Effects of medicines used to treat gastrointestinal diseases on the pharmacokinetics of co-administered drugs: A PEARRL Review

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ABSTRACT

Background

Drugs used to treat gastrointestinal diseases (GI drugs) are widely used either as prescription or over-the-counter (OTC) medications and belong to both the ten most prescribed and ten most sold OTC medications worldwide. Current clinical practice shows that in many cases, these drugs are administered concomitantly with other drug products. Due to their metabolic properties and mechanisms of action, the drugs used to treat gastrointestinal diseases can change the pharmacokinetics of some co-administered drugs. In certain cases, these interactions can lead to failure of treatment or to the occurrence of serious adverse events. The mechanism of interaction depends highly on drug properties and differs among therapeutic categories. Understanding these interactions is essential to providing recommendations for optimal drug therapy.

Objective

To discuss the most frequent interactions between GI and other drugs, including identification of the mechanisms behind these interactions, where possible.

Conclusion

Interactions with GI drugs are numerous and can be highly significant clinically. Whilst alterations in bioavailability due to changes in solubility, dissolution rate and metabolic interactions can be (for the most part) easily identified, interactions that are mediated through other mechanisms, such as permeability or microbiota, are less well understood. Future work should focus on characterizing these aspects.

KEYWORDS

Drug-Drug Interactions, gastrointestinal drugs, Pharmacokinetic Interactions, GI pH, GI solubility, permeability, dissolution rate, motility, microbiota

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1. Introduction

It is estimated that 60-70 million US-Americans suffer annually from various types of gastrointestinal (GI) diseases, with GI diseases being the underlying cause of approximately 10% of all deaths in the U.S.[1,2] In fact, statistical data on global sales of prescription medication from 2014 indicate that sales of drug products for the treatment of GI diseases rank 12th with regard to sales of prescription medication worldwide.[3]

The term gastrointestinal diseases covers a wide range of disorders, which can be either acute or chronic. Non ulcer or functional dyspepsia, for example, is usually an acute condition that affects the upper GI tract and is expressed by symptoms such as nausea, vomiting, heartburn, bloating and stomach discomfort. The treatment of functional dyspepsia can involve various drug classes depending on the symptoms as well as the possible causative factors.[4–6] Crohn's disease, by contrast, is a chronic inflammatory disorder that can affect any part of the GI tract from the mouth to the anus. Although as of yet there is no cure for Crohn's disease, there are several treatment options which can relieve the symptoms and prevent relapse.[7] As illustrated by these two examples, it is evident that a diversity of drugs with different mechanisms of action are required to address the various targets across the spectrum of GI diseases.

Frequently, patients are prescribed several drugs concomitantly. Drug-Drug Interactions (DDIs) are a common problem during drug treatment and can sometimes lead to failure of treatment, or can cause serious or even fatal adverse events.[8]

Medications used for the treatment of GI diseases can alter the GI physiology and thus interact with the absorption of concomitant medications, but they can also alter the metabolism and/or elimination of co-administered drugs, potentially resulting, on the one hand, in a lack of efficacy of the co-administered drug or, on the other hand, in adverse drug reactions. From a regulatory perspective, studies of potential drug-drug interactions which lead to changes in absorption are required for the marketing authorization of medicinal products in the European Union and United States.[8,9] In particular, these studies are designed

to evaluate the effect of increased GI pH, the possibility of complexation and alterations in GI transit time.[8] Understanding the effect of GI drugs on the physiology of the GI tract and achieving a mechanistic understanding of the interaction(s) involved are key to successfully managing concomitant drug therapy.

In clinical trials drug performance is determined under controlled conditions (e.g. with strict inclusion/exclusion criteria, under absence of, or controlled co-medication and with monitoring of compliance). But, in clinical practice, where a much wider variety of patient characteristics, disease states and multimorbidity is usual, the potential for DDIs is much greater. In fact, statistics show that one in a hundred hospital admissions occurs as a result of a drug-drug interaction.[10] The number of unreported/ less severe interactions is probably far greater.

In addition to potential interactions with prescription drugs, one must also consider the possibility of interactions with over-the-counter medication (OTC). FDA publishes information leaflets for consumers about the most typical drug interactions that occur with specific OTC medications. It is interesting to note that four out of the twelve drugs discussed by FDA in these leaflets involve drugs used to treat gastrointestinal diseases.[11] European statistics indicate that there may be similar issues with concomitant use of OTC medication in the European Union, since 20-70% of those surveyed reported using OTC medicines.[12]

Keeping in mind these statistics, as well as the fact that medications used to treat GI diseases count among the 10 most prescribed medicines - and also fall within the top 10 in terms of sales of OTC medications - worldwide,[3,13] it is evident that there is a high potential for DDIs with these medications.

The objective of this review is first, to present and discuss the effects of drugs used to treat GI diseases, both prescription and OTC, on the pharmacokinetics and bioavailability of co-administered drugs and second, to identify the mechanisms behind these interactions insofar as possible. The review is organized according to the therapeutic indication of the drug (see Figure 1 for an overview) and covers drugs used to prevent/treat all major GI diseases. Although several reviews concerning DDIs of specific GI drug classes,

119 e.g. PPIs, are available in the literature, to the best of these authors' knowledge this is the first to provide

120 an overview of interactions that are likely to occur across the range of drugs used to treat GI diseases.

2. Medicines used to treat gastrointestinal diseases and their effect on co-administered drugs

2.1 Agents affecting gastrointestinal motility

Various neurotransmitters have an effect on GI motility and its coordination. Dopamine, for example, is present in significant amounts in the GI wall and has an inhibitory effect on motility.[14,15] Dopamine receptor antagonists are currently being used for motor disorders of the upper GI tract, gastroesophageal reflux disease, chronic dyspepsia and gastroparesis and have also been investigated for therapy of motility disorders of the lower GI tract.[16,17] Acetylcholine, by contrast, stimulates GI motility through increased contractile activity by the smooth muscle.[18,19] Serotonin, which is mainly present in the enterochromaffin cells in the enteric epithelium and colon, has a wide range of effects on the GI tract. The diversity of effects can be explained by the presence of multiple subtypes of 5-HT receptors, located on different types of cells. Both agonists and antagonists of 5-HT receptors are used for the treatment of GI diseases.[20,21]

2.1.1 Prokinetic agents

Prokinetic agents promote gut wall contractions and increase their coordination, thus enhancing GI motility. However, they do not disrupt the normal physiological pattern of motility.[16,17]

2.1.1.1 Metoclopramide

Metoclopramide is a first generation prokinetic agent with antidopaminergic properties (D1 and D2 receptor antagonist). In addition, metoclopramide is a 5-HT_3 receptor antagonist and a 5-HT_4 receptor agonist. Metoclopramide promotes the response to acetylcholine in the upper GI tract and therefore accelerates gastric emptying and increases the tone of the lower esophageal sphincter.[22] The effect is observed in both healthy volunteers and those with GI diseases.[23–25] For example, Fink et al. demonstrated that metoclopramide accelerates gastric emptying in patients with gastroesophageal reflux disease independent of their gastric emptying status (Figures 2a and 2b).[25] Metoclopramide is used for the symptomatic treatment of postoperative or chemotherapy-induced nausea and vomiting, gastro-esophageal reflux disease and gastroparesis.[23] A summary of the effects of concomitant use of

145 metoclopramide on the absorption of several APIs is presented in Table 1 and mechanistic explanations
146 for the observed effects are presented in the following text.
147 It is known that migraine attacks are often accompanied by delayed gastric emptying.[26] Tokola et al.,
148 1984, investigated the effect of metoclopramide on the absorption of tolfenamic acid in patients
149 diagnosed with migraine. According to the protocol, the volunteers took part in the absorption studies
150 twice in the absence of migraine and twice as soon as possible after the beginning of a migraine attack.
151 After rectal administration of metoclopramide, the absorption of the tolfenamic acid was accelerated
152 compared to control (rectal administration of placebo) in all subjects. However, the total bioavailability of
153 tolfenamic acid did not change significantly.[27] A similar study had been conducted in 1975 by Volans, in
154 which the effect of metoclopramide on the absorption of aspirin during migraine attacks was
155 investigated.[28] In that study, the delayed gastric emptying during a migraine attack was confirmed. In
156 addition, it was shown that the plasma levels of salicylate achieved during a migraine attack, after
157 intramuscular administration of metoclopramide, were higher in comparison to those achieved without
158 metoclopramide pre-treatment.
159 Gothoni et al., 1972, reported an earlier time to achieve maximum plasma concentration (tmax) and
160 elevated serum tetracycline concentrations in six healthy volunteers after co-administration of
161 tetracycline with intramuscular metoclopramide. Nonetheless, the total area under the curve (AUC)
162 remained unaltered. In the same study, an increase in the rate of absorption of oral pivampicillin was
163 reported when administered along with metoclopramide.[29]
164 Concomitant administration of metoclopramide has also been shown to increase the absorption rate of
165 acetaminophen, mexiletine, lithium, droxicam and morphine. Nimmo et al., 1973, studied the absorption
166 of acetaminophen with and without co-administration of metoclopramide in five healthy volunteers. The
167 mean tmax was reduced from 120 min to 48 min while the mean maximum plasma concentration (Cmax)
168 increased from 125 µg/mL to 205 µg/mL. The urinary excretion of acetaminophen was not influenced.
169 Given the fact that tmax is a function of both absorption and elimination rates, the shortened tmax after

pre-treatment with metoclopramide indicates an enhanced absorption rate.[30] Similar results were obtained in the study of Wing et al., 1980, in which the authors demonstrated an increased absorption rate of mexiletine after co-administration of metoclopramide. Here too, it was observed that the bioavailability of mexiletine was unaltered, indicating that during chronic dosing of mexiletine, the antiarrhythmic effect is unlikely to change after concomitant use of metoclopramide.[31] In a further study by Crammer et al., 1974, it was shown that metoclopramide reduced the tmax of co-administered lithium by two hours.[32] Sánchez et al., 1989, investigated the effect of intravenous metoclopramide on the absorption of droxicam (a piroxicam prodrug) and Manana et al., 1988, investigated the effect of oral metoclopramide after concomitant administration of an oral controlled release formulation of morphine. In both cases, a significant reduction of tmax was observed, but other pharmacokinetic parameters were not significantly different.[33,34] Thus, in most studies it has been demonstrated that although concomitant administration of metoclopramide increases absorption rate, there is little or no effect on AUC, or clinical efficacy.

In a study by Morris et al., 1976, it was likewise observed that the co-administration of metoclopramide resulted in an increased rate of absorption of levodopa and higher peak plasma concentrations, consistent with the earlier tmax.[35] In this case, though, the authors emphasized the fact that higher peak concentrations of levodopa may result in dyskinetic movements and therefore, this should be taken into consideration when metoclopramide is co-administered with levodopa.

Considering the properties of metoclopramide and the fact that besides promoting gastric emptying, it also increases the upper small intestinal motility, administration of metoclopramide could also decrease the time available for absorption in the small intestine and thus lead to a reduction of total bioavailability. Gugler et al., 1981, explored this hypothesis by studying the absorption of cimetidine when given concomitantly with antacids or metoclopramide. The study was conducted in eight healthy volunteers and showed that there was a tendency to a shorter time to reach maximum plasma concentrations when metoclopramide was co-administered. Additionally, a decrease in AUC of approximately 22% was

observed, although in neither case did the difference reach statistical significance.[36] On the other hand, Mahony et al., 1984, conducted a clinical study with children with leukemia and reported that concomitant administration of methotrexate tablets with oral metoclopramide led to significantly lower AUC. Consistent with these findings, Pearson et al., 1985, demonstrated that a very fast or slow small intestinal transit in children with leukemia reduces the Cmax of methotrexate. [37,38]

In the studies conducted by Manninen et al., co-administration of metoclopramide with digoxin in eight healthy adults or in eleven patients on digoxin therapy resulted in reduced serum digoxin concentrations.[39,40] The lower bioavailability of digoxin was attributed to its dissolution rate-limited absorption, since the changes were only observed when digoxin was given as a tablet and not when it was given as a solution. For this reason, authors suggested that fast dissolving tablets of digoxin would be less affected by co-administration of drugs which alter the GI motility. Supporting this hypothesis, Johnson et al., 1984, demonstrated that digoxin was absorbed completely and more quickly when it was given as soft-gelatin capsules rather as a tablet. Oral metoclopramide reduced the tmax for both formulations, but only reduced the AUC of the tablet formulation.[41] From these two studies it is apparent that co-administration of metoclopramide may result in impaired drug absorption and decreased bioavailability in cases when a poorly soluble API exhibits dissolution-rate limited absorption.

