentrations, the reverse is necessary in inflammatory conditions to limit excessive rises in AUC. However, this will also depend on whether an increase in AUC correlates with an increase in the unbound form of the drug, which might not be strictly harmful to the patient. The situation inevitably becomes more complicated, however, when both conditions are present such as in IBD flare-ups.

Microbial dysbiosis has also been associated with several types of pain including visceral, inflammatory, autoimmune-related pain and migraine [46]. SIBO and *H. pylori* are associated with abdominal pain and damage the gastric and intestinal mucosa through bacterial adherence and toxin production. Similar to what was described in HIV, these products that act on enteric nerves can travel via the humoral or vagal afferent pathways to interact with systemic mechanisms to induce pain [99]. A study by Pimentel *et al*. demonstrated that 78% of patients suffering with fibromyalgia were also diagnosed with SIBO [100]. The administration of antibiotic therapy was successful in bacterial eradication, which reported improvement in GI symptoms including diarrhoea, bloating, constipation and joint pain.

Concluding remarks

Changes in the GI environment as a result of GI diseases and their impact on drug absorption have been superficially acknowledged; however, even less is known about the consequences of diseases indirectly linked to the GI tract. We report that the healthy GI environment with regards to gastric and small intestinal transit times, pH, intestinal permeability and microbial composition negatively reacts to the prevalence of CF, PD, diabetes, HIV and pain, which, in turn, collectively alter oral dosage form performance. This, however, is only the 'tip of the iceberg' in terms of fully elucidating the effect of systemic diseases. We envisage that a nonexhaustive portfolio of systemic indications has the potential to present GI manifestations and alter oral drug pharmacokinetics and pharmacodynamics. Much like drug–drug interactions being assessed during drug development, to optimise drug therapy, we therefore encourage further research in the direction of drug–disease interactions. The development of suitable *in vitro* dissolution models and *in silico* models for patients with diseases can contribute to improve overall drug therapy because patients can present co-morbidities and diverse disease backgrounds. This would advance the identification of potential differences in absorption between healthy and different diseased states and, thus, accelerate the translation of important new drugs to patients.

Acknowledgements

The authors would like to thank the Engineering and Physical Sciences Research Council (EPSRC) UK for their financial support towards this manuscript (EP/L01646X).

