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The mechanisms of pharmacokinetic food-drug interactions – A perspective from the UNGAP group

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ABSTRACT

The simultaneous intake of food and drugs can have a strong impact on drug release, absorption, distribution, metabolism and/or elimination and consequently, on the efficacy and safety of pharmacotherapy. As such, food-drug interactions are one of the main challenges in oral drug administration. Whereas pharmacokinetic (PK) food-drug interactions can have a variety of causes, pharmacodynamic (PD) food-drug interactions occur due to specific pharmacological interactions between a drug and particular drinks or food. In recent years, extensive efforts were made to elucidate the mechanisms that drive pharmacokinetic food-drug interactions. Their occurrence depends mainly on the properties of the drug substance, the formulation and a multitude of physiological factors. Every intake of food or drink changes the physiological conditions in the human gastrointestinal tract. Therefore, a precise understanding of how different foods and drinks affect the processes of drug absorption, distribution, metabolism and/or elimination as well as formulation performance is important in order to be able to predict and avoid such interactions. Furthermore, it must be considered that beverages such as milk, grapefruit juice and alcohol can also lead to specific food-drug interactions. In this regard, the growing use of food supplements and functional food requires urgent attention in oral pharmacotherapy. Recently, a new consortium in Understanding Gastrointestinal Absorption-related Processes (UNGAP) was established through COST, a funding organisation of the European Union supporting translational research across Europe. In this review of the UNGAP Working group "Food-Drug Interface", the different mechanisms that can lead to pharmacokinetic food-drug interactions are discussed and summarised from different expert perspectives.

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1. Introduction

Food-drug interactions are a major threat to safe and effective oral pharmacotherapy. Understanding the underlying mechanisms is essential in avoiding these to the best extent (O'Shea et al., 2018). Therefore, various research groups have studied a variety of mechanisms potentially leading to food-drug interactions. Based on these investigations, a distinction between pharmacokinetic (PK) and/or pharmacodynamics (PD) food-drug interactions can be made (Fleisher et al., 1999; Schmidt and Dalhoff, 2002). Pharmacodynamic food-drug interactions are caused by a specific interaction between a drug and a component of the food that results in a particular pharmacological effect. A prominent example of this type of food-drug interaction is the "cheese reaction" which is caused by the mediation between tyramine, a constituent of cheese or raw sausages, and inhibitors of the enzyme monoaminoxidase such as tranylcypromine (Brown et al., 1989). In this case, the mechanism of the food-drug interaction is well defined and thus, can be easily avoided by excluding particular foods from the daily diet or if possible, by changing the formulation of the drug product. However, owing to the growing number of nutrients and dietary supplements, pharmacodynamic interactions may remain undetected (Gurley et al., 2012; Gurley, 2012; Tsai et al., 2012). It should also be noted that this type of pharmacological food-drug interaction is not limited to orally administered drugs.

The intake of food and/or drinks other than water can also affect the pharmacokinetic profile for different specific or unspecific reasons. The most prominent example of a specific pharmacokinetic food-drug effect is the interaction between grapefruit juice and drugs like cyclosporine and felodipine (Dahan and Altman, 2004). The interaction can result through different mechanisms, including the inhibition of CYP3A4 metabolism as well as inhibition of uptake and efflux membrane transporters. This type of food-drug interaction can easily be avoided by omitting certain foods or drinks. On the other hand, for unspecific pharmacokinetic food-drug interactions, the situation is complicated from the onset of functional changes in the gastrointestinal tract induced by the intake of food and/or drink. These include altered gastric emptying kinetics, increased luminal bile salt concentrations or increased hepatic perfusion (Fleisher et al., 1999; O'Shea et al., 2018; Schmidt and Dalhoff, 2002).

This review has been established as part of the European COST initiative UNGAP ("Understanding Gastrointestinal Absorption-related Processes") working group "Food-Drug Interface" with the aim to comprehensively discuss pharmacokinetic food-drug interactions (Fig. 1). This includes an explanation of how the intake of drinks and food can change the physiology of the human GI tract and how this may affect the pharmacokinetic profile of orally administered drugs; a description of specific effects of particularly relevant liquids such as milk, grapefruit juice and alcoholic beverages; and the role of the formulation.

2. Regulatory considerations of food-drug interactions

2.1. Testing for pharmacokinetic food-drug interactions

Due to the relevance and the risk associated with certain food-drug interactions, the evaluation of the effect of food or drink on the pharmacokinetic profile of a drug is an integral part of the registration process for a new drug product, *i.e.* a drug that is registered for the first time in a specific region for human use and therefore excluding generics. Typically, the food effect on the oral bioavailability of the drug is determined in a clinical study conducted with healthy volunteers and in which plasma concentration-time profiles after fasted and fed administration of the test drug are compared on the basis of pharmacokinetic parameters. Analogous to the evaluation of bioequivalence, the presence of a food effect is assessed primarily in terms of changes in the area under the plasma-concentration-time curve (AUC), the maximum concentration in the plasma (C_{max}) and in some cases, the time at which this concentration is observed (t_{max}). The subsequent recommendation provided in the product label is dependent on the difference in exposure with or without food, as well as the relationship between concentration and effect of the drug.

Since the extent of a food effect on oral bioavailability strongly depends on the type and composition of the food as well as on the dietary protocol during the study, the United States Food and Drug Administration (FDA) issued a guidance in 2002 for conducting bioavailability and bioequivalence studies under fed conditions (FDA, 2002). In this way, an increased level of standardisation has been achieved in clinical trials, enabling a better understanding of the observed effects. In recent years, the European Medicines Agency (EMA) has largely adapted its corresponding guidelines to the recommendations of the FDA. The current FDA and EMA guidelines require the administration of a high-caloric (800–1000 kcal) and high-fat (500–600 kcal of total calories derived from fat) test meal for the investigation of food effects on oral drug bioavailability (EMA, 2012; FDA, 2002). This meal is intended to trigger a maximum physiological response and thus, represents a worst-case scenario. Both FDA and EMA guidelines further contain a concrete example for the composition of such a test meal; two slices of toast with butter, two slices of fried bacon, two eggs fried in butter, 113 g hash-brown potatoes as well as 240 mL of whole milk (EMA, 2012; FDA, 2002). This so-called FDA standard meal meanwhile represents the general standard for food effect studies and therefore, the majority of pharmacokinetic data on food effects that were published in the last 15 years are based on this particular meal. In the EU regulatory setting, in case the drug will be recommended to be taken with a meal, studies of the effects of a 'moderate' meal are endorsed and on occasions, different food compositions (such as a carbohydrate-rich meal or snacks) may be conducted as well (EMA, 2012).

As indicated in the guidelines, the drug product to be tested is administered 30 min after the beginning of meal consumption with 240 mL water. The final evaluation of the food effect is based on the 90% confidence intervals of the ratios of AUC and C_{max} obtained following drug administration under fasted and fed conditions. Based on the relationship between concentration and effect of the drug, an

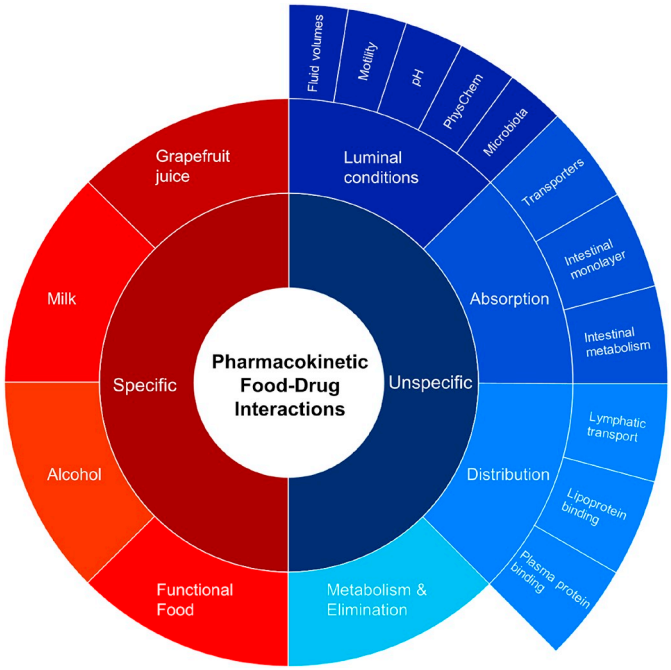

Fig. 1. Overview of specific and unspecific pharmacokinetic food-drug interactions covered in this review.

acceptance range is defined. The acceptance range may, as in bioequivalence assessments, be 80–125% but can be broader or smaller dependent on the therapeutic window of the drug. If the confidence intervals determined after drug administration in fed state are outside the predefined acceptance range, a clinically relevant food effect is considered to be present. According to the ratio of the AUC determined after fasting and after fed drug administration (Fig. 2), positive (increased oral bioavailability) and negative (reduced oral bioavailability) food effects are distinguished (FDA, 2002).