In contrast to the results discussed above, Wadhwa et al., 1986, conducted a clinical study in fourteen kidney transplant patients with the aim of increasing the bioavailability of cyclosporine. Cyclosporine is incompletely absorbed in the small intestine with a dose-dependent rate and extent of absorption. The authors reasoned the concomitant administration of cyclosporine with metoclopramide would increase the absorption rate and possibly the bioavailability of this immunosuppressive. Due to accelerated gastric emptying, there was a very significant increase in the Cmax of cyclosporine, as well as a decrease in tmax. Furthermore, an average increase of 29% in the AUC was observed ($p=0.003$). However, the authors concluded that further studies would be required to determine whether metoclopramide can reproducibly increase the absorption of cyclosporine on a long term basis.[42]

Overall, it appears that co-administration of metoclopramide, leads to a decreased tmax of the co-administered drugs, indicating a faster rate of absorption. However, the effect of concomitant use of metoclopramide on the AUC of the co-administered drug is variable. Although the reported examples are limited, it appears that after co-administration of metoclopramide small intestinal transit may be too fast for poorly permeable (e.g. cimetidine) or poorly dissolving (e.g. digoxin) drugs to be adequately absorbed. Thus, in this case, BCS classification may be helpful in identifying potential problems in bioavailability when metoclopramide is co-administered.

2.1.2 Anticholinergic agents

Propantheline is an anticholinergic agent which reduces gastrointestinal motility and prolongs gastric emptying rate. It is usually used in combination with other medicines to treat stomach ulcers. As for metoclopramide, propantheline has been investigated with respect to its potential effect on the absorption of concomitant medications. As one would anticipate, propantheline decreased the absorption rate of acetaminophen and lithium when given concurrently. [30,32] Co-administration of propantheline with a rapidly and a slowly dissolving tablet of digoxin resulted in increased serum digoxin concentrations only for the slowly dissolving formulation.[39,40]

2.1.3 Laxatives

Laxatives promote defecation and are often used OTC for the treatment of constipation. They can be grouped in osmotic, stimulant and bulk laxatives (Table 2).[43] An overview of the effects of laxatives and antidiarrheal agents on gastrointestinal physiology is given in Table 3. Osmotic laxatives (indigestible disaccharides, sugar alcohols, synthetic macromolecules, saline laxatives) attract and retain water in the intestinal lumen by increasing the luminal osmotic pressure. Stimulant laxatives (such as bisacodyl, senna and sodium picosulfate) act locally by increasing colonic motility and decreasing water absorption in the large intestine.[44] Bulk laxatives such as bran, isphagula and sterculia adsorb and retain luminal fluids and increase the fecal mass. For constipation linked with specific diseases additional treatment options are

available: Linaclotide, an agonist of guanylate cyclase-C, stimulates fluid secretion, accelerates intestinal transit and is used for constipation-predominant irritable bowel syndrome.[45]

In general, laxatives shorten GI transit time, but depending on the type of laxative, the extent of the effect on transit time through specific GI compartments may vary (Figure 3). Studies have been conducted with a variety of methods including radiopaque markers method,[46–48] following transit of a single metal sphere (diameter 6 m, density 1.4 g/ml) using a metal detector[49], [^{13}C]-octanoate and lactose-[^{13}C] ureide breath tests[50] and scintigraphy.[45,51–54]

For healthy subjects the following observations have been reported: The total GI transit time was reduced in thirteen subjects after treatment for nine days with either the bulk laxative wheat bran (39.0 h vs. 69.0 h) or the stimulant laxative senna (41.0 h vs. 69.0 h) compared to the baseline value.[46] Small intestinal transit time was reduced by bisacodyl (dose 10 mg) from approximately 2.5 h to 1.5 h in ten subjects,[49] while the osmotic laxatives polyethylene glycol and lactulose, had a minimum effect (if any) on the small intestinal transit time after being administered at a dose of 10 g twice daily for five days.[51] Administration of an isosmotic solution containing 40 g polyethylene glycol 3350 resulted in a significant decrease in oro-caecal transit time from 423.8±28.1 min to 313.8±17.2 min in twelve subjects.[50] In another study, administration of 5 mg bisacodyl in twenty-five subjects significantly accelerated the transit through the ascending colon (median 6.5 h vs. 11.0 h).[54] Similarly, 10-20 mL of lactulose (Duphalac; Duphar Laboratories Ltd., England) three times daily for five days resulted in a significant decrease of the mean proximal colon transit time from 12.9±3.7 h to 7.0±2.5 h in eleven subjects.[53] The total colonic transit time was reduced to a greater extent after administration of 10 mg bisacodyl (from 31±14 h to 7±8 h) than by treatment with 30 g lactulose (from 34±12 h to 30±19 h) in ten subjects.[49]

In patient populations the following observations have been reported: In twelve subjects with constipation-predominant irritable bowel syndrome, treatment with lincalotide (dose 100 µg or 1000 µg) did not affect the gastric or small intestinal transit time.[45] However, the ascending colon transit time was decreased by 54% at a high dose of 1000 µg of linaclotide. At a lower dose of 100 µg there was a decrease

269 of 33%, although this was not statistically significant. In line with these observations, the total colonic
270 transit time was only significantly accelerated by the higher dose.[45] In nine subjects with chronic
271 nonorganic constipation, treatment with an isosmotic electrolyte solution containing polyethylene glycol
272 4000 (14.6 g) for eight weeks did not significantly alter the transit time through the proximal colon, while
273 the transit through the left colon and rectum was significantly accelerated (46±29 h vs. 62±20 h and 37±42
274 vs. 78±21 h, respectively).[48] The results in eight patients with slow transit constipation were similar after
275 administration of 60 g polyethylene glycol 4000 daily for six weeks; the right colon transit time was not
276 significantly different compared to placebo, while the transit time through the left colon was significantly
277 accelerated (13 h vs. 45 h) resulting in a reduction of total colonic transit time from 91 h to 43 h.[47] In
278 summary, laxatives decrease transit times in healthy subjects throughout the GI tract, while in constipated
279 patients the effects are mainly limited to the colon.
280 Changes in GI transit times induced by laxatives can lead to changes in bioavailability. For example, co-
281 administration of senna (20 mL of Liquidepur, Fa. Nattermann, Cologne, Germany) with a sustained-
282 release quinidine formulation (0.5 g every 12 hours) reduced quinidine plasma levels by 25% in nine
283 patients with cardiac arrhythmia on long-term treatment, resulting in reoccurrence of supraventricular
284 extrasystoles.[55] Similarly, polyethylene glycol 4000 reduced the absorption of digoxin by 30% when co-
285 administered with digoxin tablets (dose 0.5 mg) in eighteen healthy subjects.[56] However, it is not clear
286 whether the same effect would be observed in cardiac patients or what the clinical ramifications would
287 be. Further, a trend (although not statistically significant) to decreased AUC of estradiol glucuronide (dose
288 1.5 mg) was observed when co-administered for ten days with the maximum tolerated dose of wheat bran
289 (-13%) and senna (-10%) in twenty healthy postmenopausal women.[57]
290 Many laxatives have been shown to alter the production of short chain fatty acids (SCFA). SCFA are usually
291 associated with a decrease in luminal pH. After treatment with senna or wheat bran, fecal SCFA
292 concentrations were increased in healthy subjects (n=13) by 82% and 19%, respectively.[46] After
293 administration of senna, the pH in the middle and distal colon was decreased (6.39 vs. 6.85, 6.66 vs.

294 7.14).[46] Lactulose significantly acidified the contents in the lower small intestine as well as in the right
295 colon.[58–60] Sodium sulphate also decreased the pH, with the greatest effect in the left colon.[58] By
296 contrast, wheat bran reduced the pH in the distal colon of thirteen healthy subjects only slightly (6.88 vs.
297 7.08).[46] But mechanisms other than via SCFA can also be at play. For example, the increase in the pH in
298 the lower small intestine, colon and rectum observed after administration of magnesium sulphate is
299 postulated to be the result of gastric conversion to magnesium chloride and subsequent reconversion to
300 insoluble magnesium carbonate in the colon prompted by increased colonic bicarbonate secretion.[58] The
301 possible pH changes observed with laxatives are not clearly associated with changes in drug product
302 performance. For example, mesalazine release from a delayed-release, pH-dependent formulation of
303 mesalazine (Asacol®, SmithKline Beecham, UK) was not affected by the co-administration of ispaghula husk
304 or lactulose despite their known pH-lowering effect in the colon.[61,62] Nonetheless, the UK manufacturers
305 of delayed-release mesalazine formulations (Asacol®, Allergan Ltd, Bucks, UK and Salofalk® granules, Dr.
306 Falk Pharma UK Ltd, Bourne End, UK) suggest that drug release might be impaired by preparations with
307 pH-lowering effect.[63,64]
308 With respect to the gut microbiota, the fecal microbiota of patients with chronic idiopathic constipation
309 (n=65) treated with lactulose over twenty-eight days was increased in Anaerobes by 3% and Bifidobacteria
310 by 8%, while treatment with polyethylene glycol 4000 resulted in a reduced fecal amount of Bifidobacteria
311 (-14%).[65] Lactulose administration in patients taking coumarins (acenocoumarol, phenprocoumon)
312 increased their risk of over-anticoagulation, as assessed in a population-based cohort study, because of
313 changes in the vitamin K production of the colonic bacterial flora. By contrast, concomitant intake of
314 isphagula with coumarins did not alter the risk of over-anticoagulation.[66]
315 The importance of the gut microbiota on oral pharmacotherapy is discussed in section 2.6 “Antibiotics”.

316 *2.1.4 Antidiarrheal agents*

317 Antidiarrheal agents provide symptomatic relief of diarrhea by decreasing fluid loss, by slowing down the
318 passage of the gastrointestinal contents through the digestive tract, by increasing fluid absorption and/or
319 by reducing intestinal secretions.[67] They can be classified according to their mechanism of action (Table
320 2). Opioids (such as loperamide, diphenoxylate and codeine phosphate) inhibit intestinal transit by
321 activating μ-opioid receptors. Adsorbents and bulking agents (kaolin, isphagula, methylcellulose) adsorb
322 water and increase the fecal mass, while the antisecretory action of racecadotril, an enkephalinase
323 inhibitor, is linked to reducing chloride and fluid flux into the GI lumen.

324 Differences in the GI transit time have been observed after oral loperamide administration (Figure 4). The
325 total GI transit time was increased after loperamide administration in healthy subjects (74.0 h vs. 50.3 h,
326 n=11), as measured by radiopaque marker pellets, presumably due to reduced, irregular motor activity
327 and therefore, prolonged transit time in the jejunum.[46,68,69] Gastric emptying time was not significantly
328 different in twenty-four healthy subjects treated with 4 mg loperamide compared to placebo as measured
329 with a radio-labeled meal.[70] However, gastric residence time measured with a radiotelemetry capsule
330 was increased two-fold in five healthy subjects treated with 8 mg loperamide (4 doses, every 6 hours).[71]
331 Small intestinal transit time, as measured with the hydrogen breath test, was increased by 80-130% in
332 healthy subjects receiving 4 to 8 mg of loperamide.[70–72]

333 With respect to the composition of GI fluids, loperamide has been shown to decrease prostaglandin-E2
334 induced water and electrolyte secretion in the jejunum of healthy volunteers and reduce postprandial
335 secretion of trypsin and bilirubin by more than 50% in patients with short bowel syndrome.[69,73,74]
336 Similarly, basal and amino acid stimulated gallbladder motility was decreased by loperamide (dose 8 mg)
337 in eight healthy subjects as measured by ultrasonography and bilirubin output in the duodenum.[75] After
338 loperamide administration fecal SCFA concentrations were decreased in healthy subjects (82.0 μmol/g wet
339 weight vs. 152.0 μmol/g wet weight; n=13).[46]

In terms of DDIs, administration of 4 mg loperamide 24 h, 12 h and 1 h before desmopressin administration increased the bioavailability of desmopressin in eighteen healthy subjects (AUC 3.1-fold, Cmax 2.3-fold) and prolonged the time to reach the maximum plasma concentration (2 h vs. 1.3 h) without affecting the elimination half-life.[76] These effects could be explained by the decrease in GI motility. Desmopressin is highly soluble but poorly permeable (bioavailability approx. 0.1%), so longer transit times are expected to lead to a longer contact time of the drug with the absorptive mucosa.[77] Co-administration of loperamide at the maximum tolerated dose over 10-12 days also increased the AUC of estradiol glucuronide (dose 1.5 mg) by 15% in twenty healthy postmenopausal women, although the difference did not reach statistical significance.[57]

On the other hand, a single dose of loperamide (16 mg) decreased the bioavailability of the poorly soluble drug saquinavir (dose 600 mg) by 54% in twelve healthy subjects when administered concomitantly. This could be explained by the decreased motility and/or a reduction of electrolyte and fluid secretion which could hinder dissolution.[78] Additionally, it is possible that a decreased secretion of bile salts secondary to reduced gallbladder motility[75] impeded the solubilisation of saquinavir.