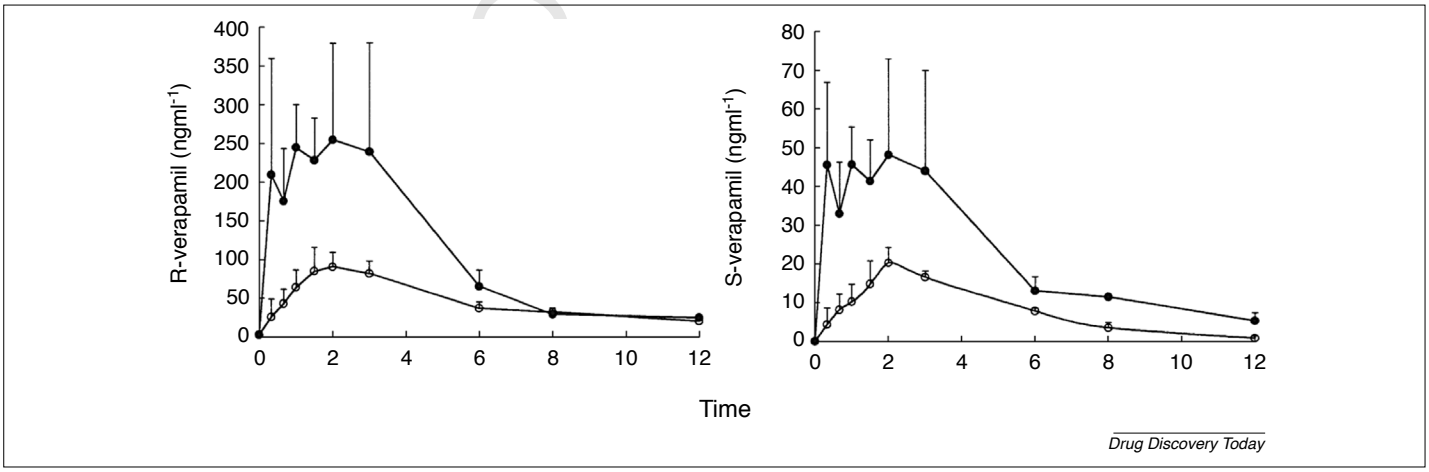

FIGURE 6

Serum verapamil enantiomer concentration–time profiles in healthy control subjects (○) and patients with rheumatoid arthritis (●) following the oral administration of 80 mg verapamil. Reproduced, with permission, from Ref. [98].