2.2. Impact of food-drug interactions on dosing instructions

The fact that food can affect the pharmacokinetics of drugs such as cyclosporine, nifedipine or theophylline has been known for > 30 years (Challenor et al., 1987; Karim et al., 1985; Mueller et al., 1994). Nonetheless, the topic of food-drug interactions remains highly relevant since many newly discovered drugs show poor aqueous solubility, but sufficient permeability (Williams et al., 2013). Consequently, their bioavailability often depends on the luminal gastrointestinal (GI) conditions and thus, drugs can sensitively react to food-induced changes of the luminal conditions in the human GI tract. Kang and Ratain stated in a recent publication that significant food-drug interactions are present for 34 of the 99 orally administered drugs approved by the FDA between January 2000 and May 2009 (Kang and Ratain, 2010). In particular, novel oral anticancer drugs often show relevant changes in oral bioavailability after administration together with food, because many of them have a poor aqueous solubility and are typically administered in relatively high doses (Willemsen et al., 2016).

The influence of food on the pharmacokinetic profile of the tyrosine kinase inhibitor lapatinib is a particularly striking example in this regard. Compared to its administration in fasted state, the oral bioavailability of a single dose of 1500 mg lapatinib increases on average by 325% (4.25 fold) after administration with a high-caloric standard meal (Koch et al., 2009). Thus, the oral exposure of one tablet administered with food is comparable to more than four tablets administered in fasted state. Nonetheless, it is recommended to take lapatinib either 1 h before or 1 h after eating, rather than taking a smaller dose with the meal itself. This intake advice was the topic of an intense debate that started already in 2007 and that was initiated by the American oncologists Mark Ratain and Ezra Cohen (Ratain and Cohen, 2007). They suggested to reconsider this intake advice, arguing that the food-induced increase in oral bioavailability would enable smaller doses and thus, reduce the cost of treatment with this highly expensive drug. They stated that in the US $1700 per month per patient can be saved by dosing the drug with food. In addition, they argued that the severe GI side effects of this drug, which are triggered primarily by the non-absorbed portion of the drug, could possibly be reduced. Thus, extensive discussions in patient access to and reimbursement of expensive drugs may benefit from user instructions offering two different approaches to the recommended dose and associated user instruction. For the anti-tumor drug vemurafenib, for which AUC increases approximately 5-fold when given with food, in the EU product information (*i.e.*, the Summary of Product Characteristics and Package Leaflet; (SmPC/PL)) the advice is given that it "may be taken with or without food, but consistent intake of both daily doses on an empty stomach should be avoided", however, no lower dose in the presence of food is actually advised. To the best of our knowledge, there is not yet any authorised dosing instructions that uses a food-drug interaction to lower the dose as compared to the situation without food. An extensive risk evaluation of such approach would be warranted first. Aspects to be considered would, for example, need to include the risk of swapping doses and instructions by a variety of patients and in a variety of settings, the ability of patients to consistently take (high-caloric) meals, the risk for weight gain/obesity, or the risk of incidentally taking the drug without food.

In real world settings, patients commonly take oral products with food or drink. From a regulatory perspective, this can only be accepted when the instruction to take the drug with food or a drink other than water is recommended in the SmPC. However, health care professionals and patients commonly consider that this regulatory approach is unrealistic given that such recommendations are failing for many marketed products just because of the lack of data rather than a real interaction. Thus, health care professionals urgently require deeper knowledge regarding the underlying mechanisms of food-drug interactions to understand which recommendations and/or warnings require urgent attention in real-life settings. At the same time, both patients and health care professionals would benefit if industry would update the product information from "old" products by clearly indicating if a food-drug interaction may occur or not, meaning that regulators would need to accept statements like "A food-drug interaction has not been observed with a high caloric meal etc."

3. Food-induced changes of human GI physiology and their relevance for oral drug delivery

Food intake leads to various changes of the physiological conditions in the human gastrointestinal (GI) tract, which can affect the pharmacokinetic profile of a drug by changing its release, absorption, distribution, metabolism and/or elimination. These food-drug interactions are unspecific, which means that they will apply to any formulation that is orally ingested. However, their relevance depends on the properties of the drug and the formulation. For instance, if solubility is limiting oral drug absorption, the availability and composition of luminal fluids will be of major importance. In the following chapters, we describe how food changes the luminal conditions in the human GI tract and how this can affect drug absorption.

3.1. Fluid volumes and their kinetics in stomach and intestine

The availability of luminal fluids in the gastrointestinal tract is a prerequisite for drug release and absorption of orally administered drugs. In addition, the volume of fluid available for drug dissolution may determine the luminal concentration and in the case of drugs with

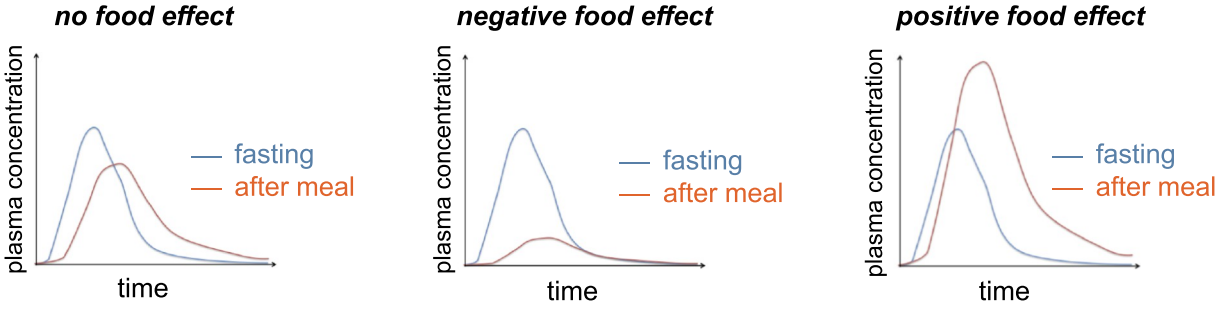

Fig. 2. Pharmacokinetic classification of food-drug interactions (food effects). Adapted from Koziolek et al., 2016.

poor aqueous solubility, the amount of drug that can be dissolved in certain parts in the human GI tract. Therefore, it is important to know the volumes of fluids present in the stomach and the small intestine. The presence of a concentration gradient between the intestinal lumen and the blood is the driving force for passive drug uptake (Grimm et al., 2018b; Koziolek et al., 2016; Van Den Abeele et al., 2017b). Additionally, various transporters and drug-metabolising enzymes in the enterocytes may be saturable and therefore, small changes in the luminal concentration can have dramatic effects due to non-linear pharmacokinetics in case of drugs with poor aqueous solubility. Besides various effects on luminal drug concentrations, the volume of the gastric content exerts important effects on formulation transit, particularly on gastric residence time. This aspect will be considered in more detail in other parts of the review.

For bioequivalence and bioavailability studies, an overnight fasting period of at least 8 h (EMA) or 10 h (FDA) is requested in the regulatory guidelines (EMA, 2010; FDA, 2002). Recent Magnetic resonance imaging (MRI) studies in healthy volunteers have shown that after such an overnight fast, fluid volumes of about 10–50 mL are typically present in the stomach (Table 1). A pronounced intra-individual variability of these values has been reported and needs to be taken into consideration as the remaining fluid partially defines the physicochemical starting conditions after intake of an oral formulation.

Nonetheless, these low residual fluid volumes after a long overnight fast do not represent the initially available fluid volume after formulation intake. In clinical trials, an oral formulation is typically administered with a defined volume of water, *i.e.* at least 150 mL according to EMA guidelines (EMA, 2010) and 240 mL according to FDA guidance (FDA, 2002). The fluid volumes initially available after the intake of 240 mL water are summarised in Table 1. Due to technical reasons, these values were typically collected around 2 min after water intake. The administered volume of water is typically emptied rapidly within 15–45 min most often following a first-order kinetic (Fig. 3) (Grimm et al., 2017; Mudie et al., 2014).

Since fluid volumes have a multitude of effects on luminal drug concentration, it is also expected to significantly contribute to the occurrence of food effects on oral drug bioavailability. As aforementioned, for bioavailability and bioequivalence studies conducted under fed conditions, the high-fat and high-caloric FDA standard meal is typically applied (EMA, 2010; FDA, 2002). The standardisation of meal composition is essential since caloric density and specific effects of macronutrients are known to affect the gastric content volume (Goetze et al., 2007; Grimm et al., 2017). MRI investigations have shown that initially after intake of the FDA standard meal, the postprandial gastric content volume amounts to 580 ± 38 mL (n = 12) (Koziolek et al., 2014b). These strongly elevated gastric volumes are present for several hours (Fig. 3) since caloric chyme is typically emptied with a rate of 2–4 kcal/min (Koziolek et al., 2013). This results in an apparent gastric emptying rate of 1.7 ± 0.3 mL/min. Thus, even 6 h after intake of the standard high-caloric and high-fat meal subjects cannot be assumed to be fasted. This is also supported by transit data of telemetric capsules (Koziolek et al., 2015b). Thus, the common intake advice to take a drug 2 h after meal will not result in a fasted state administration of the drug, if a larger meal was consumed. Thus, food effects on oral bioavailability may still occur. Also after a moderate meal (approximately 400–500 kcal with fat contributing to around 150 kcal) as advised in the EU guidelines (EMA, 2012), fasting conditions are unlikely to be present 2 h after the intake of such a meal (Armand et al., 2004).