On the other hand, loperamide co-administration (8 mg every 6 hours) in twelve healthy male subjects decreased the absorption rate of theophylline from a sustained-release 600 mg formulation (Cmax 3.2 mg/L vs. 4.6 mg/L, tmax 20 h vs. 11 h), which could be explained by impeded release from the formulation due to a decrease in hydrodynamics (decreased motility) or perhaps a prolonged gastric residence time of the formulation/released drug. However, the AUC was not affected.[79]

Last but not least, the surface of bulk laxatives and bulking agents offers a site for drug adsorption. Concomitant administration of kaolin-pectin decreased the absorption of tetracycline (20%), aspirin (5-10%), procainamide (30%), quinidine (58%), trimethoprim (12-20%), lincomycin (90%), chloroquine (29%) and digoxin (15-62%), which is most likely the result of adsorption of the drugs onto kaolin.[80–88] Drug

adsorption is also observed onto dietary fibers and therefore, similar DDIs to those observed with dietary fibers are further considered in section 2.2.

An overview of the effects of antidiarrheal agents on gastrointestinal physiology is given in Table 3.

2.2 Dietary fibers

The use of dietary fibers in the treatment of various diseases, such as diabetes, hypercholesterolemia, obesity, chronic constipation and gastrointestinal motility disorders, has increased over the last years. However, there are few studies that have investigated the impact of concomitant use of dietary fibers with other drugs. From the studies available it seems that the effect of the concomitant use of dietary fibers depends on the type of fiber used.

The interaction of levothyroxine with dietary fibers is well established. Concomitant use of dietary fibers, such as oat bran, soy fiber and ispaghula husk, result in decreased bioavailability of levothyroxine, due to adsorption of the drug to the fibers in the GI tract.[89] The authors commented that the adsorption of levothyroxine to soluble fibers and the consequent reduction in bioavailability might be greater than its adsorption to insoluble fibers. The interaction with levothyroxine is also noted by FDA in a consumers' information leaflet regarding drug interactions with food.[90]

In a case study reported by Perlman, the blood levels of lithium were decreased by 48%, when a patient was treated simultaneously with lithium and ispaghula husk .[91] There is also some evidence that fibers interact with some tricyclic antidepressants. The clinical effectiveness of tricyclic antidepressants appears usually after an administration period of 2-6 weeks. During this period, due to anticholinergic effects of the drugs, constipation is a common side effect. Therefore, patients receiving antidepressant medication often ingest dietary fibers. Already in 1992, Stewart observed a decrease in plasma concentrations of three tricyclic antidepressants (amitriptyline, doxepin and imipramine) in three patients, who concurrently ingested a diet rich in fibers.[92]

There are conflicting inputs in the literature about the interaction of dietary fibers and digoxin. Brown et al., 1977, reported a significant decrease in the bioavailability of digoxin when given to twelve healthy volunteers with regular or high fiber diet concomitantly, as opposed to administering digoxin alone in the fasted state.[93] Albert et al., 1978, reported that when kaolin-pectin suspension was given simultaneously with digoxin, the total amount of digoxin absorbed was decreased by 62%. However, no significant interactions were observed when digoxin was given 2 h before the administration of the fiber suspension.[85] However, studies by Lembcke et al., 1982, and Kasper et al., 1979, found no effect on the bioavailability of digoxin when it was administered together with guar gum or other fibers.[94,95] In a later study Huupponen et al., 1984, investigated the effect of guar gum on the absorption of digoxin in ten healthy volunteers. It was demonstrated that co-administration of guar gum with digoxin resulted in reduced plasma concentrations of digoxin and a decrease of 15% of the AUC for the first six hours ($p < 0.05$).[96]

Holt et al., 1979, investigated the effect of co-administration of the soluble fibers guar gum and pectin on the absorption of acetaminophen. Concomitant administration with these fibers resulted in delayed absorption and decreased Cmax. However, the total absorption of acetaminophen was not significantly reduced. The authors attributed their results to delayed gastric emptying. Moreover, they argued that because guar gum, when hydrated, forms a viscous colloidal suspension, the high viscosity of this suspension could be a possible reason for the observed delay in gastric emptying.[97] The results from this study correlate well with the study conducted by Reppas et al., 1998, in mongrel dogs, in which the effect of elevated luminal viscosity on the absorption of acetaminophen, hydrochlorothiazide, cimetidine and mefenamic acid was investigated.[98] Elevated luminal viscosity was achieved by administering saline solutions of the water-soluble guar gum. When given concurrently with the guar gum solutions, the Cmax and AUC of the highly soluble acetaminophen and hydrochlorothiazide were significantly decreased, suggesting that the decreased rate of dissolution, due to the higher luminal viscosity, led to lower concentrations at the absorption sites. In the case of cimetidine, concurrent administration of the guar

gum solution led only to a decrease in Cmax and not AUC. For the poorly soluble but highly permeable mefenamic acid, neither the Cmax nor the AUC were significantly affected by the concomitant administration of the guar gum in dogs.[98] Huupponen et al., 1984, reported a decrease in Cmax and AUC of penicillin when given together with guar gum.[96] Finally, Astarloa et al., 1992, investigated the effect of a diet rich in insoluble fiber on the pharmacokinetics of levodopa. Consumption of two months of the dietary supplement with the usual dose of levodopa led to elevated plasma levels of levodopa especially at 30 and 60 minutes after oral administration.[99,100]

It is evident from these studies that it is currently not possible to make any generalizations about DDIs with dietary fibers although it seems that there is a tendency for decreased maximum plasma concentrations of the co-administered drug. These events are likely attributable to slower gastric emptying, higher viscosity and, perhaps in some cases, adsorption phenomena.[101] It also seems that the type of interaction, if any, is highly dependent on the type of dietary fiber used. It remains to be investigated whether these interactions, such as they exist, lead to clinically significant differences.

2.3 Antiemetics

Antiemetics are classified according to their mechanism of action. There are five receptors that play a key role in the vomiting reflex; muscarinic, dopaminergic, histaminic, serotoninergic and substance P/neurokinin receptors.

Aprepitant is a very potent neurokinin-1 receptor antagonist used for the prevention of acute and delayed chemotherapy-induced nausea and vomiting.[102,103] Aprepitant is metabolized primarily by CYP3A4 and secondarily by CYP1A2 and CYP2C19. It also acts as a moderate inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2E1 and as a weak inducer of CYP2C.[102,103] Caution is therefore necessary, especially when administered concomitantly with chemotherapy agents that are metabolized primarily by CYP3A4, as inhibition by aprepitant may lead to higher plasma levels and toxic side effects. According to the Public Assessment Report, EMEND® capsules (which contain aprepitant as API), should not be concomitantly

administered with ergot alkaloid derivatives, pimozide, terfenadine, astemizole, or cisapride, as the competitive inhibition of the CYP3A4 by aprepitant results in elevated plasma concentrations, leading to adverse effects.[103] Further pharmacokinetic interactions that have been reported for aprepitant in the literature are those with midazolam, warfarin, dexamethasone and methylprednisolone.[22,104]

Majumdar et al., 2003, investigated the effect of aprepitant on the pharmacokinetics of single dose midazolam on day 1 and on day 5 during daily administration of aprepitant for five days. In this study, two dose regimens of aprepitant were used; 125/80 mg and 40/25 mg. It was concluded that co-administration of midazolam with the 125/80 mg regimen (125 mg on day 1 and 80 mg on days 2-5) resulted in a 2.3-fold increase in midazolam AUC on day 1 and a 3.3-fold increase on day 5. The plasma concentrations achieved 1 h after dosing (C_{1h}) and the half-life ($t_{1/2}$) were also increased due to the inhibition of first pass and systemic metabolism and subsequent reduction in clearance. Although co-administration of midazolam with the 40/25 mg dose regimen did not result in any significant change in the pharmacokinetics of midazolam, this lower dose is not used in clinical practice.[105] Majumdar et al., 2007, later investigated the effect of aprepitant on intravenously administered midazolam and the findings were consistent with the first study, but with an increase in AUC of 1.47-fold. The authors suggested that the lower increase in AUC observed after intravenous administration of midazolam, might be due to lack of inhibition of presystemic metabolism when midazolam is given intravenously.[106]

In an analogous study by McCrea et al., 2003, the effect of a 5-day administration of 125/80 mg aprepitant regimen on the pharmacokinetics of orally administered methylprednisolone and dexamethasone was evaluated. Due to the inhibition of CYP3A4 by aprepitant, the Cmax of methylprednisolone was increased 1.5-fold while the AUC increased 2.5-fold. An increase of 2.2-fold in AUC was observed for dexamethasone.[107] Clinically, unnecessary high exposure to corticosteroids should be avoided due to the potential risk of adverse effects such as hyperglycemia and increased susceptibility to infections. For these reasons, it is suggested that the oral doses of dexamethasone and methylprednisolone should be reduced by half when used for the management of chemotherapy-induced nausea and vomiting concurrently with

aprepitant.[107] The interaction of aprepitant with warfarin is less clear.[108] In a study by Takaki et al., 2016, a decrease in warfarin plasma levels was observed, but no significant interaction between warfarin and aprepitant was established. One possible reason for the lack of interaction could be the fact that the volunteers who took part in this clinical study were also receiving several other chemotherapeutic agents. In any case, careful monitoring of patients on chronic warfarin therapy is required.[104,109]

Serotonin plays an important role in various body functions. Most serotonin is synthesized in the GI tract and it affects various aspects of intestinal physiology. Multiple subtypes of 5-HT receptors exist on various types of cells, such as smooth muscle and enterocytes, and agonists or antagonists of 5-HT receptors are used in the treatment of different gastrointestinal disorders.[21] 5-HT_3 receptor antagonists, for example ondasentron and granisetron, have been successfully used in the treatment of chemotherapy-induced nausea and vomiting. Recommendations, published by the American Society of Clinical Oncology (ASCO) for the use of the 5-HT_3 receptor antagonists, do not distinguish among them with regard to their safety and efficacy. Nonetheless, these compounds differ significantly in their pharmacokinetic properties and especially with respect to their potential to interact with CYP enzymes.[110,111] Granisetron, for example, does not inhibit any of the CYP enzymes which are commonly involved in drug metabolism, whereas ondansetron inhibits both CYP1A2 and CYP2D6 and can thus interact with various concurrently used drugs. However, the interactions reported in literature are not solely attributed to their enzyme inhibitory properties. Concomitant use of ondansetron with cyclophosphamide resulted in reduced systemic exposure, probably due to increased systemic clearance.[112,113] In any case, there is a need for more studies to increase knowledge about drug interactions of chemotherapeutic agents with commonly used antiemetics, as even a slight change in the pharmacokinetic parameters or pharmacodynamics of the anti-cancer medication could jeopardize the effectiveness of chemotherapy.[112]

2.4 Gastric acid reducing agents and Antacids

Proton-pump inhibitors (PPIs), H_2-receptor antagonists (H_2RAs) and antacids are widely used in the treatment of various gastric acid related disorders, such as peptic ulcers and gastroesophageal reflux disease. In fact, PPIs and H_2RAs are classified among the three most prescribed drug classes for the years 2011-2014 and the situation is similar today.[114] Indeed, esomeprazole, a proton-pump inhibitor, ranks among the top five most prescribed medications worldwide.[115] Of particular concern for these drugs is their increasing OTC use. Despite the fact that gastric antisecretory agents or antacids are tolerated well, with a low overall frequency of adverse reactions,[116] their concurrent use with other medications can have a great effect on drug absorption. If prescribed, identification of potential interactions by the prescribing physician and/or dispensing pharmacist is possible, but this control mechanism is largely lost if the drugs are obtained OTC or via e-pharmacies.