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

References

1 Hatton, G.B. *et al.* (2015) Animal farm: considerations in animal gastrointestinal physiology and relevance to drug delivery in humans. *J. Pharm. Sci.* 104, 2747–2776
2 Abuhelwa, A.Y. *et al.* (2017) Food, gastrointestinal pH, and models of oral drug absorption. *Eur. J. Pharm. Biopharm.* 112, 234–248
3 Hens, B. *et al.* (2017) Exploring gastrointestinal variables affecting drug and formulation behavior: methodologies, challenges and opportunities. *Int. J. Pharm.* 519, 79–97
4 Merchant, H.A. *et al.* (2016) Age-mediated changes in the gastrointestinal tract. *Int. J. Pharm.* 512, 382–395
5 Trenfield, S.J. *et al.* (2018) 3D printing pharmaceuticals: drug development to frontline care. *Trends Pharmacol. Sci.* 39, 440–451
6 Yadav, V. *et al.* (2016) Inflammatory bowel disease: exploring gut pathophysiology for novel therapeutic targets. *Transl. Res.* 176, 38–68
7 Ashiru, D.A. *et al.* (2008) Polyethylene glycol 400 enhances the bioavailability of a BCS class III drug (ranitidine) in male subjects but not females. *Pharm. Res.* 25, 2327–2333
8 Effinger, A. *et al.* (2018) Impact of gastrointestinal disease states on oral drug absorption – implications for formulation design – a PEARRL review. *J. Pharm. Pharmacol.* http://dx.doi.org/10.1111/jphp.12928 Q5
9 Hatton, G.B. *et al.* (2018) All disease begins in the gut: influence of gastrointestinal disorders and surgery on oral drug performance. *Int. J. Pharm.* 548, 408–422
10 Mirtajani, S. *et al.* (2017) Geographical distribution of cystic fibrosis: the past 70 years of data analysis. *Biomed. Biotechnol. Res. J.* 1, 105–112
11 Proesmans, M. and De Boeck, K. (2003) Omeprazole, a proton pump inhibitor, improves residual steatorrhoea in cystic fibrosis patients treated with high dose pancreatic enzymes. *Eur. J. Pediatr.* 162, 760–763
12 Duffield, R.A. (1996) Cystic fibrosis and the gastrointestinal tract. *J. Pediatr. Health Care* 10, 51–57
13 Jusko, W.J. *et al.* (1975) Enhanced renal excretion of dicloxacillin in patients with cystic-firbrosis. *Pediatrics* 56, 1038–1044
14 Spino, M. *et al.* (1984) Cloxacillin absorption and disposition in cystic fibrosis. *J. Pediatr.* 105, 829–835
15 Vinks, A.A. *et al.* (2007) Pharmacokinetics of aztreonam in healthy subjects and patients with cystic fibrosis and evaluation of dose-exposure relationships using Monte Carlo simulation. *Antimicrob. Agents Chemother.* 51, 3049–3055
16 de Lisle, R.C. *et al.* (2009) Mast cells and gastrointestinal dysmotility in the cystic fibrosis mouse. *PLoS One* 4, e0004283
17 de Lisle, R.C. *et al.* (2010) Enteric circular muscle dysfunction in the cystic fibrosis mouse small intestine. *Scand. J. Gastroenterol.* 22, 341–387
18 Hallberg, K. *et al.* (2001) Gastric secretion in cystic fibrosis in relation to the migrating motor complex. *Scand. J. Gastroenterol.* 36, 121–127
19 Bali, A. *et al.* (1983) Prolonged small-intestinal transit time in cystic fibrosis. *Br. Med. J.* 287, 1011–1013
20 Hedsund, C. *et al.* (2012) Gastrointestinal transit times and motility in patients with cystic fibrosis. *Scand. J. Gastroenterol.* 47, 920–926
21 Collins, C.E. *et al.* (1997) Gastric emptying time is faster in cystic fibrosis. *J. Pediatr. Gastroenterol. Nutr.* 25, 492–498
22 Gilbert, J. *et al.* (1988) Ileal pH in cystic fibrosis. *Scand. J. Gastroenterol.* 143, 132–134
23 Tang, L. *et al.* (2009) Mechanism of direct bicarbonate transport by the CFTR anion channel. *J. Cyst. Fibros.* 8, 115–121
24 Barraclough, M. and Taylor, C.J. (1996) Twenty-four hour ambulatory gastric and duodenal pH profiles in cystic fibrosis: effect of duodenal hyperacidity on pancreatic enzyme function and fat absorption. *J. Pediatr. Gastroenterol. Nutr.* 23, 45–50
25 Youngberg, C.A. *et al.* (1987) Comparison of gastrointestinal pH in cystic-fibrosis and healthy-subjects. *Dig. Dis. Sci.* 32, 472–480
26 Knoop, C. *et al.* (2005) Tacrolimus pharmacokinetics and dose monitoring after lung transplantation for cystic fibrosis and other conditions. *Am. J. Transplant.* 5, 1477–1482
27 Sikma, M.A. *et al.* (2015) Pharmacokinetics and toxicity of tacrolimus early after heart and lung transplantation. *Am. J. Transplant.* 15, 2301–2313
28 Burke, D.G. *et al.* (2017) The altered gut microbiota in adults with cystic fibrosis. *BMC Microbiol.* 17, 58–69
29 Flass, T. *et al.* (2015) Intestinal lesions are associated with altered intestinal microbiome and are more frequent in children and young adults with cystic fibrosis and cirrhosis. *PLoS One* 10, e0116967
30 Lisowska, A. *et al.* (2011) Oral antibiotic therapy improves fat absorption in cystic fibrosis patients with small intestine bacterial overgrowth. *J. Cyst. Fibros.* 10, 418–421