Data for gastric volumes after different meals were reported to be even higher than 1000 mL. Thus, although the FDA standard breakfast is regarded as a worst-case scenario, higher fluid volumes can occur in real life (Koziolek et al., 2013). However, for drug dissolution, the volume of free fluid is of major importance and this will be significantly lower than the volume of the gastric contents in total. It should be noted that the FDA standard meal consists partially of solids. Most likely, a large portion of the watery fluids will be absorbed by food components such as toast. In addition, the FDA standard meal consists of larger amounts of lipids. Recent MRI studies have reported values of approximately 9.5% (v/v) fat for the gastric content after ingestion of the FDA standard meal (Koziolek et al., 2014b). Thus, it remains unclear how much free fluid is really available for disintegration and/or dissolution processes. Due to secretory activity, free watery fluid will be mainly present near the stomach wall (Marciani et al., 2001). This aspect is highly relevant for luminal drug distribution. If a formulation is deposited in the fundus or corpus, a homogeneous distribution of the drug throughout the whole stomach will be unlikely owing to the highly viscous and heterogeneous nature of the gastric content after the intake of solid meals (Koziolek et al., 2014a). Several groups have shown that the gastric content is highly heterogeneous after intake of a solid meal, with sedimentation and pronounced layering of solids, fats and fluids. Both, the gastric secretions and the fat components were observed to lay on top of the chyme depending on the meal composition and on the time of evaluation (Goetze et al., 2006; Koziolek et al., 2014b; Sauter et al., 2012; Steingoetter et al., 2015). Thus, the homogenisation of meal components which is often done for *in vitro* simulations produces an artificial situation with respect to the amount and the physicochemical properties of the luminal contents. A more detailed explanation of the physicochemical conditions in stomach and small intestine can be found in the following paragraphs.

In addition to the gastric content volume after meal intake, one also needs to consider the volume as well as the fate of the fluid co-administered during drug intake. As aforementioned, a formulation is typically ingested with 150 or 240 mL of water in clinical trials. Assuming perfect mixing of chyme with the co-administered water, water intake would result in a gastric content volume of 679 ± 80 mL (Koziolek et al., 2014b). However, recent data have shown that this seems to be incorrect for most solid meals (Grimm et al., 2017). It has been shown in recent MRI studies that the water does not mix very well with the highly viscous and fatty chyme of the standard meal. As a consequence, it is rapidly emptied from the stomach along the stomach wall. This physiological phenomenon is called *Magenstrasse*, from the German meaning stomach road. Therefore, higher amounts of freely available fluid may only be present shortly after formulation intake and typically only in regions near to the stomach wall (Grimm et al., 2017; Koziolek et al., 2014b, 2016; Pal et al., 2007). This phenomenon can have certain consequences for oral drug delivery as the water flow can

Table 1
Gastric and small intestinal fluid volume determined at different conditions.

	Gastric fluid volume		Small intestinal fluid volume	
	Mean ± SD	Ref.	Mean ± SD	Ref.
10 h overnight fast	35 ± 7 mL (n = 12)	[a]	43 ± 14 mL (n = 12)	[a]
	25 ± 18 mL (n = 120)	[b]	51 ± 33 mL (n = 24)	[d]
			105 ± 72 mL (n = 12)	[f]
			91 ± 68 mL (n = 16)	[g]
240 mL of water	242 ± 9 mL (n = 12)	[a]	Maximum of 92 ± 24 mL after 12 min (n = 12)	[a]
	256 ± 36 mL (n = 8)	[b]		[d]
	292 ± 21 mL (n = 8)	[c]	Maximum of 107 ± 69 mL after 15 min (n = 6)	
	270 ± 20 mL (n = 6)			
FDA breakfast	580 ± 38 mL (n = 12)	[e]	n/a	

[a] Mudie et al., 2014.
[b] Grimm et al., 2018a.
[c] Grimm et al., 2017.
[d] Grimm et al., 2018b.
[e] Koziolek et al., 2014b.
[f] Schiller et al., 2005.
[g] Marciani et al., 2010.

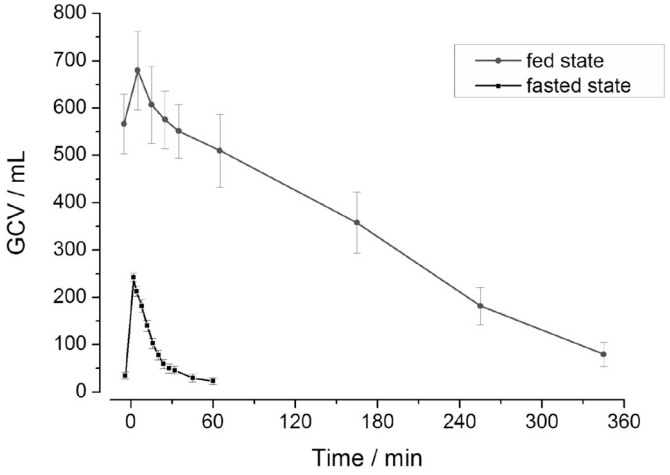

Fig. 3. Mean gastric content volume (GCV) ± SD determined in 12 healthy volunteers immediately before and after up to 360 min after intake of 240 mL of water in clinically relevant fasted state and fed state scenarios.
Adapted from Koziolek et al., 2014b and Mudie et al., 2014.

entrain a certain amount of drug from the stomach. Thus, a drug becomes available for absorption in the small intestine much faster than it would be possible in case of the slower gastric emptying together with chyme (Koziolek et al., 2016).

After the formulation itself, or a dispersion or solution of the drug substance is emptied from the stomach, the small intestinal volumes will represent the dissolution medium and determine the resulting concentrations of the drug. Recent MRI studies have investigated small intestinal fluid volumes after an overnight fast and after intake of fluids and food.

As can be seen from Table 1, after intake of a formulation with 240 mL of water, the available small intestinal fluid volume in the fasted state is not as high as the administered fluid volume. In contrast, it is rather comparable to or slightly higher than residual fluid volumes. Fig. 4 illustrates the increase in small intestinal fluid volume within the first minutes that is followed by a decrease to mean values between 70 mL and 80 mL from 30 min after intake (Grimm et al., 2018b; Mudie et al., 2014).

Moreover, it must be considered that the fluids present in the small intestinal volume are not coherent and that the different regions in the small intestine are not constantly wetted. In fact, the small intestinal fluid volume is typically distributed in several fluid pockets along the small intestines (Grimm et al., 2018b; Mudie et al., 2014; Schiller et al., 2005). Before the administration of the formulation together with water, there are approximately 8 ± 1 fluid pockets present that have a mean volume of 4 ± 1 mL each. Subsequently, the number of pockets increases to about 15 ± 1 fluid pockets with a volume of approximately 7 mL 12 min after administration. Although the number of pockets decreases afterwards, their mean volume remains elevated (Mudie et al., 2014). Since most of the fluid pockets are rather small, oral formulations are most of the time either only partially in contact with fluids or without any contact to fluids during intestinal transit. For example, Schiller et al. have reported that about 50% of the tested monolithic formulations are not or only partially in contact with intestinal fluids after fasted intake (Schiller et al., 2005). Thus, the available volume for dissolution processes might be overestimated in common approaches, even if a physiological amount between 50 and 100 mL is simulated.

It is generally believed that elevated small intestinal fluid volumes in the fed state can contribute to the occurrence of food effects by influencing the luminal concentration as well as the intestinal surface area available for drug absorption (Grimm et al., 2018b). Although this theory seems obvious, it is not clear whether small intestinal fluid volumes are really elevated after food intake. Schiller et al. reported a decreased small intestinal fluid volume 1 h after the intake of a standardised meal (Schiller et al., 2005). However, the determination of fluid volumes in the small intestine can be strongly affected by the imaging procedure. In the heavily T2-weighted MRI acquisitions that are commonly used for this purpose, only freely mobile water provides a high signal intensity (Hoad et al., 2007). However, the small intestine is mainly filled with chyme, which has a lower signal intensity. Therefore, luminal contents with a signal intensity below the quantification threshold of these MRI sequences are not fully captured. That leads to a possible underestimation of the total fluid volume present in the small intestine. Nonetheless, although the water content of the chyme is less mobile, bound or trapped in the food matrix, it might still be available for dissolution processes. This needs to be kept in mind when interpreting these data as considered in a recent article which called the evaluated volume “apparent small intestinal water content” (Marciani et al., 2013). Furthermore, it needs to be considered that the apparent fluid volume is dynamically distributed throughout the whole small intestinal lumen and that absorption and secretion of water are highly dynamic processes. This leads to a specific net flux of water across the intestinal wall. Thus, free fluids present in the small intestinal lumen do not necessarily arise from the ingestion of fluid, but can also result from intestinal secretion. The direct effect of this flux on drug absorption in humans seems to be negligible (Artursson et al., 1999; Lennernäs et al., 1994), although the flux itself and therefore the intestinal fluid volume indeed depends on several components present with food (*e.g.* sodium or carbohydrates) (Erokhova et al., 2016; Grimm et al., 2018b).