2.4.1 Proton Pump Inhibitors

Proton-pump inhibitors are a group of substituted benzimidazole sulfoxide drugs with strong inhibitory effects on gastric acid secretion from the parietal cells in the stomach. At present, six PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) are available on the market.[117] PPIs are used in the treatment of acid-related disorders and for the prevention of gastrointestinal bleeding in patients receiving dual antiplatelet therapy of clopidogrel and aspirin. Furthermore, they are used as a component of combination therapy for the eradication of H. pylori, because their properties enhance the anti-H. pylori activities of the co-administered antibacterials (clarithromycin and amoxicillin).[118] PPIs can affect the absorption of the co-administered drugs to a great extent, mainly due to the increase in gastric pH. In a recent study, the effect of 40 mg of pantoprazole administered orally once per day for four days and 20 mg of the H_2RA famotidine administered orally twice within 12 hours, on the GI physiology of eight healthy male volunteers was investigated.[119] In both cases, the gastric pH differed significantly in comparison to the control group (Figure 5). However, PPIs can also

affect the pharmacokinetics of co-administered drugs through other mechanisms,[120] and several excellent reviews have been written regarding the drug-drug interactions of PPIs.[121–123]

As already mentioned, gastric pH is an important parameter that can affect absorption of drugs, especially these which are poorly soluble weak bases. For example, Jaruratanasirikul et al., 1998, investigated the effect of 40 mg oral omeprazole on the pharmacokinetics of a single 200 mg capsule of itraconazole in eleven healthy volunteers. Concomitant use of omeprazole resulted in reduction of the mean AUC and Cmax of itraconazole by 64% and 66% respectively. No interaction due to omeprazole's inhibition of CYP3A4 was reported.[124] On the other hand, Johnson et al., 2003, investigated the effect of concomitant use of 40 mg oral omeprazole with a 40 mg dose oral solution of itraconazole in twenty volunteers. It was reported that there was no statistically significant difference on the AUC, tmax and Cmax with the co-administration of omeprazole.[125] The results of these two clinical studies (one with a solid dosage form, one with itraconazole in solution) suggest that co-administration of omeprazole and elevation of gastric pH, affects the dissolution of itraconazole capsules rather than the permeability of itraconazole. The results regarding ketoconazole are similar. In 1995, Chin et al., conducted a clinical study with nine healthy volunteers, in which the effects of 60 mg oral omeprazole or an acidic beverage on the pharmacokinetics of orally administered 200 mg ketoconazole were investigated. Pre-treatment with omeprazole resulted in significantly lower AUC and Cmax and a prolongation of tmax.[126] Ketoconazole and itraconazole are both practically insoluble at pH>4. Co-administration of PPIs with poorly soluble imidazole antifungal agents when given as capsules or tablets is, therefore, not recommended.[127] Interestingly, the elevated gastric pH does not affect the bioavailability of fluconazole tablets.[128] This lack of interaction is underscored by the high solubility of fluconazole over the whole pH range of the GI tract. Thus, stomach acidity does not limit the dissolution rate of fluconazole or its absorption.[129,130]

The increase in the gastric pH caused by PPIs can also greatly affect the bioavailability and effectiveness of anti-retroviral agents, depending on their pH/solubility profiles. Tappouni et al., 2008, conducted a clinical study with sixteen patients, in which the effect of omeprazole on indinavir was evaluated. With pre-

treatment and co-administration of 20 mg oral omeprazole, the Cmax of indinavir decreased by 29% and the AUC by 34%, whereas at a higher dose of 40 mg omeprazole, the Cmax and AUC of indinavir decreased by 41% and 47% respectively.[131] Co-administration of omeprazole resulted in reduction to the systemic exposure to both nelfinavir and its metabolite. In particular, the AUC of nelfinavir was decreased by 36%.[132] Tomilo et al., 2006, reported a 94% and 91% decrease in AUC and Cmax, respectively, of 400 mg oral atazanavir, when co-administered with 60 mg lansoprazole in ten healthy volunteers.[133] The results were similar when omeprazole was co-administered.[134] However, the clinical impact of this drug-drug interaction on the clinical effect of atazanavir is not clear.[135,136] It seems that co-administration of PPIs with an atazanavir/ritonavir regimen does not affect the ability of atazanavir to achieve the minimum plasma concentration necessary for the virologic response, i.e. the concomitant use of atazanavir/ritonavir regimen and PPIs was not associated with higher virologic failure rate. [135] Nonetheless, further studies, in which both the pharmacokinetic parameters and the clinical response rates are simultaneously investigated, are needed to understand the interaction and its consequences more fully.

In contrast to the results mentioned so far, in the study of Winston et al., 2006, co-administration of 40 mg oral omeprazole with 1000 mg saquinavir (given orally as 1000 mg saquinavir/100 mg ritonavir combination) resulted in an 82% increase in the mean AUC of saquinavir in eighteen healthy volunteers. The increase did not result in an increase in adverse effects. The authors commented that further work is necessary in order to understand the mechanism of this DDI and to address whether the effects of omeprazole on saquinavir's pharmacokinetics would be the same even in the absence of ritonavir. The authors also discussed the possibility of whether the increase could be the result of inhibition of transmembrane-transporters, such as P-gp or MRP by omeprazole.[137]

As for most of the antifungal and antiviral drugs, the absorption of mycophenolate mofetil is impaired by concomitant administration of PPIs. Kofler et al., 2009, measured the levels of mycophenolic acid (active metabolite) in thirty-three patients concurrently receiving 40 mg oral pantoprazole. Cmax and AUC of mycophenolic acid were significantly lower when patients were pretreated with pantoprazole.[138] As

anticipated, co-administration of pantoprazole with an enteric coated formulation of mycophenolic acid had no significant effect on its pharmacokinetics.[139]

Apart from affecting the solubility of APIs in the stomach, an increase in the gastric pH can jeopardize the bioavailability of formulations with pH-dependent release. The effect of concomitant administration of esomeprazole on the bioavailability of risedronate sodium DR was evaluated in a clinical study involving eighty-seven postmenopausal women. The results showed that esomeprazole administration one hour before dinner or one hour before breakfast resulted in 32% and 48% reduction in the bioavailability of risedronate sodium DR, respectively. In the report, it was suggested that an increase in the gastric pH may compromise the enteric coating of risedronate delayed release formulation, thus resulting in release of risedronate sodium in the stomach, where it could convert to the less soluble free acid.[140] However, as it has been shown that PPIs (pantoprazole) decrease buffer capacity as well as increase gastric pH,[119] a premature release due to enteric coating failure appears unlikely.

A review of all the available clinical data from literature describing the effect of the administration of various gastric acid reducing agents on the absorption and bioavailability of co-administered weakly basic anticancer drugs was published by Budha et al.[141] The authors attempted to correlate the physicochemical properties and pH-solubility profiles of the different anticancer drugs with the observed effect on the absorption caused by the elevation of the gastric pH after the administration of the acid reducing agents (PPIs, H_2RAs and antacids). It was concluded that the impact of the elevation of gastric pH is more prominent for the anticancer drugs which exhibit an exponentially decreasing solubility in the pH range 1-4 and for which the maximum dose strength is not soluble in 250 mL of water. Elevation of gastric pH is expected to substantially decrease the dissolution rate of these drug products, thus leading to incomplete dissolution of the dose and impaired absorption.

In 2013, Mitra and Kesisoglou described strategies to minimize or avoid reduced absorption of weakly basic drugs resulting from elevated gastric pH.[142]

The observed DDIs with PPIs occur not only because of their elevation of gastric pH, but can also arise from other properties. It has been shown that concurrent administration of 10 mg of nifedipine with 20 mg of omeprazole for eight days (short-term treatment) resulted in an AUC increase of 26%, whereas no increase was observed after co-administration of a single 20 mg dose of omeprazole.[143] The authors hypothesize that the higher levels might be due to inhibition of CYP3A4, but they note that this increase is not likely to have major clinical relevance, especially when taking into account the intra- and inter-individual variability observed for nifedipine.[143] In contrast, in the study by Bliesath et al., 1996, co-administration of 20 mg of nifedipine with 40 mg of pantoprazole for ten days, had no effect on the pharmacokinetics of nifedipine.[144] This apparent discrepancy in DDI tendency might be due to the different CYP-isoenzymes inhibitory properties of the two PPIs. It is believed that among all PPIs, omeprazole is the one which has the greatest potential for drug interactions, since it has a high affinity for CYP2C19 and CYP3A4.[145–148]

Another example of a non-pH related DDI with PPIs is the delayed elimination of plasma methotrexate, independent of renal function.[149]

Last, but not least, there has been an increasing interest in investigating the mechanism of drug interactions of PPIs with clopidogrel. Clopidogrel is a prodrug that requires activation via cytochrome P450 isozymes (CYP2C19, CYP3A4, CYP3A5) in order to transform to its pharmacologically active form. Therefore, inhibition of the cytochrome isoenzymes, which are involved in the metabolic pathway of clopidogrel, may reduce its antiplatelet activity and potentially increase the risk of thrombosis. In fact, in 2009 FDA published a warning note on the drug label of Plavix® (clopidogrel, Sanofi Clir SNC, France) and continues to warn the public against concomitant use of clopidogrel and omeprazole. It should be noted that, although studies have demonstrated that concomitant use of clopidogrel and PPIs, especially omeprazole, reduces the antiplatelet effect of clopidogrel, the mechanism behind this interaction and the clinical importance (cardiovascular risk) has not yet been clearly established.[150–155]

603 *2.4.2 H_2 receptor antagonists*

604 The H_2RAs are another drug class used to treat gastric acid related disorders. These compounds bind to
605 histamine H_2 receptors on parietal cells and antagonize the action of histamine, which is the major
606 transmitter for stimulation of acid secretion.[156] As with the PPIs, there are DDIs with different classes of
607 drugs and these are mainly attributed to the elevation of the gastric pH (see Figure 5). For example,
608 ketoconazole and itraconazole demonstrate impaired drug absorption when they are concomitantly used
609 with H_2RAs as well as with PPIs. Piscitelli et al., 1991, investigated the effect of 150 mg orally administered
610 ranitidine on 400 mg oral ketoconazole in six healthy volunteers. The decreased Cmax and AUC and
611 bioavailability of ketoconazole in this study was attributed to the elevated gastric pH, which resulted in a
612 decreased and incomplete ketoconazole dissolution.[157] The results were similar when the effect of
613 cimetidine on the absorption and pharmacokinetics of ketoconazole was investigated.[122] Lim et al., 2007,
614 investigated the effect of famotidine on the absorption of fluconazole and itraconazole. Twenty healthy
615 volunteers received orally 40 mg famotidine with 200 mg itraconazole or 100 mg fluconazole. Co-
616 administration of famotidine resulted in a 52.9% decrease in Cmax and a 51.1% decrease in the AUC of
617 itraconazole, but no difference was observed in the pharmacokinetics of fluconazole.[158] This different
618 behavior of fluconazole had previously been observed by Blum et al., 1991 and can be explained by its
619 much higher solubility (see 2.4.1).[159]

620 The situation is similar with anti-retroviral medications.[160] Analogous to the PPIs/saquinavir interaction,
621 co-administration of cimetidine resulted in increased exposure to saquinavir. [137,161]

622 Russell et al., investigated the effect of a single dose of 40 mg of famotidine on the pharmacokinetics of
623 the weak base dipyridamole in eleven elderly adults with normal gastric acid secretion. After co-
624 administration of famotidine, the Cmax and absorption constant (k_a) of dipyridamole decreased
625 significantly. The total AUC decreased by 37%, but this decrease was not found to be statistically
626 significant. The authors attributed the observed differences to slower dissolution rate of dipyridamole
627 tablets at elevated gastric pH.[162] In other studies, co-administration of ranitidine with two weak bases,

enoxacin and cefpodoxime, resulted in decreased bioavailability, which was again attributed to decreased solubility in the gastric environment at elevated pH.[163,164]

As with the PPIs, DDIs with H_2RAs can occur not only because of their elevation of gastric pH, but can also arise from their other properties. In particular, it has been shown that, among the various H_2RAs, cimetidine is the most potent inhibitor of the CYP450 enzymes. The inhibition is attributable to the imidazole ring in its structure, and results in changes in the metabolism of various co-administered drugs.[165] In cases where a clinical significant interaction is suspected, other H_2RAs (e.g. ranitidine, famotidine) are preferred over cimetidine.[166,167] Among the various metabolic interactions that have been reported after co-administration of cimetidine,[165] the metabolic interactions observed with warfarin and propranolol have been most intensively studied and the clinical significance of these interactions has also been evaluated. Toon et al., investigated the effect of a nine-day short treatment of cimetidine and ranitidine (800 mg oral dose daily and 300 mg oral dose daily respectively) on the pharmacokinetics of 25 mg of racemic warfarin, administered orally starting on the fourth day of cimetidine treatment and continuing for the next five days, in nine healthy volunteers.[168] The prothrombin time and Factor VII clotting time were also evaluated. Whilst ranitidine had no effect on the pharmacokinetics of either of the two enantiomers of warfarin, cimetidine significantly increased the elimination half-life and decreased the clearance of the (R)-enantiomer of warfarin. In contrast, the pharmacokinetics of the (S)-enantiomer of warfarin were not affected by co-administration of cimetidine. Nonetheless, co-administration of either ranitidine or cimetidine did not result in a clinically significant difference in terms of the anti-coagulation effect of warfarin.[168] These results were further confirmed by a later study from Niopas et al.[169] It should be noted however, that both studies were conducted in healthy volunteers and therefore, the clinical effects on patient populations could differ.