31 Cersosimo, M.G. *et al.* (2013) Gastrointestinal manifestations in Parkinson's disease: prevalence and occurrence before motor symptoms. *J. Neurol.* 260, 1332–1338
32 Hirsch, L. *et al.* (2016) The incidence of Parkinson's disease: a systematic review and meta-analysis. *Neuroepidemiology* 46, 292–300
33 Abbott, R.D. *et al.* (2007) Bowel movement frequency in late-life and incidental Lewy bodies. *Mov. Disord.* 22, 1581–1586
34 Woitalla, D. and Goetze, O. (2011) Treatment approaches of gastrointestinal dysfunction in Parkinson's disease, therapeutical options and future perspectives. *J. Neurol. Sci.* 310, 152–158
35 Pfeiffer, R.F. (2011) Gastrointestinal dysfunction in Parkinson's disease. *Parkinsonism Relat. Disord.* 17, 10–15
36 Jost, W.H. and Schimrigk, K. (1991) Constipation in Parkinson's disease. *Klin. Wochenschr.* 69, 906–909
37 Davies, K.N. *et al.* (1996) Intestinal permeability and orocaecal transit time in elderly patients with Parkinson's disease. *Postgrad. Med. J.* 72, 164–167
38 Tanaka, Y. *et al.* (2011) Is there a delayed gastric emptying of patients with early-stage, untreated Parkinson's disease? An analysis using the 13C-acetate breath test. *J. Neurol.* 258, 421–426
39 Edwards, L.L. *et al.* (1991) Gastrointestinal symptoms in Parkinson's disease. *Mov. Disord.* 6, 151–156
40 Muller, T. *et al.* (2006) Impact of gastric emptying on levodopa pharmacokinetics in Parkinson disease patients. *Clin. Neuropharmacol.* 29, 61–67
41 Deleu, D. *et al.* (1991) Clinical and pharmacokinetic comparison of oral and duodenal delivery of levodopa/carbidopa in patients with Parkinson's disease with a fluctuating response to levodopa. *Eur. J. Clin. Pharmacol.* 41, 454–458
42 Pfeiffer, R.F. and Quigley, E.M.M. (1999) Gastrointestinal motility problems in patients with Parkinson's disease — epidemiology, pathophysiology and guidelines for management. *CNS Drugs* 11, 435–448
43 Contin, M. *et al.* (1999) Concentration-effect relationship of levodopa-benserazide dispersible formulation versus standard form in the treatment of complicated motor response fluctuations in Parkinson's disease. *Clin. Neuropharmacol.* 22, 351–355
44 Nyholm, D. (2006) Enteral levodopa/carbidopa gel infusion for the treatment of motor fluctuations and dyskinesias in advanced Parkinson's disease. *Expert Rev. Neurother.* 6, 1403–1411
45 Algeri, S. *et al.* (1976) Effect of anticholinergic drugs on gastro-intestinal absorption of L-dopa in rats and in man. *Eur. J. Pharmacol.* 35, 293–299
46 Felice, V.D. *et al.* (2016) Microbiota-gut-brain signalling in Parkinson's disease: implications for non-motor symptoms. *Parkinsonism Relat. Disord.* 27, 1–8
47 Bjarnason, I.T. *et al.* (2005) Role of chronic infection and inflammation in the gastrointestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 2: response of facets of clinical idiopathic parkinsonism to *Helicobacter pylori* eradication. A randomized, double-blind, placebo-controlled efficacy study. *Helicobacter* 10, 276–287
48 Pierantozzi, M. *et al.* (2001) Reduced L-dopa absorption and increased clinical fluctuations in *Helicobacter pylori*-infected Parkinson's disease patients. *Neurol. Sci.* 22, 89–91
49 Deshpande, A.D. *et al.* (2008) Epidemiology of diabetes and diabetes-related complications. *Phys. Ther.* 88, 1254–1264
50 Zheng, Y. *et al.* (2018) Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat. Rev. Endocrinol.* 14, 88–98
51 Ma, J. and Vella, A. (2018) What has bariatric surgery taught us about the role of the upper gastrointestinal tract in the regulation of postprandial glucose metabolism? *Front. Endocrinol.* 9, 324
52 Tambascia, M.A. *et al.* (2014) Influence of gastric emptying on the control of postprandial glycemia: physiology and therapeutic implications. *Einstein (São Paulo)* 12, 251–253
53 Zhao, M. *et al.* (2017) Diabetes-induced mechanophysiological changes in the small intestine and colon. *World J. Diabetes* 8, 249–269
54 Vaarala, O. *et al.* (2008) The perfect storm for type 1 diabetes – the complex interplay between intestinal microbiota, gut permeability, and mucosal immunity. *Diabetes* 57, 2555–2562
55 Dotevall, G. (1961) Gastric secretion of acid in diabetes mellitus during basal conditions and after maximal histamine stimulation. *Acta Med. Scand.* 170, 59–69
56 Hasler, W.L. *et al.* (2008) Differences in intragastric pH in diabetic vs: idiopathic gastroparesis: relation to degree of gastric retention. *Am. J. Physiol. Gastrointest. Liver Physiol.* 294, 1384–1391
57 Nowak, T.V. *et al.* (1995) Highly variable gastric-emptying in patients with insulin-dependent diabetes-mellitus. *Gut* 37, 23–29
58 Charman, W.N. *et al.* (1997) Physicochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. *J. Pharm. Sci.* 86, 269–282