Due to the complex shape and inhomogeneous signal arising from mixed/solid meals such as the FDA standard meal with most imaging techniques, no data is currently available on the corresponding postprandial small intestinal fluid volumes for the FDA standard breakfast and only very few data available for other meals. For a (semi-)solid meal of rice pudding with bran, postprandial changes in small intestinal water content are characterised by an instantaneous decrease of volume followed by a slow increase of small intestinal filling (Marciani et al., 2010). An increase in small intestinal water content was also reported for meals consisting of lettuce or rhubarb (Wilkinson-Smith et al., 2018). On the other side, specific food components can also decrease the freely available water as was shown for whole meal bread (Marciani et al., 2013). The effect of different caloric liquids on small intestinal media volume has been studied by various research groups. Interestingly, the presence of glucose typically reduces the amount of available fluids (Grimm et al., 2018b; Marciani et al., 2010; Murray et al., 2014),

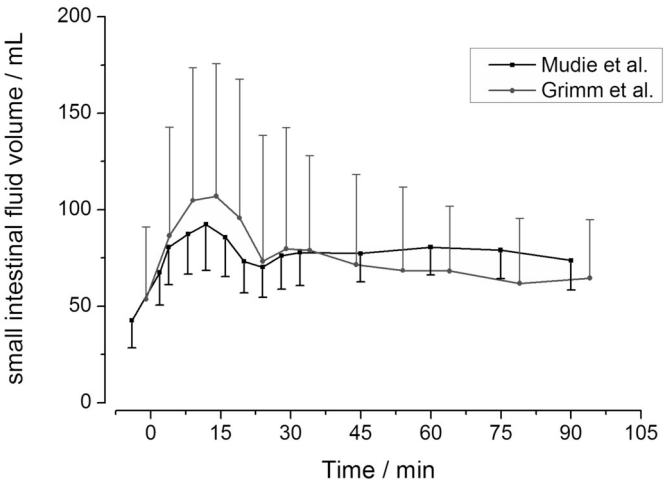

Fig. 4. Small intestinal fluid volumes (mean ± SD) after intake of 240 mL water in fasted state.
Adapted from Mudie et al., 2014 (n = 12) and Grimm et al., 2018b (n = 6).

whereas fat has been shown to increase substantially the amount of fluid in the small intestine (Hussein et al., 2015). Further studies have demonstrated that grapefruit juice or beverages containing fructose can increase the small intestinal fluid volume in a considerable manner. Thus, the effect of grapefruit juice on the pharmacokinetic profile of an orally administered drug is not necessarily caused by specific interactions with uptake and efflux transporters or metabolising enzymes but can also be caused by changed luminal conditions.

After small intestinal transit, the colonic volumes can also be relevant if meaningful drug absorption can occur in the colon or if colon-targeted formulations are applied. Generally, colonic transit is much longer and hence, it is more difficult to dissect whether food effects result from co-administration of food with the drug product, or from food intake that happened hours before intake of a formulation. With regard to transit times of food components and chyme as well as of formulations, a drug product inside the colon might face a milieu determined also by meals that were ingested long before the intake of the drug product itself (Camilleri et al., 1989; Chaddock et al., 2014; Schneider et al., 2016). It must be considered that the idea of a 'fasting colon' is highly artificial and can only be achieved by the use of laxatives. In contrast, during clinical studies the dietary protocol is highly standardised and therefore, an orally administered formulation that enters the colon either intact or in form of dispersed API, will mostly face a 'non-fasted colon'. A standardisation of the subjects' feeding regimen should ideally start days before a drug is administered in a clinical study.

The volume of colonic contents can be up to 1 L (Sandberg et al., 2015), but these high volumes consist mainly of food residues and human and bacterial cells as well as cell debris. Due to high viscosity and the limited amount of free fluid, this volume is typically not available for dissolution processes. With respect to free watery fluid, which is of higher relevance for oral drug delivery, it can be noted that the volumes are typically low and that the fluids are distributed in irregular fluid pockets. These are mainly present in the proximal part of the colon. A very variable amount of free fluid volume of 13 ± 12 mL (n = 12) with a range of 1–44 mL inside these pockets was reported for entire colon (Schiller et al., 2005). Another MRI study observed comparable values of 0–49 mL available free fluid distributed over 11 ± 5 pockets fluid pockets in the whole colon (Murray et al., 2017). Although there can be long-term effect of several food components on colonic filling, due to spatial separation rapid and direct effects of food intake on a formulation already residing in the colon are less likely.

In conclusion, the altered volume of luminal fluids, especially in stomach and small intestine, as well as their kinetics are likely to play a major role in the occurrence of food effects. In particular, even isolated changes in available fluid and gastric emptying are considered to be factors which may lead to changed t_{max}, C_{max} or multiple peaks without necessarily altering bioavailability.

3.2. Gastric and intestinal motility, gastric emptying and intestinal transit

The intake of food leads to an increase in the motility that is different in each part of the gastrointestinal tract and this motor response is expected to affect the dissolution and absorption of the drug.

Anatomically, the stomach is divided into a fundus, corpus and antrum region, but when it comes to motor function, two parts can be distinguished: the proximal stomach, consisting of the fundus and the proximal part of the corpus, and the distal stomach consisting of the distal part of the corpus and the antrum. The motility of the proximal stomach is characterised by a maintained status of contraction of the smooth muscle (tone), whereas the distal stomach generates phasic contractions. During the interdigestive phase, the proximal stomach muscle tone is high. The distal stomach however is engaged in a recurrent motor pattern known as the migrating motor complex (MMC) (Janssen, 2011). This complex involves the stomach and the majority of the small intestine (but not the distal small intestine) with three phases: phase I, a quiescent phase with no contractions; phase II with until recently considered random contractions; phase III with a sudden onset of repetitive contractions that also ends abruptly. Phase III can start in the stomach or in the proximal small intestine and migrate toward the distal ileum. Antral phase III activity is defined as the occurrence of regular contractions for at least 2 min at a frequency of 2–3 contractions per min simultaneous with, or preceding, phase III activity in the proximal duodenum. In the duodenum, phase III contractions have a frequency of 11–12 contractions per min and last for at least 3 min. The duration of the cycle is approximately 130 min and feeding interrupts the complex. The contribution of each phase to the cycle length in the antrum is 55% for phase I, 41% for phase II and 4% for phase III. Gastric pH fluctuates during the MMC, with the antral pH being lowest (more acidic) just prior to the start of phase III contractions, and higher at the start of phase I. This change in pH is due to an increase in acid and pepsin secretion that accompanies phase III of the MMC, and bile-free, bicarbonate reflux from the duodenum. Intestinal and pancreatic secretion of water, bicarbonate and pancreatic enzymes increase during phase III contractions of the small intestine. The integrated secretory activity that occurs in parallel with the motility phases has been referred to as the secretory component of the MMC (Deloose et al., 2012).

As soon as food is ingested, stomach motility changes. The proximal stomach relaxes to accommodate the incoming food, then a tonic contraction of the proximal stomach pushes the food distally, whereas the distal stomach mixes and grinds the food by powerful and regular contractions. The duodenum is exposed to nutrients early after the ingestion of food, which activates a multitude of duodeno-gastric negative-feedback mechanisms, mediated through vago-vagal reflexes and hormonal signals (GLP-1, PYY, and CCK, among others). The role of this feedback is to delay the arrival of acidic, hyperosmotic, or calorie-rich gastric contents into the duodenum by inhibiting proximal gastric tone, gastric phasic contractions, and by stimulating closure of the pylorus (Farré and Tack, 2013).

It has been demonstrated that the physical consistency, fat content and caloric load of the meal play a relevant role in regulating the motor response of the stomach. In general, liquids of low caloric density empty under the pressure gradient created by the fundus tone and the little motor action of the distal stomach in exponential fashion. Higher caloric liquids or homogenised solids empty almost linearly under the pressure gradient from the fundus and coordinated antropyloroduodenal motility. Digestible food of more solid consistency requires antral trituration until the particle size is reduced (Pasricha et al., 2017). Historical data indicated that the particle size needs to be in the order of 2 mm, but more recent studies with indigestible markers showed that gastric emptying of 4.2 mm diameter cubes was similar to the emptying of smaller markers (Stotzer and Abrahamsson, 2000). Food reduced to small particles empties linearly from the stomach at a rate similar to that of a homogenised solid meal. Trituration involves establishing liquid shearing forces where solids and liquids are repeatedly pushed against a closed pylorus. The time that the stomach takes to reduce the particles may explain the lag phase observed before emptying can start. Thus, gastric emptying occurs in 2 periods: the lag period and the post-lag, linear emptying period. Non-digestible solids are usually emptied from the stomach with the inter-digestive MMC (Pasricha et al., 2017). Depending on physical consistency, fat content and caloric load of the meal, the gastric residence time of non-digestible solids can be up to several hours (Weitschies et al., 2010). The same applies to non-disintegrating formulations such as enteric-coated or matrix tablets. These are not emptied by the fed motility pattern and can only be emptied if the MMC returns. The gastric residence time of non-disintegrating formulations generally depends on the prandial status, the timing of dosing as well as the properties of the formulation. Gastric emptying of non-disintegrating radio-labelled tablets was reported to be quicker in the fasted (37 min) when compared to fed state (149 min) (Fadda et al., 2009).