The effect of a daily oral dose of 1000 mg cimetidine on the steady state plasma levels of propranolol, administered as a 160 mg sustained-release formulation daily, was evaluated in seven healthy volunteers during a thirteen-day treatment (administration of cimetidine started on the eighth day).[170] It was

concluded that co-administration of cimetidine resulted in decreased clearance of propranolol and thus increased propranolol plasma levels at steady state. In a similar study, Reimann et al. investigated the effect of cimetidine (1000 mg daily, one day oral pretreatment) and ranitidine (300 mg daily oral dose, one and six days pretreatment) on the steady state propranolol plasma levels (160 mg sustained-release capsule, once daily) of five healthy volunteers.[171] It was shown that one-day pretreatment with cimetidine resulted in elevated propranolol plasma levels at steady state, while ranitidine pretreatment for one or six days did not affect significantly the propranolol plasma levels at steady state. However, the authors stated that the elevated plasma levels of propranolol observed after pretreatment with cimetidine did not lead to a clinically significant effect.[171] Again, the study was conducted in healthy volunteers and the clinical effects on patient populations could differ. Nonetheless, it should be noted that the companies are required by the regulatory authorities to inform the patients that there is a potentially clinically significant DDI of cimetidine and propranolol in the patient information leaflets.[172]

It is obvious that there are many interactions of PPIs and H_2RAs with other concomitantly used drugs, especially poorly soluble weak bases, and that their use should be monitored, particularly in cases where the DDI is well established. Besides the elevation of gastric pH and the interactions with metabolic pathways, it should be noted that PPIs and H_2RAs can also affect other aspects of the physiology in the gastrointestinal tract. Recent data in literature suggest that administration of PPIs or H_2RAs can be accompanied by reduced buffer capacity, chloride ion concentration, osmolality and surface tension in stomach and an increase in the pH of the upper small intestine of up to 0.7 units, an increase that would be especially relevant for compounds (basic or acidic) with pKas between 6 and 7.[119] Carefully designed DDI studies, in terms of dosing and duration of treatment, are needed in order to accurately determine the effect of H_2RAs or PPIs on the pharmacokinetics of co-administered drugs and investigate the clinical consequences of these interactions.

2.4.3 Antacids

The term “antacids” describe a category of salts, formulated as the combination of polyvalent cations such as calcium, aluminium, or magnesium with a base, such as hydroxide, trisilicate or carbonate. Aluminium hydroxide alone, or in combination with magnesium hydroxide, is the main ingredient of many antacid products. Since the appearance of the PPIs and H_2RAs, which are more potent drugs and can be used for a wide variety of gastrointestinal disorders, antacids have been mainly marketed as OTC medications. However, the concomitant use of antacids with other drugs can significantly affect their absorption or even their therapeutic effect. Considering the fact that the use of OTC antacids is widespread, there is a particular need for appropriate information for patients, doctors and pharmacists. Besides interactions associated with increased pH, the major DDIs with antacids involve chelation reactions. Various categories of drugs, such as quercetin, catechol derivatives and tetracyclines, are known to form drug/metal chelates.[173–175] Fluoroquinolones also interact with multivalent cations and this interaction can lead to reduced antimicrobial activity.[176]

Deppermann et al., 1989, and Garty et al., 1980, investigated the effect of H_2RAs or antacids (mixture of aluminium hydroxide and magnesium hydroxide) on the oral absorption of various tetracycline antibiotics. The antacids resulted in reduction of the oral bioavailability of tetracyclines by 80% or more, whereas co-administration of the H_2RAs did not affect the pharmacokinetic parameters of tetracyclines.[177,178] For this reason, it was concluded that chelation rather than elevation of gastric pH is the probable mechanism of this DDI. The complexes that are formed by chelation are insoluble and therefore they precipitate, preventing absorption. The results are similar with co-administration of antacids and fluoroquinolones. Aluminium ions form a stable and insoluble complex with quinolones, thus preventing their intestinal absorption and reducing their bioavailability.[179,180] By contrast, concomitant administration of an H_2RA did not have a significant effect on the AUC of ciprofloxacin.[177] Since the formation of the chelate complex is the limiting factor to absorption of quinolone antibiotics, many studies have been conducted in order to

establish an optimal interval of antacid dosing before or after the administration of the antimicrobial agents. With regard to fluoroquinolones, it has been concluded that administration of antacids four hours earlier or two hours later than the administration of the antibiotic, would circumvent the interaction.[181–185]

As with the PPIs and H_2RAs, the elevation of gastric pH that is observed after administration of antacids could also impact the dissolution or oral solid formulations and change their pharmacokinetics. Indeed, co-administration of itraconazole with antacids resulted in decreased AUC.[186] However, in a pilot study by Brass et al. (n=4) the absorption of ketoconazole was not significantly decreased. [187]

The interaction of antacids and NSAIDs is also an interesting case. NSAIDs are among the most popular OTC and frequently prescribed medications for acute or short-term pain and chronic inflammatory diseases. Since NSAIDs cause dyspepsia and damage in the upper gastrointestinal mucosa they are often given with antacids. Interactions of antacids with NSAIDs are not clearly established and no general recommendations can be made for this drug category. However, there are studies indicating that co-administration with antacids containing magnesium hydroxide or sodium bicarbonate could enhance the rate and possibly the extent of absorption of some NSAIDs, i.e. ibuprofen, tolfenamic and mefenamic acid, diflunisal and naproxen.[188–191] This has been attributed to the fact that magnesium hydroxide, in addition to increasing gastric pH, also accelerates gastric emptying. Such effects have not been observed for aluminium hydroxide, which in contrast to magnesium hydroxide prolongs gastric emptying[192]

There have been many further studies investigating the interactions of antacids with APIs from various drug classes, including corticosteroids, cardiovascular agents and antidiabetic agents. However, it has not been possible to make any generalizations about the observed interactions. Furthermore, in some cases there is no evidence that differences in pharmacokinetic parameters translate into clinically significant differences.[192]

2.5 Probiotics

It is well known that the intestinal microflora plays a key role in physiological, metabolic, immunological and nutritional processes in the human body. For this reason, there is currently great interest in influencing the composition of the microflora and its activity using probiotics for both the prevention and treatment of various diseases.[193] According to WHO, probiotics are "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host".[194] There are several clinical studies that have illustrated their beneficial effects on gastrointestinal disorders such as diarrhea and irritable bowel syndrome. The gram-negative bacterium Escherichia coli Nissle 1917, for example, has been used since 1920 for the treatment or prevention of irritable bowel syndrome, chronic constipation, non-ulcer dyspepsia and other gastrointestinal disorders.[195] The mechanism of action of the probiotics is not yet fully understood. It seems that they may modulate the intestinal epithelial barrier and transport across it, noting that in inflammatory bowel diseases, e.g. ulcerative colitis and Crohn's disease, the barrier properties of the epithelium are compromised due to secreted cytokines and/or medication.[196]

Despite the wealth of evidence regarding their advantageous and well-tolerated use, the literature on interactions between concomitantly administered probiotics and drugs with respect to drug pharmacokinetics is mainly limited to animal experiments. In the study of Mikov et al., 2006, the effect of co-administration of probiotics (oral 2 g dose of freeze dried powder of a mixture of the strains Lactobacillus acidophilus L10, Bifidobacterium lactis B94 and Streptococcus salivarius K12 every 12 h for three days) on sulfasalazine metabolism (sulfasalazine administered as an oral dose of 100 mg/kg dissolved in saline via gavage 6 h after completing the three day treatment with probiotics) in the rat gut lumen was investigated. The authors showed that administration of probiotics significantly increased the conversion of sulfasalazine to sulfapyridine and 5-aminosalicylic acid by increasing azoreductase activity. This could possibly enhance sulfasalazine therapy, which would be important in patients with reduced gut microflora, subsequent to antibiotic therapy, or in severe diarrhea.[197] Lee et al., 2012, confirmed an increase of

azoreductase activity in *ex vivo* colon rat fluids. However, no differences were found in the pharmacokinetic parameters of sulfasalazine and sulfapyridine.[198] Kunes et al., 2011, investigated the effect of E. coli Nissle 1917 probiotic medication on the absorption kinetics of 5-aminosalicylic acid in rats. The results showed that there was no difference in the pharmacokinetics of 5-aminosalicylic acid and that E. coli Nissle 1917 medication did not affect the absorption of 5-aminosalicylic acid.[199] Al Salami et al., 2008, investigated the effect of a mixture of three probiotics in diabetic rats on gliclazide pharmacokinetics. They observed that gliclazide's absorption and bioavailability were reduced in healthy rats. The authors attributed this change to several possible causes, most of which had to do with intestinal efflux drug transporters.[200] Saksena et al., 2011, reported that Lactobacilli or their soluble factors significantly enhanced P-gp expression and function under normal and inflammatory conditions in mice.[201] Finally, Matuskova et al., 2014, investigated the effect of administration of E. coli Nissle 1917 on amiodarone absorption in rats. This resulted in 43% increase in the AUC of amiodarone. Interestingly, this effect was not observed when E. coli Nissle 1917 was replaced by a reference non-probiotic E. coli strain suggesting that the increase in AUC of amiodarone was due to the administration of the probiotic.[202] Clearly, studies in humans are needed in order to investigate whether these results can be extrapolated well to patients with altered intestinal microflora.

2.6 Antibiotics used for gastrointestinal infections

Antibiotics aim to attack targets specific to bacterial organisms such as bacterial cell walls, bacterial cell membranes, bacterial metabolism or replication, in order to avoid damage to human cells. However, antibiotics are not 100% selective for bacteria that are pathogenic for the host organism. As a result, the GI microbiota is frequently disturbed after treatment with antibiotics.[203,204] In fact depending on the antibiotic, 5-25% of patients treated experience diarrhoea.[205,206]

769 Sullivan et al. reviewed the effect of various antibiotics on the abundance of bacterial types and
770 species.[204] Differences in the composition of the microbiota could alter the composition of colonic fluids
771 and permeability of the gut wall as well as the abundance of bacterial enzymes.
772 Colonic bacteria are involved in the cleavage of dietary fibres to oligosaccharides and monosaccharides
773 and their further fermentation to short chain fatty acids (SCFAs) such as acetate, propionate and
774 butyrate.[207] Patients treated with antibiotics showed a decreased colonic carbohydrate fermentation and
775 consequently lower fecal concentrations of SCFAs.[208–212] In other studies it was shown that SCFAs
776 stimulate ileal and colonic motility.[213–215] The inhibition of gastric emptying by nutrients that reach the
777 ileo-colonic junction, the so-called "ileocolonic brake", is also associated with SCFAs.[216] But GI transit
778 times can also be affected by certain antibiotics through other mechanisms: for example, erythromycin
779 accelerates gastric emptying (-25% to -77%) by acting as a motilin agonist, while prolonging small intestinal
780 transit time (+20% to +45%) for liquids and solids in healthy volunteers and patients.[217–222] For example,
781 when erythromycin was co-administered with a controlled-release formulation of pregabalin, designed to
782 remain for a prolonged time in the stomach, in eighteen healthy subjects there was a reduction of AUC
783 and Cmax by 17% and 13% respectively, due to erythromycin's prokinetic action.[223] Since the pregabalin
784 exposure was still in the range calculated for patients receiving an immediate release formulation of
785 pregabalin, the interaction was deemed not to be clinically relevant.
786 If bacterial enzymes are involved in the biotransformation of a drug, the intake of antibiotics can affect its
787 metabolism by changing the composition of the microbiota and thus altering the bacterial enzyme
788 activity.[224,225] At least thirty commercially available drugs have been reported to be metabolised by
789 bacterial enzymes in the gastrointestinal tract.[224] The serum concentrations of digoxin, which is partly
790 metabolised by gut microbiota, increased two-fold after administration of erythromycin or tetracycline for
791 five days in four healthy volunteers.[226] In another report, toxic digoxin plasma levels were observed in a
792 patient after co-treatment with erythromycin, possibly due to the inhibition of *Eubacterium lentum* which
793 converts digoxin to its reduced derivatives.[227] Incubation of flucytosine with fecal specimens of

neutropenic patients before and after treatment with antibiotics (ciprofloxacin, penicillin, co-trimoxazole) and antimycotics (amphotericin B, fluconazole, nystatin) indicated that the transformation of flucytosine to its active metabolite, fluorouracil, was reduced.[228] Similarly, concomitant administration with ampicillin (250 mg four times daily for five days) with sulfasalazine (single dose 2 g) led to a decrease in the AUC of sulfapyridine by 35% in five healthy subjects suggesting a decrease in azoreductase activity and prodrug activation.[229]