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009

59 Caballeroplasencia, A.M. *et al.* (1994) Gastroparesis of digestible and indigestible solids in patients with insulin-dependent diabetes-mellitus or functional dyspepsia. *Dig. Dis. Sci.* 39, 1409–1415
60 Eliasson, B. *et al.* (1995) Hyperinsulinemia impairs gastrointestinal motility and slows carbohydrate-absorption. *Diabetologia* 38, 79–85
61 Bushen, O.Y. *et al.* (2004) Diarrhea and reduced levels of antiretroviral drugs: improvement with glutamine or alanyl-glutamine in a randomized controlled trial in northeast Brazil. *Clin. Infect. Dis.* 38, 1764–1770
62 Dostalek, M. *et al.* (2012) Diabetes mellitus reduces the clearance of atorvastatin lactone. *Clin. Pharmacokinet.* 51, 591–606
63 Triantafyllou, K. *et al.* (2007) Video-capsule endoscopy gastric and small bowel transit time and completeness of the examination in patients with diabetes mellitus. *Dig. Liver Dis.* 39, 575–580
64 Elbarbry, F. (2016) Influence of diabetes mellitus on pharmacokinetics of drugs. *MOJ Bioequivalence Bioavailability* 2, 3–4
65 Kanbay, M. *et al.* (2018) The crosstalk of gut microbiota and chronic kidney disease: role of inflammation, proteinuria, hypertension, and diabetes mellitus. *Int. Urol. Nephrol.* 50, 1453–1466
66 Salamon, D. *et al.* (2018) Characteristics of the gut microbiota in adult patients with type 1 and 2 diabetes based on the analysis of a fragment of 16S rRNA gene using next-generation sequencing. *Pol. Arch. Intern. Med.* 6, 336–343
67 Bauer, P.V. *et al.* (2018) Metformin alters upper small intestinal microbiota that impact a glucose-SGLT1-sensing glucoregulatory pathway. *Cell Metab.* 27, 101–117
68 Forslund, K. *et al.* (2015) Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature* 528, 262–266
69 McCreight, L.J. *et al.* (2016) Metformin and the gastrointestinal tract. *Diabetologia* 59, 426–435
70 Dostalek, M. *et al.* (2012) Diabetes mellitus reduces the clearance of atorvastatin lactone: results of a population pharmacokinetic analysis in renal transplant recipients and *in vitro* studies using human liver microsomes. *Clin. Pharmacokinet.* 51, 591–606
71 GBD 2015 HIV Collaborators (2016) Estimates of global, regional and national incidence, prevalence and mortality of HIV, 1980-2015: the Global Burden of Disease Study 2015. *Lancet* 3, 361–387
72 Delezay, O. *et al.* (1997) Direct effect of type 1 human immunodeficiency virus (HIV-I) on intestinal epithelial cell differentiation: relationship to HIV-I enteropathy. *Virology* 238, 231–242
73 Belitsos, P.C. *et al.* (1992) Association of gastric hypoacidity with opportunistic enteric infections in patients with AIDS. *J. Infect. Dis.* 166, 277–284
74 Blum, R.A. *et al.* (1991) Increased gastric pH and the bioavailability of fluconazole and ketoconazole. *Ann. Intern. Med.* 114, 755–757
75 Zimmermann, T. *et al.* (1994) Influence of concomitant food-intake on the oral absorption of 2 triazole antifungal agents, itraconazole and fluconazole. *Eur. J. Clin. Pharmacol.* 46, 147–150
76 Tseng, A.L.I. and Foisy, M.M. (1997) Management of drug interactions in patients with HIV. *Ann. Pharmacother.* 31, 1040–1058
77 Lim, S. *et al.* (1993) Intestinal permeability and function in patients infected with human immunodeficiency virus: a comparison with coeliac disease. *J. Scand. Gastroenterol.* 28, 573–580
78 Tepper, R. *et al.* (1994) Intestinal permeability in patients infected with the human immunodeficiency virus. *Am. J. Gastroenterol.* 89, 878–882