Gastric motility also plays a crucial role for the *in vivo* performance

of modified release (MR) formulations. It is known that during gastric transit high shear forces of up to 500 mbar can arise and cause dose dumping (Koziolek et al., 2018). This effect was nicely shown for various hydrogel matrix tablets by Garbacz et al. (2010, 2014). In a recent Magnetic Marker Monitoring study, Jain et al. have demonstrated that the rate of erosion of hydrogel matrix tablets is different after fasted and fed administration of the formulation due to different motility patterns (Jain et al., 2014). The continuous motility in the fed stomach caused a faster erosion. The loss of modified release characteristics, after administration of a non-disintegrating MR product in the fed state, has been described in several studies as the most likely reason for the observed changes in plasma levels compared with the fasted state (Davis et al., 2009; Karim et al., 1985; Schug et al., 2002a, 2002b, 2002c).

In contrast, only few studies have investigated the possible role of gut motor response in affecting drug dissolution and absorption of immediate release (IR) products. Oral formulations that disintegrate in the stomach will be emptied together with the gastric contents, but the rate of gastric emptying depends on the distribution of the drug within the stomach. This process is also affected by gastric motility. It is generally assumed that mixing is poor in the proximal part, whereas it is more effective in the distal part. Studies with magnetically labelled extended release tablet have demonstrated that increased plasma peak drug concentrations after intake of food were mainly caused by the poor mixing in the proximal part of the stomach (Weitschies et al., 2005). Thus, the initial deposition behavior of a formulation will affect the rate of drug delivery to the small intestine (Koziolek et al., 2016).

More recent studies, in which high-resolution antro-duodenal manometry was applied along with aspiration of contents and blood sampling, have suggested that the phase of MMC seems to influence both drug absorption and dissolution (Van Den Abeele et al., 2017a). Evaluation of drug concentrations measured in different regions of the stomach with the well-established technique of the intraluminal sampling has shown a clear trend toward better mixing of an orally administered drug with gastric contents when dosed in the presence of gastric contractions. This results in a more homogeneous distribution of the drug throughout the stomach compared to dosing in the absence of gastric contractions (Van Den Abeele et al., 2017a). In addition, Hens et al. have shown in another study that C_{max} seems to be higher if the time to phase III contraction is shorter (Hens et al., 2017).

In contrast, the small intestine postprandial motility is still poorly understood. It has been indeed demonstrated that meals induce different contractions according to solubility and viscosity, but a clear influence of nutrient composition has not been reported. Normal small intestine transit takes up to 5 h (Farré and Tack, 2013). A recent study has shown that the small intestinal transit time of non-disintegrating radio-labelled tablets was similar in fasted and fed state (204 *vs.* 210 min) (Fadda et al., 2009). This circumstance is not surprising since the formulations were most likely emptied into a fasted small intestine by the MMC. When the same tablets were ingested after a first meal but 45 min before a second meal, two different patterns could be observed. Some subjects had an accelerated small intestinal transit (100 min), whereas some other subjects showed a similar small intestinal time transit to the fed state (185 min). This difference was the result of different time points of gastric emptying. If the tablet was emptied before the next meal, incoming food pushed the tablet through the small intestine, which resulted in faster transit. If the tablet was retained until intake of the next meal, it could not be emptied by the fed motility pattern and was emptied by the MMC after the stomach returned into fasted state. Even if drug absorption was not evaluated in this study, the authors speculated that for drugs with a narrow small intestinal absorption window and modified release (MR) systems, the timing of food administration after dosing could be critical.

Recent findings applying high-resolution manometry have demonstrated that colonic motility is mainly represented by non-propagating (simultaneous) contractions and retrograde activity and both these activities increased soon after the meal. These colonic motor patterns have the role of retarding the arrival of colonic content to the rectum and of favouring the retrograde filling of the transverse and ascending colon where the propagating contractions normally start. Propagating contractions, including the high-amplitude propagating contractions associated with movements of solid colon content, represent a minority of the colonic activity and are normally more frequent about 1–2 h after the meal and upon awakening (Corsetti et al., 2018). The reason of this is probably related to the fact that, in these moments of the day, the arrival of the content accumulated in the distal small intestine during the night and during the inter-digestive periods determine the distension of the ascending and transverse colon that trigger the propagating activity. The prevalence of non-propagating activity explains the fact that the normal colonic transit time is slower (about 35 h) when compared with the small intestine. This allows the colon to perform its functions of absorption, fermentation and reservoir organ. The colonic motor response to food is slower in onset but more prolonged with a fatty meal compared with a carbohydrate meal. Ingestion of lipids stimulates mainly non-propulsive colonic motility. Non-absorbable carbohydrates inhibit colonic water absorption and stimulate colonic transit.

3.3. Luminal pH values

Due to the growing number of poorly water-soluble drugs, solubility issues are becoming increasingly important in oral drug delivery. In that regard, luminal pH is one of the most important parameters since many drugs are ionisable above or below a certain pH value. Greater ionisation of the dissolving drug typically facilitates the process of drug dissolution. Therefore, changes of the luminal pH values may be translated directly into changes of drug solubility and potentially, into an altered oral bioavailability. The intake of food or drinks changes the luminal conditions in the stomach and the small intestine. The resulting pH profiles in these parts of the human GI tract are highly dynamic and the result of the complex interplay between the amount and properties of the ingested contents, oral and gastric secretions, digestion, absorption and the transfer of material along the GI tract. In Fig. 5, an exemplary luminal pH profile that was measured after the administration of the telemetric SmartPill® capsule in the fed state, is depicted (Koziolek et al., 2015b).

This graph shows that the human stomach is typically characterised by acidic conditions, whereas in the small intestine, pH values of

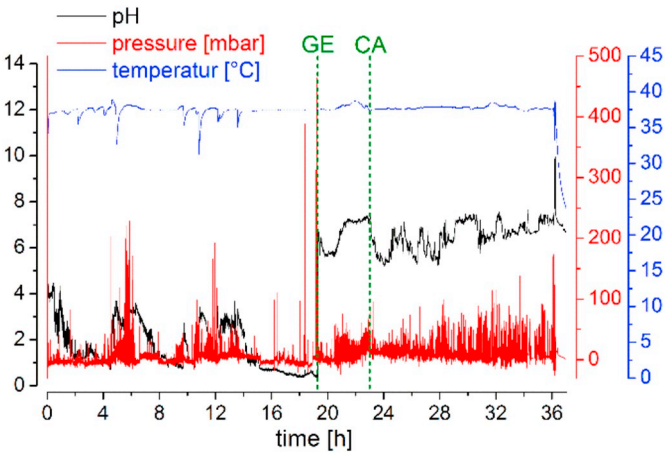

Fig. 5. Exemplary luminal pH (black), pressure (red) and temperature (blue) profiles over time obtained after administration of a telemetric motility capsule in fed state by subject 9 (GE – gastric emptying, CA – colonic arrival). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Reprinted from Koziolek et al., 2015b, with permission from Elsevier.

pH 6–8 occur. The gastric pH values measured directly after SmartPill administration under fed conditions are around pH 4 and subsequently, luminal pH decreases to pH 1, which is more or less equivalent to the pH value of the gastric secretions. At this time, the gastric contents are highly diluted by oral and gastric secretions. The re-acidification of the stomach is illustrated in Fig. 6.

By simply comparing the range of pH values measured in fed state with range of pH values that are measured in the fasted state, it is obvious that fasted state pH values cover a similar range (Koziolek et al., 2015a, 2015b). However, the transit time through the fed stomach is significantly longer and thus, more time is available for drug dissolution (Koziolek et al., 2014b, 2016). Moreover, the contents are continuously emptied into the small intestine. Providing that absorption is faster than precipitation or that certain micellar structures solubilise the drug, the administration of a weakly basic drug after food intake can lead to positive food effects (increased oral drug bioavailability). Interestingly, various weakly basic drugs (*e.g.* itraconazole, erlotinib), for which the gastric pH is expected to be the main reason for a positive food effect, experience reduced oral bioavailability if the drug is co-administered with acid-reducing agents. For example, itraconazole (pK_a = 3.7) experiences a positive food effect, but co-medication with omeprazole leads to a decrease of the $AUC_{0-24\ h}$ by 64% [75]. Similar effects were also observed for various oral anticancer drugs (*e.g.* erlotinib or pazopanib) [17]. However, if precipitation is much faster than absorption, the pH-shift in the small intestine caused by the secretion of bicarbonate induces the precipitation of the drug. Thus, all the benefits in terms of solubility that resulted from a prolonged contact with acidic contents in the stomach will be circumvented. In terms of luminal drug concentrations, the effect of food components and digestion products on luminal buffer composition in stomach, upper intestine and proximal colon must be considered as well. It was shown in *in vitro* experiments that the buffer species can affect drug release as well as drug precipitation in the small intestine (Vertzoni et al., this issue).