An altered colonic microflora could also adversely affect the drug release from colon-targeting formulations coated with water-insoluble polysaccharides.[230] Since polysaccharides such as guar gum, pectin and chitosan are degraded by bacterial enzymes in the colon, release of the drug relies on the abundance and activity of the polysaccharide-specific bacterial enzymes. Samples (fecal slurries) from volunteers treated with antibiotics within the last three months should be excluded from the evaluation of such formulations in *in vitro* dissolution tests.[230]

The microbiota is also involved in the modification of primary bile acids to secondary bile acids, such as deoxycholic acid and lithocholic acid, via microbial 7α-dehydroxylase and in the deconjugation of conjugated bile acids.[231] Unconjugated bile acids are less likely to be reabsorbed in the terminal ileum and therefore, bacterial action promotes the excretion of bile acids.[232] Thus, antibiotic treatment may cause changes in the bile acid pool. Indeed, treatment with oral vancomycin decreased fecal levels of secondary bile acids and increased fecal levels of primary bile acids in healthy volunteers (n=10). By contrast, treatment with oral amoxicillin showed no such effect.[233] It has also been hypothesized that antibiotic-induced differences in the bile acid composition could affect the solubilisation of lipophilic drugs. However, a recent study evaluating the differences in the solubilisation capacity of primary and secondary bile acids for nine poorly water-soluble drugs revealed at most minor differences between conjugated and unconjugated bile acids. Only dehydroxylation at C-7 improved drug solubilisation significantly for the compounds investigated.[234]

With regard to DDIs at the level of metabolism, the effect of antibiotics on metabolic enzymes is often specific to the antibiotic agent. Macrolide antibiotics interact with substrates metabolized by CYP3A4 (i.e. carbamazepine, terfenadine, cyclosporine) depending on the macrolide's specific affinity for CYP3A4. The interaction potential can be high (troleandomycin, erythromycin), moderate (clarithromycin, roxithromycin) or low (azithromycin).[235] For example, concomitant administration of erythromycin (500 mg three times daily for seven days) with midazolam (single dose 15 mg) resulted in a 4-fold increase of the AUC of midazolam in fifteen healthy subjects.[236] Similarly, when administered with clarithromycin (500 mg twice daily for 7 days), the bioavailability of midazolam (single dose 4 mg) was increased 2.4-fold in sixteen healthy subjects.[237] But, after pretreatment with azathioprine (500 mg daily for three days), no significant effect on the pharmacokinetics of midazolam (single dose 15 mg) was observed in twelve healthy subjects.[238]

For the fluoroquinolones, depending on the fluoroquinolone's specific affinity for CYP1A2, interactions with CYP1A2 substrates (i.e. clozapine, theophylline) have been observed.[239] Concomitant oral administration of enoxacin (400 mg twice daily for six days) with theophylline (250 mg twice daily for eleven days) resulted in a reduction in total clearance of theophylline by 74% in six healthy subjects,[240] while ciprofloxacin (500 mg twice daily for two and a half days) reduced theophylline's total clearance by 19% after a single oral dose of theophylline syrup (3.4 mg/kg) in nine healthy subjects.[241] In contrast, concomitant administration of norfloxacin (400 mg twice daily for four days) with theophylline (200 mg three times daily for four days) had no significant effect on theophylline's total clearance in ten healthy subjects.[242] For more detailed information, the reader is referred to several review articles.[235,239,243]

2.7 Anti-inflammatory drugs for IBD

Anti-inflammatory agents, such as aminosalicylates and corticosteroids, are the most commonly used drugs in inflammatory bowel disease (IBD). Treatment with aminosalicylates includes a range of prodrugs (sulfasalazine, olsalazine, balsalazine) or modified release formulations to deliver aminosalicylates to their

target site in the intestine. If remission cannot be achieved with aminosalicylates, the next treatment option consists of different corticosteroids ranging from locally acting drugs (budesonide) to systemic acting ones (hydrocortisone, prednisolone, dexamethasone).

Aminosalicylates have shown to alter the GI physiology. In terms of GI transit time, olsalazine accelerated transit, with a mean gastric emptying time of 45.3±24.2 min vs. 67.3±33.1 min, a mouth to caecum transit time of 242±41 min vs. 325±33 min and whole gut transit time of 37.8±17.8 h vs. 60.5±26 h in six patients with ulcerative colitis whereas intake of sulfasalazine had no effect in six healthy subjects (measured by scintigraphy of a solid radio-labelled meal or hydrogen breath test).[244–246] The authors commented that this may be the result of a direct action of olsalazine on contractile activity in the small intestine, inducing hypersecretion or decreasing fluid absorption.[245]

With respect to luminal pH, treatment with sulfasalazine in patients with ulcerative colitis in remission resulted in a decrease in colonic pH to 4.90±1.3 compared to treatment with Asacol® (mesalazine) with a colonic pH of 5.52 ±1.13 or Dipentum® (olsalazine) with a pH of 5.51±0.37.[247] Nugent et al. postulated that reduced colonic pH may impair drug release from delayed-release formulations targeting the terminal ileum/colon (trigger pH for release is >6-7) or alter bacterial enzyme activity.[248]

Regarding permeability, jejunal perfusion studies showed a decreased absorption of water, sodium, potassium and chloride in the presence of olsalazine or sulfasalazine.[249] In ileal perfusion studies, reduced absorption of water and glucose was observed, when olsalazine was present, which in turn could explain the higher volume of ileostomy fluid observed after oral administration of this drug.[249,250] By contrast, no changes in absorption or volume of fluids was observed in ileal perfusion studies in the presence of sulfasalazine.[249] With regard to specific uptake mechanisms, sulfasalazine reduced the uptake of folic acid and methotrexate by folate transporters in biopsy specimens taken from the duodenojejunal region while olsalazine only decreased folic acid uptake.[251] In an intervention study, sulfasalazine treatment was discontinued in rheumatoid arthritis patients who had previously received a combination of sulfasalazine and methotrexate. The intervention resulted in a more than 2-fold increase of methotrexate serum

concentrations, in line with the ability of sulfasalazine to compete with methotrexate for the folic acid transporter.[252]

After treatment with sulfasalazine the fecal microbiota of patients with rheumatoid arthritis was richer in Bacillus, whereas decreased numbers of aerobic bacteria, Escherichia coli, Clostridium perfringens and Bacteroides were observed.[253–255] Treatment with mesalazine resulted in a decreased diversity of the intestinal microbiota and also reduced the quantity of fecal bacteria in patients with diarrhea-predominant irritable bowel syndrome.[256,257] These changes in colonic bacteria may have ramifications for drugs like digoxin, which are partly metabolised by bacterial enzymes (see section 2.6 “Antibiotics”).[258–260]

With regard to DDIs, pre-treatment with sulfasalazine (500 mg for six days) in ten healthy subjects decreased the AUC of digoxin by 25% after being administered as oral solution (dose 0.5 mg).[261] The mechanism of the interaction is not yet understood. Differences in bioavailability could possibly be attributed to a direct action of sulfasalazine on the intestinal mucosa or induced differences in the gut microbiota enhancing digoxin metabolism. For a patient on concomitant treatment with cyclosporin (480 mg daily) and sulfasalazine (1.5 g daily), increased plasma concentrations of cyclosporine were observed five days after the treatment of sulfasalazine was stopped making it necessary to reduce the dose of cyclosporine by 60%.[262] While the interaction is not yet understood, an induction of metabolic enzymes is plausible considering the time course of the observation. For 6-mercaptopurine (50-75 mg), a metabolic interaction was observed with concomitantly administered olsalazine (1000-1750 mg) in a patient with Crohn’s disease, resulting in bone marrow suppression and required dose reduction of 6-mercaptopurine.[263] This interaction may be caused by the inhibition of thiopurine methyltransferase, which is responsible for 6-mercaptopurine metabolism; inhibition of this enzyme by aminosalicylates has been demonstrated in *in vitro* enzyme kinetic studies.[264]

After treatment with corticosteroids, the phospholipid mucus layer can be fluidized, resulting in a thinner mucus barrier.[265] Impairment of membrane integrity can cause side-effects such as gastrointestinal

bleeding and bowel perforation.[266] The corticosteroids can also affect active transport mechanisms such as bile salt reuptake and exo-transport. Treatment with budesonide results in upregulation of the apical sodium-dependent bile acid transporter in the terminal ileum, which enhances bile acid absorption in both healthy controls and patients with Crohn's disease.[267,268] Consequently, lower luminal bile salt concentrations may impede solubilisation and absorption of lipophilic poorly soluble compounds.[269] In terms of transporters, budesonide and prednisone are substrates of the efflux transporter P-glycoprotein.[270] However, it is unclear whether these alterations result in clinically significant DDIs.

The main elimination pathway of corticosteroids is the metabolism by intestinal and hepatic CYP3A4 which is especially important for high-clearance corticosteroids such as budesonide and prednisone.[271] Co-administration of prednisone with metronidazole in six patients with Crohn's disease reduced the bioavailability of metronidazole by 31%, most likely attributed to the induction of liver enzymes responsible for metabolizing metronidazole.[272] Likewise, co-treatment with prednisone resulted in decreased serum concentrations of salicylates in a 11-year-old child with juvenile rheumatoid arthritis due to the induction of salicylate clearance by prednisone.[273] On the other hand, drugs inhibiting CYP3A4 in the intestinal wall and liver such as ketoconazole, itraconazole, clarithromycin and HIV-protease inhibitors reduce the metabolism of corticosteroids and increase their bioavailability.[274–277]

2.8 Immunosuppressive agents for IBD

Immunosuppressive agents are frequently used in gastroenterology for the treatment of inflammatory bowel disease, autoimmune hepatitis, autoimmune pancreatitis, sclerosing cholangitis and in the post-transplantation setting.[278] Especially in IBD, therapy with immunosuppressive agents has gained in importance over the last few years.[279] Immunosuppressive agents can be classified in immunomodulators (e.g., thiopurines (6-mercaptopurine, azathioprine), methotrexate, tacrolimus, sirolimus, everolimus, cyclosporine A) and biologics (e.g., monoclonal antibodies: infliximab, adalimumab, vedolizumab, golimumab).[279] Depending on the specific immunosuppressive agent, gastrointestinal transit time, bile

915 flow and/or permeability can be altered, which could further affect drug product performance of co-
916 administered drugs.
917 Regarding transit time, gastric emptying time (as measured with magnetic markers after a standardized
918 meal using Alternating Current Biosusceptometry) was decreased in patients treated with tacrolimus after
919 kidney transplant (47±34 min) compared to healthy subjects (176±42 min) or patients treated with
920 cyclosporine A (195±42 min).[280]
921 In terms of drug absorption, immunosuppressants can result in increased permeability on the one hand,
922 but decreased surface area on the other hand. Intestinal permeability was increased (75% of median value;
923 indicated by an increased lactulose/L-rhamnose excretion ratio) in liver graft recipients treated with
924 tacrolimus (n=12) compared to healthy subjects (n=9) and by 48% compared to untreated liver transplant
925 patients (n=5).[281] Only the permeability via the transcellular pathway seems to be increased by
926 tacrolimus, as indicated by an increased lactulose/L-rhamnose ratio (+160%) and unchanged excretion of
927 lactulose in treated orthotopic liver transplantation patients.[281,282]
928 Another side-effect of immunosuppressive therapy, especially with methotrexate (including low-dose
929 therapy) is GI mucositis resulting in the loss of villi in the duodenum, crypts in the colon and
930 enterocytes.[283–287] Oral mucositis is a side-effect of azathioprine therapy.[288] In patients with oral
931 mucositis, bupivacaine absorption from lozenges was increased and a trend to higher fentanyl absorption
932 administered with a sublingual spray was observed but did not reach statistical significance.[289,290] The
933 effect may be due to impairment of the barrier function of the mucosa.
934 In terms of transporter systems and metabolism, immunosuppressants (cyclosporine A, tacrolimus,
935 everolimus and sirolimus) are substrates of P-glycoprotein and CYP3A4.[291–293] As a result, various drug
936 interactions with P-gp substrates such as aliskiren and anthracyclines have been reported for cyclosporine
937 A.[294–296] Additionally, concomitant administration of inhibitors (e.g. azole antifungal drugs, macrolide
938 antibiotics) and inducers (e.g. anti-convulsants, rifampicin) of CYP3A4 can modify therapeutic response
939 and toxicity of the abovementioned immunosuppressants.[297–299] Methotrexate intra muscular or

subcutaneous co-treatment in patients with Crohn's disease or oral co-treatment in patients with rheumatoid arthritis resulted in increased infliximab concentrations, most likely due to a decrease in the development of infliximab antibodies.[300,301] Co-administration of azathioprine in patients treated with warfarin resulted in higher warfarin doses needed to reach therapeutic anticoagulant effects but the mechanism of the interaction is unclear.[302–304]

2.9 Bile acid sequestrants

Bile acid sequestrants (BAS) such as cholestyramine, colesevelam and colestipol are used for the treatment of primary hyperlipidaemia, as monotherapy or in combination with statins or ezetimibe, and in the treatment of gastrointestinal diseases.[305] Cholestyramine is indicated for diarrhea associated with Crohn's disease, ileal resection, vagotomy, diabetes, diabetic vagal neuropathy and radiation.[306] Whilst colesevelam is not licensed for the treatment of bile acid malabsorption, several clinical trials have demonstrated positive outcomes which has provoked its off-label use in this indication.[307–309]

Bile acid sequestrants are positively charged ion-exchange resins which bind bile acids in the intestine to form insoluble complexes and as a consequence reduce the bile acid pool.[306] As a result of decreased luminal bile acid concentrations, BAS are expected to interfere with the bioavailability of lipophilic, low-soluble compounds by impeding their solubilization. For several drugs, such as rifaximin[310] and troglitazone[311] the presence of bile acids was shown to increase drug solubility and therefore, their absorption may be impeded by co-therapy with BAS.