79 Gurumurthy, P. *et al.* (2004) Decreased bioavailability of rifampicin and other anti-TB drugs in patients with advanced HIV disease. *Clin. Pharmacol. Ther.* 75, P29
80 Peloquin, C.A. *et al.* (1996) Low antituberculosis drug concentrations in patients with AIDS. *Ann. Pharmacother.* 30, 919–925
81 Poles, M.A. *et al.* (2001) HIV-related diarrhea is multifactorial and fat malabsorption is commonly present, independent of HAART. *Am. J. Gastroenterol.* 96, 1831–1837
82 Kapembwa, M.S. *et al.* (1996) Impaired absorption of zidovudine in patients with AIDS-related small intestinal disease. *AIDS* 10, 1509–1514
83 Sahai, J. *et al.* (1997) Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. *Ann. Intern. Med.* 127, 289–293
84 Gengiah, T.N. *et al.* (2011) Initiating antiretrovirals during tuberculosis treatment: a drug safety review. *Expert Opin. Drug Saf.* 10, 559–574
85 Dinh, D.M. *et al.* (2015) Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection. *J. Infect. Dis.* 211, 19–27
86 Bandera, A. *et al.* (2018) Altered gut microbiome composition in HIV infection: causes, effects and potential intervention. *Curr. Opin. HIV AIDS* 13, 73–80
87 Wei, X. *et al.* (1995) Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* 373, 117–122
88 Huang, F. *et al.* (2009) Pharmacokinetics of BILR 355 after multiple oral doses coadministered with a low dose of ritonavir. *Antimicrob. Agents Chemother.* 53, 95–103
89 Li, Y. *et al.* (2012) Metabolic switching of BILR 355 in the presence of ritonavir. II. Uncovering novel contributions by gut bacteria and aldehyde oxidase. *Drug Metab. Dispos.* 40, 1130–1137
90 Wilkinson, E.M. *et al.* (2018) Microbiota-drug interactions: impact on metabolism and efficacy of therapeutics. *Maturitas* 112, 53–63
91 de Souza, J.B. *et al.* (2017) Prevalence of chronic pain, treatments, perception, and interference on life activities: Brazilian population-based survey. *Pain Res. Manag.* http://dx.doi.org/10.1155/2017/4643830
92 Moloney, R.D. *et al.* (2015) Stress-induced visceral pain: toward animal models of irritable-bowel syndrome and associated comorbidities. *Front. Psychiatry* 6, 15–45
93 Konturek, P.C. *et al.* (2011) Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. *J. Physiol. Pharmacol.* 62, 591–599
94 Lin, Z. *et al.* (2003) Gastric myoelectrical activity, gastric emptying and correlation with symptoms in children with functional abdominal pain. *Gastroenterol* 124, 513
95 Jamali, F. and Kunz-Dober, C.M. (1999) Pain-mediated altered absorption and metabolism of ibuprofen: an explanation for decreased serum enantiomer concentration after dental surgery. *Br. J. Clin. Pharmacol.* 47, 391–396
96 Christensen, T. (1995) Postoperative fatigue. *Dan. Med. Bull.* 42, 314–322
97 Brouns, F. and Beckers, E. (1993) Is the gut an athletic organ — digestion, absorption and exercise. *Sports Med.* 15, 242–257
98 Mayo, P.R. *et al.* (2000) Decreased dromotropic response to verapamil despite pronounced increased drug concentration in rheumatoid arthritis. *Br. J. Clin. Pharmacol.* 50, 605–613
99 Kountouras, J. *et al.* (2012) *Helicobacter pylori* infection and Parkinson's disease: apoptosis as an underlying common contributor. *Eur. J. Neurol.* 19, 56
100 Pimentel, M. *et al.* (2010) Small intestinal bacterial overgrowth: a possible association with fibromyalgia. *J. Musculoskelet. Pain* 9, 105–113

Please cite this article in press as: Hatton, G.B. et al. Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.11.009