As can be seen from Fig. 5, luminal pH values in the small intestine increases from pH 6–7 in proximal parts to values of pH 7–8 in distal parts (Koziolek et al., 2015b). Several studies have shown that food intake can cause minor changes of the intestinal pH value. Directly after food intake, the luminal pH value in the proximal small intestine can be around one pH unit lower than in the fasted state, which can be explained by the emptying of buffered, acidic contents into the duodenum (McCloy et al., 1984). Thus, drugs with a pK_a value in the range of 5–7 may be affected by this luminal pH change, but the relevance of this effect in terms of food-drug interactions was not shown so far. The pH values in the colon are highly variable and it seems as if they are not directly affected by food intake. Therefore, they are not further discussed at this point. However, the intake of food leads to the gastroileal reflex which can cause pH changes in the ascending colon (Reppas et al., 2015).

3.4. Physicochemical aspects of luminal media

The intake of a meal generates physiological responses which lead to various changes with respect to the physicochemical properties of the luminal contents (Fig. 7) which can affect intraluminal formulation performance. Meal-induced changes in the physicochemical characteristics of intraluminal contents, apart from pH (Section 3.3), are summarised below. It is important to note that relevant changes in stomach and upper intestine (duodenum and proximal jejunum) to date have been investigated mainly after administration of liquid meals.

In the stomach, buffer capacity (specifically, the resistance of content in increasing intragastric pH values) and osmolality are higher in the fed state (Pentafragka et al., 2018). Due to increased volumes of gastric contents in the fed state, pepsin levels are only slightly higher and gastric lipase levels are lower in the fed state (Pentafragka et al., 2018). However, both show increased activity, due to more favourable pH values. The altered physicochemical characteristics of gastric contents in the fed state could lead to delayed disintegration of IR products. Meal-induced delays in tablet disintegration (Kelly et al., 2003) and in capsule disintegration (Cole et al., 2004; Digenis et al., 2000) have been reported by using scintigraphic techniques. The formation of a film of precipitated food components, mainly proteins, around the tablets which slows water penetration and prevents effective tablet disintegration (Abrahamsson et al., 2004) and meal induced viscosity (Cvijić et al., 2014) have been speculated as potential reasons, based on *in vitro* data.

With regard to intraluminal viscosity, only values for the contents of the fasted stomach have been reported (Litou et al., 2016; Pedersen et al., 2013). The limited number of human aspiration studies performed after administration of solid meals and the difficulty to specify viscosity values of non-Newtonian fluids in highly variable environment are two potential reasons. Published data suggest that input viscosity values of the order of 2000 mPa s (100 s^{-1}) lead to clinically important changes in plasma levels of highly permeable compounds (Carver et al., 1999; Reppas et al., 1993). It should be noted that relevant data have been collected by employing a non-digestible, non-absorbed viscosity inducing agent (hydroxypropyl methylcellulose, HPMC). The meal that it is typically used in oral drug absorption studies has a much lower input viscosity, about 430 mPa·s (100 s^{-1}) (Klein et al., 2004). Furthermore, canine data indicate that, after administration of McDonalds's cheeseburger with French fries and 300 mL water (viscosity of 1310 ± 940 mPa·s at 100 s^{-1}, n = 9), the viscosity in the middle of the canine small intestine becomes 30 ± 50 mPa·s (determined at 100 s^{-1} in 3 dogs, 2–3 administrations per dog) (Greenwood, 1994); in 2 of the 3 dogs the viscosity was approximately 1 mPa s, *i.e.* similar with that of water (Greenwood, 1994). More data are needed in order to confirm whether luminal viscosity is an important parameter to consider when evaluating drug dissolution and transport in the contents of the small intestine in the fed state.

In the upper intestine (duodenum and upper jejunum), the buffer capacity (specifically, the resistance of contents in decreasing their pH) in the fed state is more than double when compared with the buffer capacity in the fasted state (Pentafragka et al., 2018). Unlike in the

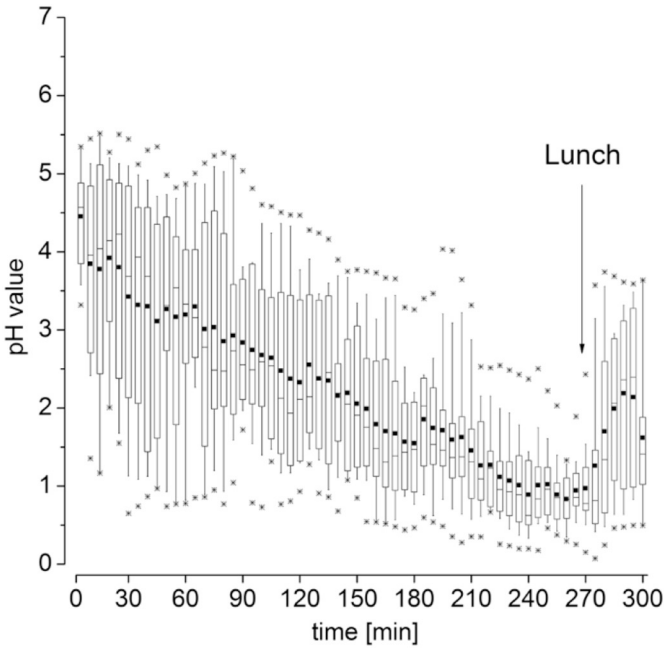

Fig. 6. Re-acidification of the stomach over a period of 5 h after intake of the FDA standard breakfast. Each box represents a 5 min interval. Box: 50%, whisker: 10–90%, square: mean, asterisks: max/min; n = 16.
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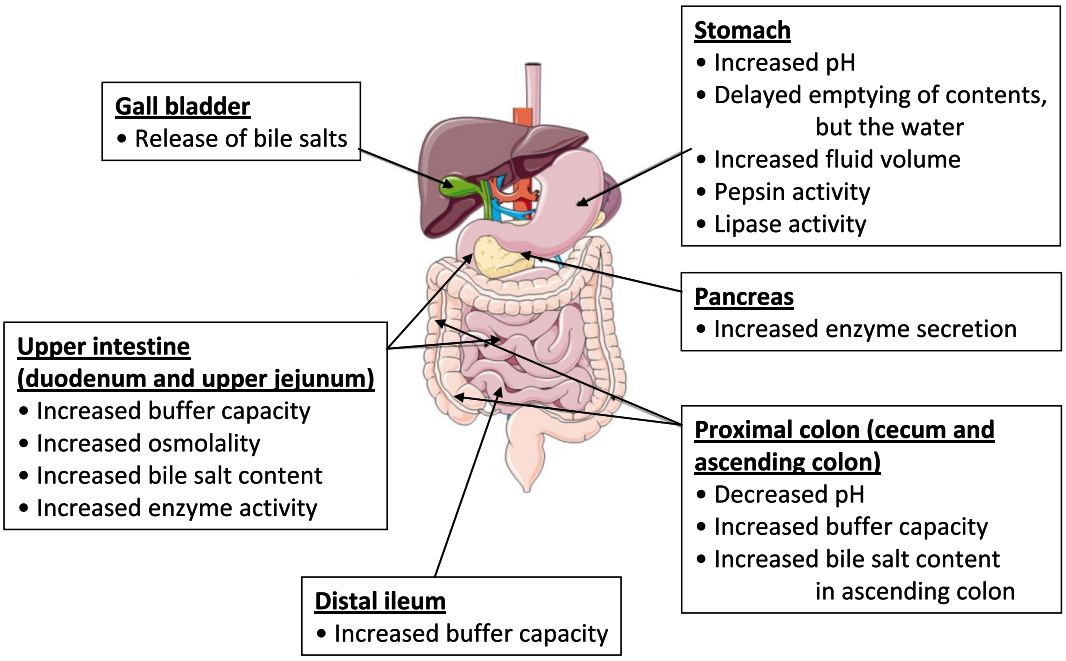

Fig. 7. Major physiological responses and changes in the luminal physicochemical characteristics after meal intake. Data in distal ileum and proximal colon refer to about 5 min after meal intake.
Adapted from O'Shea et al., 2018.

fasted state, duodenal contents in the fed state are hyperosmotic, in most cases. A 5-fold increase of phospholipase A2 secretion and at least 5-fold increase of pancreatic lipase secretion are observed in the fed state. Bile salts and phospholipid concentrations are highly variable however, on average, greater than in the fasted state. The bile salt/phospholipid ratio remains fairly constant (about 3.4), significantly lower than that in the fasted state (about 11.5) (Pentafragka et al., 2018). Changes in luminal cholesterol levels tend to echo those of the bile salts and phospholipids, with which they coexist in the form of mixed micellar structures. Depending on the dissolving particle size and the lipophilicity of the drug, changes in colloidal species composition and concentrations in the lumen induced by food intake (Vertzoni et al. this issue) could impact drug release and dissolution by reducing the surface tension and facilitating wetting and by inducing solubilisation effects. For drugs being classified as poorly soluble, highly permeable according to Biopharmaceutical Classification System (BCS Class II drugs), the increased presence of solubilising agents in the upper GI lumen after meal consumption generally enhances the dissolution of the dose. However, the potentially decreased diffusivity of colloidal solubilising species may adversely affect the absorption process (Vertzoni et al., 2012). For BCS Class IV drugs (poorly soluble and poorly permeable), the impact of extensive luminal solubilisation in the fed state is even less straightforward as, in this case, transport through the mucosa may also be influenced by changes in the membrane fluidisation (which may be induced by the interaction with surfactants) or the activity of membrane transport carriers (Porter et al., 2007).