The positive charge of BAS leads to a high affinity for deprotonated acidic drugs in the intestine. Binding of these anions increases the excretion and impedes the absorption of acidic co-administered drugs. Drugs that are known to be affected by this mechanism are furosemide,[312] warfarin,[313] phenprocoumon,[314,315] sulindac,[316] cerivastatin,[317] levothyroxine,[318] glipizide,[319] mycophenolic acid,[320] folic acid[321] and valproate[322]. The binding affinity for co-administered drugs can vary among the different BAS e.g., cholestyramine, which has a high affinity for hydrophobic compounds,[305,323] decreased ibuprofen and

964 diclofenac absorption to a higher extent than colestipol; and colesevelam has a favorable DDI-profile
965 compared to other BAS.[324–326]

966 High-molecular lipophilic drugs are typical substrates for enterohepatic recirculation.[327] By binding drugs
967 or drug metabolites that undergo enterohepatic recirculation, BAS can enhance drug elimination of the
968 victim drug even if the administration was not concomitant. Drugs affected by this mechanism include oral
969 anticoagulants,[313–315] cardiac glycosides[328] and mycophenolate mofetil[320]. It is difficult to predict which
970 drugs that undergo enterohepatic recirculation will be affected by BAS, since various factors such as
971 polarity, ionization properties and metabolism by liver and microbiota all influence biliary excretion.[329]
972 Prolonging the interval between administration of BAS and co-medication often reduces the potential for
973 drug interactions and must be adapted for extended-release formulations.

974 BAS can also affect gastrointestinal transit time: Cholestyramine prolonged the transit time in the
975 transverse colon by up to eight hours in thirteen patients with idiopathic bile acid diarrhea (as measured
976 with radiopaque markers), while total colonic transit was not altered.[330] After concomitant administration
977 of a sustained-release formulation of verapamil (dose 240 mg) with colesevelam (dose 4.5 g), a reduction
978 in AUC of 11% and decreased plasma levels of verapamil were observed in thirty-one healthy subjects.[331]
979 This interaction was deemed not to be clinically relevant.[331]

980 An overview of DDIs of bile acid sequestrants and their mechanism is given in Table 4.

3. Conclusions and future perspectives

Gastrointestinal events and conditions play a key role in the bioavailability of an orally administered drug and its therapeutic action. Concomitant use of various medications can affect the absorption and the pharmacokinetics of the administered drugs and therefore, their performance. As presented in this review article, various interactions between drugs used to treat gastrointestinal diseases and co-administered drugs have been identified. These interactions are of particular concern, since GI drugs are commonly prescribed and many of them are also available OTC. Prescribing physicians and pharmacists need to be aware of and monitor these potential interactions. Furthermore, information involving interactions with GI drugs should be made available not only to clinical practitioners, but also to patients, in order to prevent the appearance of adverse effects, on the one hand, and failure of treatment on the other hand.

It should be noted, however, that despite the large number of DDI studies with GI drugs reported in literature, most studies have only investigated the effects of short-term treatment and little is known about the ramifications of long-term administration on DDIs. Furthermore, most DDI studies have been conducted in healthy volunteers and may not necessarily reflect the degree of interaction in patients. As most of the DDIs have been based on changes in pharmacokinetics, it is also not clear in all cases whether the DDI has any ramifications for the therapeutic effect. Indeed, some studies have suggested that even quite significant changes in pharmacokinetics do not always lead to a change in the clinical response. More work on pharmacokinetics/pharmacodynamics (PK/PD) relationships and the influence of DDIs on them will be necessary to tease out the clinical implications of DDIs.

However, the number of studies that can be conducted to test for potentially clinically relevant DDIs is limited, due to both ethical and cost-related issues. So there is a need for innovative evaluation methods to address knowledge gaps and provide key information on safe and effective drug use.[332] In the last ten years, there has been an increasing use of Physiologically Based Pharmacokinetic (PBPK) modelling and simulation at different stages of drug development.[333] To date, PBPK modelling and simulation has been

mostly used for predicting enzyme interactions which, as mentioned in this article, can also occur with concomitant administration of GI drugs.[334–339] PBPK modelling is gaining acceptance at the various regulatory agencies as a tool to qualitatively and quantitatively predict DDIs and, in some cases, the simulation results may even be used to support labeling, depending on the clinical importance of the interaction.[8]

One of the advantages of PBPK modelling is that it is able to account for both formulation characteristics and physiological parameters. As such, it can be used to help define a "safe space" by identifying the range of dosing conditions under which the pharmacokinetic parameters will not be significantly affected by changes in the release properties of the dosage form. This approach, which is sometimes referred to as "virtual bioequivalence", has already been used to explore whether bioequivalence decisions based on clinical trials in healthy adults can be extrapolated to special populations, such as the hypochlorhydric or achlorhydric population, in whom the gastrointestinal physiology differs from that of healthy adults.[340–342]

The same approach could be extended to predict pre-absorptive DDIs with GI drugs, since these are intended to modify gastrointestinal physiology. First attempts have already been made for acid reducing agents, with results from *in vitro* dissolution experiments , which are tailored to mimic the changes in the upper gastrointestinal tract after the administration of these drugs, combined with PBPK models for healthy adults.[340,341,343] This approach should be broadened to encompass other classes of GI drugs. Possible future steps include tailoring dissolution tests and PBPK models to the physiological conditions observed in special populations, thus allowing for predictions of the *in vivo* performance of drug products in special populations (pediatrics, geriatrics, ethnic groups, the obese, hepatically impaired etc.) who concomitantly receive GI drugs. This approach will provide the way forward to predicting pharmacokinetic differences resulting from these combinations and, especially when coupled with PK/PD relationships, whether these are likely to be clinically significant, in a wide variety of populations and dosing conditions.

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Tables

Table 1: Reported Pharmacokinetic Interactions with Metoclopramide

	Interaction with:	***Effect***				***References***
		Rate of absorption	***Cmax***	***Tmax***	***AUC***	
Drug-Drug Interactions with Metoclopramide	Acetaminophen	↑	↑	↓		Nimmo et al., 1973[30]
	Cimetidine		↓		↓	Gugler et al., 1981[36]
			↓			Lee et al., 2000[344]
	Cyclosporine		↑	↓	↑	Wadhwa et al., 1986[42]
	Digoxin			↓	↓ (only for tablet)	Johnson et al., 1984[41]
			↓			Manninen et al., 1973[40]
	Droxicam			↓		Sánchez et al., 1989[33]
	Levodopa	↑	↑	↓		Morris et al., 1976[35]
	Lithium			↓		Crammer et al., 1974[32]

	Methotrexate				↓ (pediatrics)	Mahony et al., 1984[37]
	Mexiletine	↑				Wing et al., 1980[31]
	Morphine			↓		Manara et al., 1988[34]
	Salicylic acid		↑ plasma levels (in patients with migraine attacks)			Volans et al., 1975[28]
	Tetracycline			↓		Gothoni et al., 1972[29]
	Tolfenamic acid	↑				Tokola et al., 1984[27]

1992

1993 *Table 2: Classification of laxatives and antidiarrheal agents* [43–45]

	Class	***Subgroup***	***Examples***
Laxatives	Osmotic laxatives	Indigestible disaccharides	Lactulose
		Sugar alcohols	Sorbitol
		Synthetic macromolecules	Polyethylene glycol 4000
		Saline laxatives	Sodium sulphate Magnesium sulphate

	Stimulant laxatives		Bisacodyl Senna Phenolphthalein Casanthranol Sodium picosulfate
	Bulk laxatives		Wheat bran Isphagula Sterculia
	Others		Linaclotide
Antidiarrheal agents	Opioids		Loperamide Diphenoxylate Codeine phosphate
	Adsorbents/Bulking agents		Kaolin Isphagula Methylcellulose
	Miscellaneous		Racecadotril

1994

1995 *Table 3: Effects of laxatives and antidiarrheal agents on gastrointestinal conditions*[45,46,49,51–54,58–60,65,345,346]

Drug category	***Implication on gastrointestinal conditions***	
Laxatives	↓Gastrointestinal transit time	Small intestinal transit time (bisacodyl) Colonic transit time (bisacodyl, linaclotide, lactulose, polyethylene glycol)

		Whole gastrointestinal transit time (wheat bran, senna, bisacodyl)
	pH in the colon	↓ pH (lactulose, senna, wheat bran, sodium sulphate) ↑ pH (magnesium sulphate)
	Fecal short chain fatty acids	↑ (bisacodyl, senna, wheat bran)
	Differences in gut microbiota	↑ Anaerobes, Bifidobacteria (lactulose) ↓ Bifidobacteria (polyethylene glycol-4000)
	Haustra (small pouches in the colon)	↓ (chronic use of stimulant laxatives)
Antidiarrheal agents	↑ Gastrointestinal transit time	↑ intestinal transit time (loperamide)
	Fecal short chain fatty acids	↑ (loperamide)

Table 4: Drug-Drug Interactions with concomitant administration of bile acid sequestrants

Implication on gastrointestinal conditions	***Associated risk for co-medication***	***Reported interactions***
Binding of weakly acidic drugs	↓Bioavailability of co-administered drug	Furosemide[312] warfarin,[313] phenprocoumon,[314,315] sulindac,[316] cerivastatin,[317] levothyroxine,[318] glipizide,[319] mycophenolic acid,[320] folic acid,[321] valproate[322]

Disruption of enterohepatic recirculation of drugs	↑ Excretion of co-administered drug	Anticoagulants,[313–315] cardiac glycosides,[328] mycophenolate mofetil[320]
Possible impact on gastrointestinal transit time	↓↑Time available at gastrointestinal absorption site, effect on tmax	Sustained-release formulation of verapamil[331]*
Reduced concentrations of bile acids for drug solubilization	↓ Absorption of low-soluble compounds	

**not clinically significant due to high variability in the pharmacokinetics of verapamil*

Figure Captions

Figure 1: Gastrointestinal drugs discussed in this review.

Figure 2: Gastric emptying results in twelve gastroesophageal reflux patients with delayed basal emptying rates (A) and in fourteen gastroesophageal reflux patients with normal basal emptying rates (B), in a two-way crossover design consisting of a control phase and a phase in which 10 mg metoclopramode was ingested orally. The data are expressed as the mean percent (± 1 SEM) isotope remaining in the stomach for a period of 90 min after ingestion of an isotope-labeled test meal.[25] Figure reprinted from Fink et al. with permission from Springer Nature.

Figure 3: Impact of laxatives on colonic transit times of a) healthy subjects and b) patients, measured by scintigraphy (^{1}), metal detector (^{2}) or radiopaque markers method (^{3}); patterned bars represent controls.[45,47–49,53,54]

Figure 4: Effect of loperamide on gastrointestinal transit time after oral administration in healthy subjects.[46,70–72]

Figure 5: pH in the stomach of fasted healthy adults as a function of time, after administration of 240 mL table water into the antrum of the stomach. Key: (From left to right boxes) White boxes, Phase 1 (control phase); Light pink boxes, Phase 2 (pantoprazole phase); Dark blue boxes, Phase 3 (famotidine phase). Each box was constructed by using 7–8 individual values.[119]

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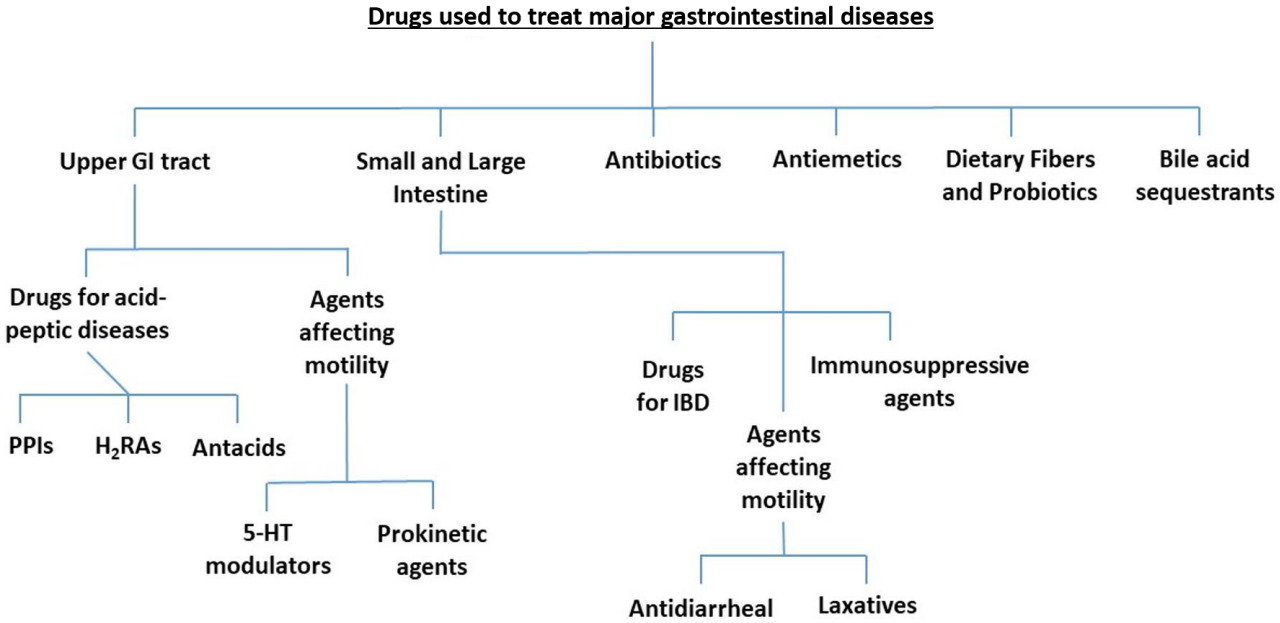

2025

2026

2027 Figure 1

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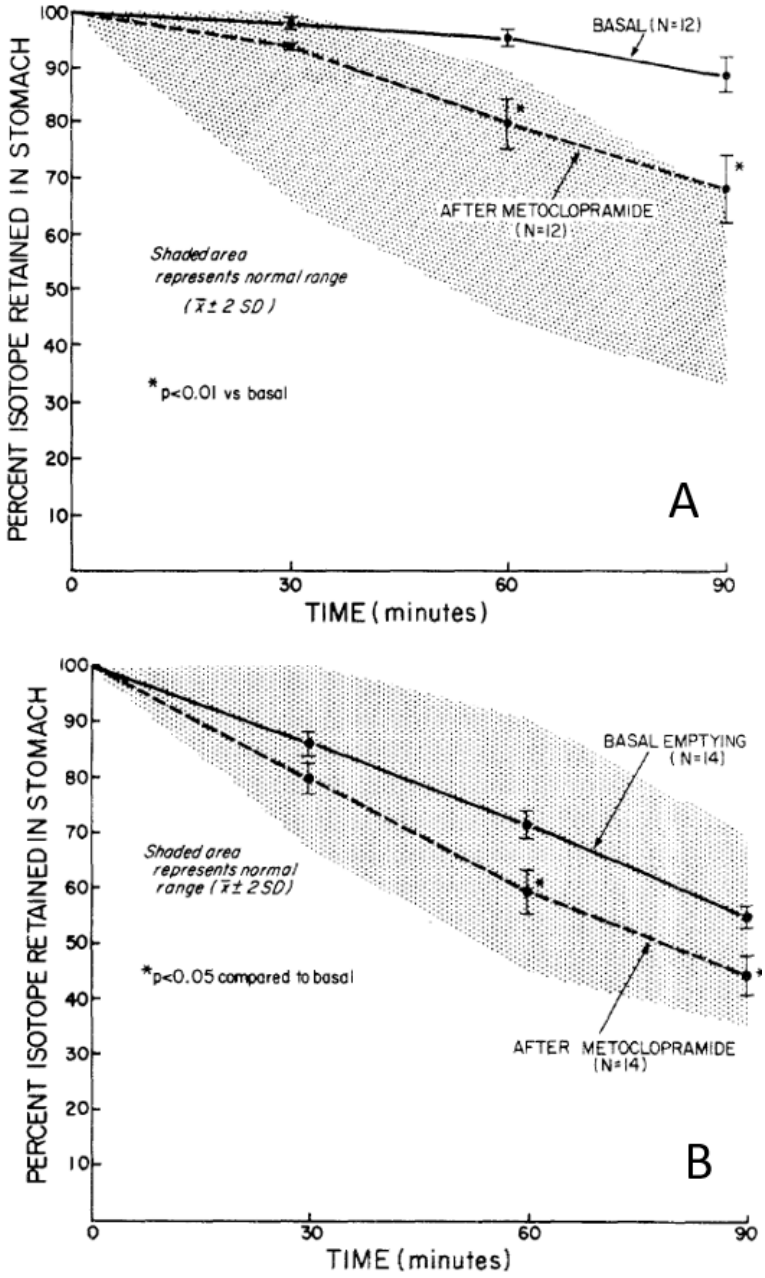
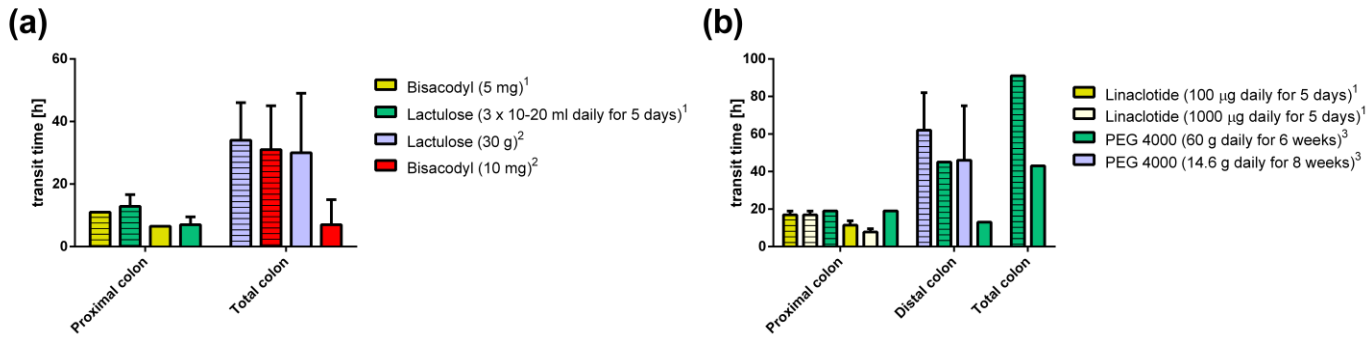

PERCENT ISOTOPE RETAINED IN STOMACH
100
90
80
70
60
50
40
30
20
10
0
30
60
90
TIME (minutes)
BASAL (N=12)
AFTER METOCLOPRAMIDE (N=12)
Shaded area represents normal range (x̄ ± 2 SD)
*p<0.01 vs basal
A
PERCENT ISOTOPE RETAINED IN STOMACH
BASAL EMPTYING (N=14)
Shaded area represents normal range (x̄ ± 2SD)
*p<0.05 compared to basal
AFTER METOCLOPRAMIDE (N=14)
B
TIME (minutes)

Figure 2

2034



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2037 Figure 3

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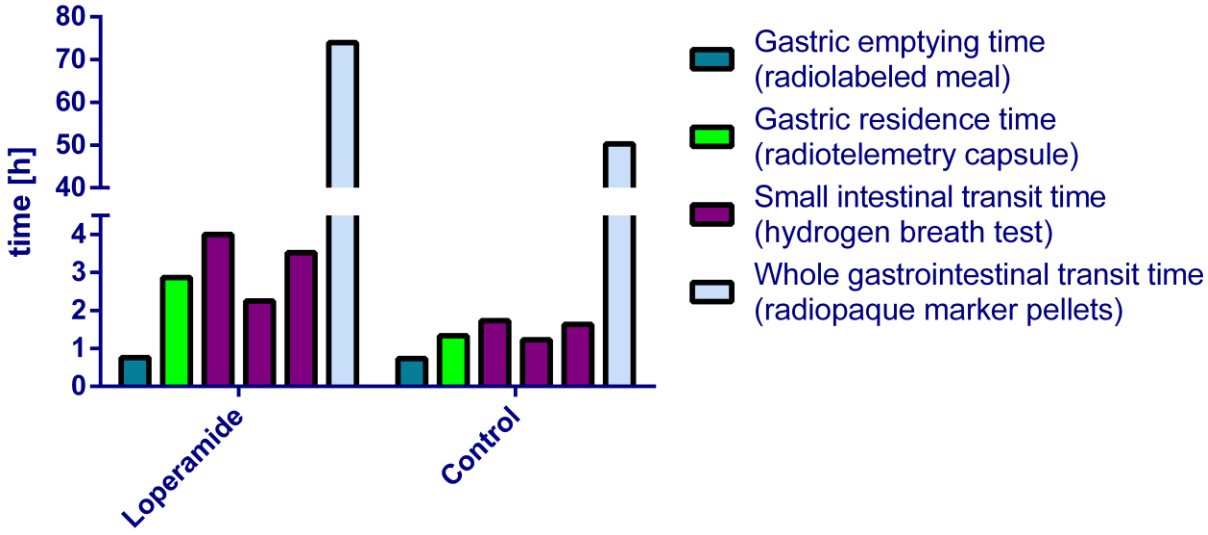

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2043 Figure 4

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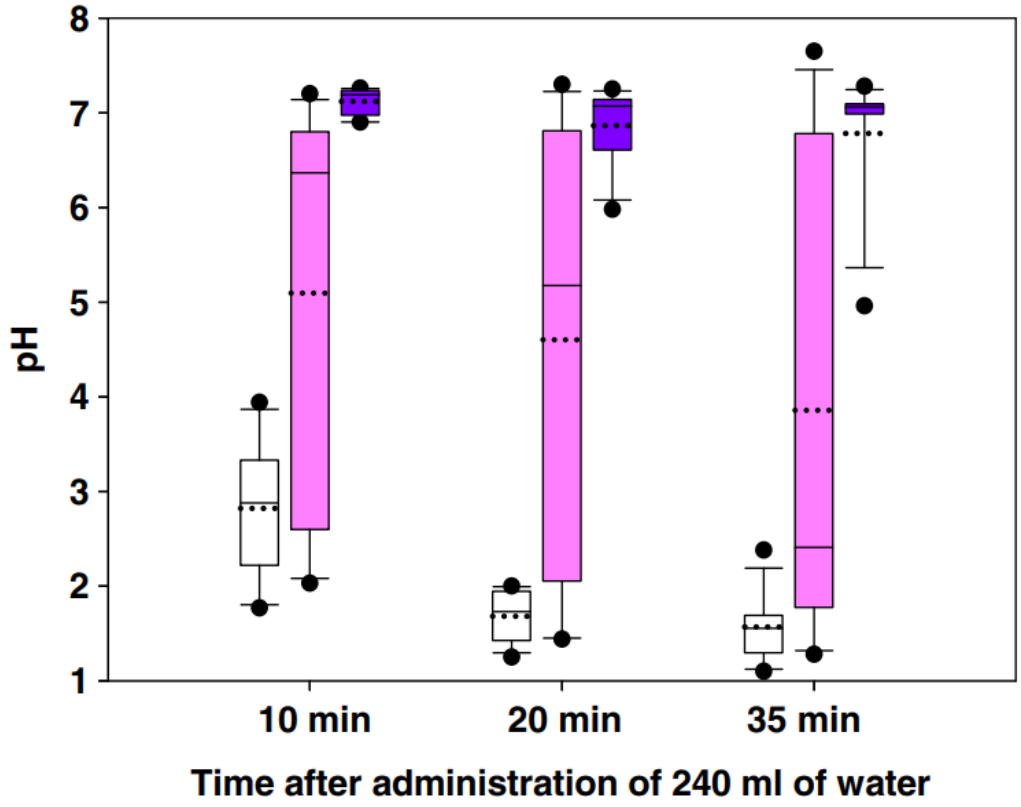

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2049 Figure 5