In the lower intestine (distal ileum and proximal colon), most data have been collected 5 h after the administration of high calorie, high fat meal, *i.e.* about the time which drugs administered as IR products or multi-particulate MR products are expected to reach the region, after oral administration. The buffer capacity is significantly higher in the fed state (Pentafragka et al., 2018). Contents are hypo-osmotic in the fed as in the fasted state with values lower than in the fasted duodenum. Bile salt concentrations are much lower than in the upper intestine, regardless the prandial state. In the ascending colon, bile salt contents are higher 5 h after administration of the high-caloric, high-fat meal than 5 h after a glass of water in fasted adults (Pentafragka et al., 2018). High variability in composition of contents makes difficult to detect significant differences other luminal substances between prandial conditions, if any.

3.5. Interaction of food with intestinal microbiota

100 trillion microbes present in the gut lumen secrete a diverse array of enzymes capable of metabolising various drugs, including their reduction, hydrolysis, removal of succinate group, dehydroxylation, acetylation, deacetylation, cleavage of N-oxide bonds, proteolysis, denitration, amine formation and hydrolysis of amide linkages, deconjugation, thiazole ring-opening, isoxazole scission, deglycosylation, and *N*-demethylation. To date, at least thirty commercially available drugs are identified as substrates for these bacterial enzymes and thanks to modified release systems and drugs with poor solubility and/or poor permeability (Dvorackova et al., 2013), many others are likely to be discovered (Sousa et al., 2008).

Furthermore, pro-drugs poorly absorbed in the stomach and small intestine as well as drug delivery systems specifically targeting the colon (*e.g.* drug delivery systems based on polysaccharide substrates of colonic bacteria) are designed to release the pharmacologically active substance by microbial activity (Sousa et al., 2014). It is therefore now increasingly accepted that the gut microbiota influences drug bioavailability, pharmacokinetics, efficacy or adverse effects (Enright et al., 2016). Indeed, administration of probiotics led to increased bioavailability of amiodarone in male Wistar rats (Matuskova et al., 2014), of gliclazide in diabetic rats (Mikov et al., 2018) and of amlodipine in rabbits (Saputri et al., 2018). To the best of our knowledge, almost no human data are available to date. The producers of probiotics only recommend a 2 h-interval between their administration and administration of antibiotics (Mikawlrawng et al., 2016). In other cases, microbes seem to lower the bioavailability of certain drugs. For instance, the increase in tacrolimus dosing in kidney transplant patients was positively correlated with the increased *Faecalibacterium prausnitzii* abundance in faecal samples in the first week of transplantation (Lee et al., 2015). Other examples can be found in a review by Enright et al. that was published in 2016 (Enright et al., 2016).

Composition of the gut microbiome, nutritional status, age, disease and the co- or pre-administration of other drugs are environmental (epigenetic) factors that form the metabolic phenotype and that are responsible for inter-individual variation in drug effects (Clayton et al., 2006). The composition of colonic microbiota is, in turn, highly variable and dependent on different factors, including age (Margalef et al., 2016; Merchant et al., 2016), ethnicity (Lee et al., 2017; Stearns et al., 2017), diseases such as cirrhosis or Crohn's disease (Enright et al., 2017) or use of probiotics (Matuskova et al., 2014), antibiotics or specific inhibitors (Enright et al., 2016). An important factor which determines the structure of gut microbial community is the individual's diet as the gut microbiome can rapidly respond to a changed diet (David et al., 2014). Indeed, even short-term consumption of exclusively animal or plant diets have an important impact on gut microflora composition and overwhelmed inter-individual differences in microbial gene expression. The animal-based diet increased the proportion of bile-tolerant microbes (*Alistipes, Bilophila*, and *Bacteroides*) and decreased the levels of plant polysaccharides metabolising Firmicutes (*Roseburia, Eubacterium rectale*, and *Ruminococcus bromii*) (David et al., 2014). On the other hand, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) was associated with reduced *Bifidobacterium* and Actinobacteria in patients with irritable bowel syndrome (Bennet et al., 2018).

Altered composition of intestinal microbiome affects the pharmacokinetics of drugs mostly by the specific metabolic activity of microbes which differ among various microbial species (Enright et al., 2016).

Drug metabolism by the intestinal microbiome is likely to result in a different metabolite profile than that formed by host cells. This might potentially result in different levels of activation or inactivation of the pharmacological and/or toxicological actions of the molecule(s) when compared with that obtained by the host cells (Kang et al., 2013). The metabolite formed can be less active than the parent compound or toxic (Sousa et al., 2008). The role of microbiota in food-drug interactions, besides the direct biotransformation of the drug by the microbes, is mediated by various additional mechanisms. One of them involves the role of bile salts, their deconjugation by microbial bile salt hydrolase (BSH) and hydroxylation by 7α-dehydroxylase. While the former influences micellar solubilisation capacity for some poorly water-soluble drugs, the latter significantly affect the solubilisation capacity of bile salt micelles (Enright et al., 2017). This process is further affected by food related postprandial increase in bile secretion into the intestine (Lentz, 2008). Another aspect is the microbial production of short chain fatty acids and especially butyrate, which improves epithelial barrier integrity (Geirnaert et al., 2017). In addition, metabolites formed by the microbiota can affect drug transport; treatment of healthy rats with probiotics upregulate the mucosal efflux drug transporters (MRP2) that control gliclazide transport. In contrast, in diabetic rats, treatment with probiotics increased fluxes of gliclazide through normalisation of the functionality of the drug transporters *ex vivo* (Al-Salami et al., 2008).

As the role of gut microbiome on food drug interactions has been explored only in recent years, many other aspects are likely to be discovered in the future. In any case, the contribution of intestinal microorganisms to the determination of drug bioavailability and pharmacokinetics should now be taken into consideration in drug development process (Enright et al., 2017).

4. Food effects on drug absorption

Following physical and chemical processing of ingested food, nutrient molecules are presented to the intestine to be absorbed and further metabolised. Absorption can occur passively (through concentration gradients) or actively (by transporters). Enterocytes contain a high variety of transporters and enzymes specialised to absorb, expel and metabolise a high variety of nutrients. As drug molecules can use identical pathways to reach the systemic circulation, food-drug interactions at the level of the intestinal monolayer are inevitable. Here, we briefly illustrate these interactions using some key examples; for a detailed review on the mechanisms underlying food-drug interactions, we refer to the excellent review written by Won et al. (2012).

4.1. Interaction with uptake and efflux transporters

Food-drug interactions often originate from drug and nutrient molecules competing for the same route of transport. The list of uptake and efflux transporters in the human intestine (and other organs) is extensive, a comprehensive list can be found in a research article by Hilgendorf et al. (2007)). Several groups have reviewed literature regarding potential food-drug interactions with specific focus on transporter interactions (Custodio et al., 2008; Nakanishi and Tamai, 2015; Rodríguez-Fragoso et al., 2011).

4.1.1. Organic anion transporting polypeptides (OATP)

Organic anion transporting polypeptides (OATP) are a family of uptake transporters of proteins, which can be found in both, liver and intestine (Niemi, 2007). Specifically, OATP2B1 (and to a lesser extent OATP1A2) are present in the apical membrane of intestinal enterocytes. OATP2B1 is recognised as highly involved in nutrient and drug absorption from the digestive tracts in humans. Although the precise mechanism is unknown, a pH-dependence is often suggested (Kobayashi et al., 2003; Nozawa, 2003). OATP transporters are involved in transport of endogenous substrates including bile acids, thyroid hormones, prostaglandins and bilirubin glucuronides (Hagenbuch and Meier, 2003; Shitara et al., 2013). Common drug substrates include statins, protease inhibitors, fexofenadine, midazolam, montelukast, aliskiren and talinolol (Nakanishi and Tamai, 2015; Shitara et al., 2013; Tamai, 2012). Multiple studies in humans have proven a clinically significant reduction in intestinal absorption of these drugs when ingested with grapefruit, orange and apple juices (Imanaga et al., 2011; Mougey et al., 2009; Shirasaka et al., 2013; Tapaninen et al., 2010). A large variety of flavonoids present in these juices are considered responsible for this activity. *In vitro*, flavonol glycosides and catechins present in herbal extracts and green tea have been observed to inhibit OATP1A2 as well (Fuchikami et al., 2006; Roth et al., 2011).

4.1.2. Oligopeptide transporter (PEPT1)

Oligopeptide transporters are mainly found in the apical membranes of intestinal epithelial cells and are known to participate in the absorption of di- and tri-peptides and peptide-like drugs. These transporters use a proton gradient as a driving force and recognise a broad range of oligopeptides (Smith et al., 2013). The most common drug substrates include β-lactam antibiotics, cephalosporines, L-dopa prodrugs and some ACE-inhibitors (Brandsch, 2013; Brodin et al., 2002). Theoretically, an interaction could occur when an oligopeptide competes with a peptidomimetic drug, although clinically relevant interactions have not been reported in human subjects (Nakanishi and Tamai, 2015). Tsui et al. observed that Parkinson patients performed better on a low-protein diet compared to a high protein diet, although this could not be correlated to systemic L-dopa levels (Tsui et al., 1989). Furthermore, fasting has been reported to increase PEPT1 transcription in mice and zebrafish, theoretically implying increased absorption of peptidomimetic drugs (Koven and Schulte, 2012; Nässl et al., 2011).

4.1.3. P-glycoprotein (P-gp)

P-glycoprotein is the most studied efflux transporter and a known mediator for clinically relevant food-drug interactions. This transporter can be found in a broad range of tissues although its pronounced intestinal presence is most relevant in the context of food-drug interactions (Marchetti et al., 2007). Although the exact mechanisms of action remain to be elucidated, ATP hydrolysis is known to be involved. A broad range of substrates has been identified including antiarrhythmics, antihypertensive drugs, cyclosporine, tacrolimus and morphine

(Nakanishi and Tamai, 2015). Furanocoumarins and flavonoids present in a large variety of fruits and vegetables are considered the main dietary inhibitors of P-gp. *In vitro*, common lipid degradation products and sodium taurocholate (bile salt) have been demonstrated to inhibit P-gp activity (Ingels et al., 2004; Konishi et al., 2004a, 2004b). For an extended list of P-gp substrates and inhibitors we refer to Didziapetris et al. (2003) and Fenner et al. (2009). Several clinically relevant interactions have been reported when grapefruit juice is ingested with known P-gp substrates (see Section 7.1). Furthermore, extracts of St. John's wort, available over-the-counter, can induce P-gp transporter activity affecting drug absorption of digoxin, indinavir and cyclosporine (Zhou et al., 2004). A noteworthy example is fexofenadine, a substrate for both OATP (uptake) and P-gp (efflux). The overall bioavailability of fexofenadine is decreased when ingested with a fruit juice due to a more pronounced inhibition of OATP relative to P-gp (Dresser et al., 2002, 2005).

4.1.4. Other efflux transporters

Besides P-gp, other efflux transporters including multidrug resistance associated proteins (MRPs) and breast cancer resistance protein (BCRP) are expressed in the apical membrane of intestinal cells. MRPs are more commonly found in the liver although some variants can be found at the basolateral side of intestinal epithelial cells transporting molecules to the portal vein. In general, MRP effluxes conjugated metabolites including glutathione, glucuronides or sulphate adducts from the enterocyte (Keppler, 2011). Flavonoids are common inhibitors of these transporters. Van Zanden et al. found that phase II metabolites of quercetin (especially glucuronides) are potent MRP inhibitors *in vitro* (van Zanden et al., 2007). Chalet et al. observed rapid formation and apical excretion of these metabolites in the small intestine of human volunteers after ingestion of quercetin (Chalet et al., 2018). Though these observations suggest possible food-drug interactions, no relevant interactions involving MRPs have been reported (Takano et al., 2006). Likewise, BCRP transports conjugated metabolites, however *in vivo*, conjugated BCRP substrates are limited (Leslie et al., 2005). Some common BCRPs substrates include conjugated statins, steroid hormones, folic acids and vitamins B_2 and K_3 (Nakanishi and Ross, 2012). Deviating pharmacokinetic profiles of these drugs have been linked to genetic polymorphisms of BCRP in individuals, albeit no relevant food-drug interactions have been reported (Nakanishi and Tamai, 2015; Takano et al., 2006).

4.2. Interaction with intestinal monolayer: membrane fluidity

Molecules that increase the intestinal monolayer fluidity can theoretically influence drug absorption as an increase in fluidity can increase the diffusion rate of some drugs (Friedlander et al., 1990). Flavonoids, cholesterol and α-tocopherol have all been shown to partition into cellular membranes thereby increasing their fluidity (Arora et al., 2000). However, the clinical relevance of these *in vitro* findings has not been demonstrated yet.

4.3. Interaction with intestinal drug-metabolising enzymes

Human small intestine epithelial cells (enterocytes) are typically the first site of drug metabolism of orally administered drugs. As can be seen from Fig. 8, CYP3A and CYP2C9 are the major CYP enzymes in the small intestine, accounting in total for > 95% of the total CYP content (Paine et al., 2006). However, it should be noted that the distribution of drug-metabolising enzymes can vary along the small intestine and that CYP abundance in the small intestine differs strongly from CYP abundance in the liver (Drozdzik et al., 2018; Fritz et al., 2018).

The intestinal metabolism by CYP3A enzymes contributes to the first-pass metabolism of many drugs such as cyclosporine, verapamil, felodipine, midazolam, tacrolimus, simvastatin or nifedipine and the effect can be augmented by inducers of these enzymes such as rifampicin (Galetin et al., 2010; Glaeser et al., 2004; Gorski et al., 2003; Holtbecker et al., 1996; Kyrklund et al., 2000; Peters et al., 2016; Tannergren et al., 2004; Uesugi et al., 2006; Wu et al., 1995). For various drugs, the intestinal metabolism by CYP3A4 seems to be even more important than hepatic metabolism in the overall first-pass effect (Galetin et al., 2010; Lin, 2006).

The most important food-drug interactions mediated by inhibition or down-regulation both of phase I and phase II intestinal drug metabolism enzymes as well as intestinal transporters by food constituents including fruit juices, phenolic and polyphenolic compounds were reviewed in 2012 by Won and colleagues (Won et al., 2012). The most important food-drug interactions with grapefruit juice and some polyphenolic compounds are also mentioned in chapters 7.1.1. and 7.4.1. of this review.

The phase I enzymes in the enterocytes mediate various drug-drug but also food-drug interactions (Won et al., 2012). In this respect, citric fruit juices (in particular grapefruit juice, see also Section 7.1) have been shown to increase the systemic exposure of several CYP3A substrates in humans. In most cases, the effect is limited to oral (as opposed to i.v.) administration, indicating the importance of intestinal CYP3A in mediating food-drug interactions. Considering the extent of the observed effect, adverse events cannot be ruled out for some classes of drug (*e.g.* muscle pain with statins). While the possible role of alcoholic beverages and green tea in CYP3A-mediated food-drug interactions has been reported as well, the clinical relevance remains uncertain.

Overall, multiple studies have demonstrated food-drug interactions at the level of the intestinal monolayer. In clear cases, these interactions will affect systemic drug pharmacokinetics potentially imposing dangerous scenarios for drugs with a narrow therapeutic index. The potential for food-drug interactions to cause adverse events led the FDA to publish multiple guidances, encouraging the pharmaceutical industry to research interactions during drug development (Huang et al., 2008). It should be noted, however, that robust research in this field is often hindered by (i) the complex nature of food and drinks, making it hard to understand food-drug interactions at a molecular level, (ii) the *in vitro-in vivo* discrepancy, questioning the clinical relevance of several *in vitro* findings, and (iii) the impact of genetic polymorphisms for intestinal transporters and enzymes (Yoshida et al., 2013), leading to a highly variable impact of food-drug interactions.

5. Food effects on drug distribution

As seen in the preceding sections, food induces myriad changes in the gastrointestinal tract that can increase, decrease, delay or accelerate the intestinal absorption of a drug depending on the physicochemical properties of the drug (Carver et al., 1999). Many studies in the

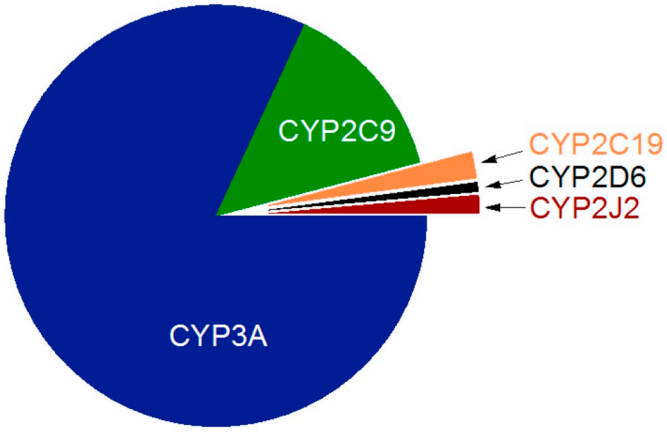

Fig. 8. The abundance of drug-metabolising enzymes in the proximal small intestine (n = 31).
Adapted from Paine et al., 2006.

literature have focussed on meal-induced changes in gastrointestinal drug absorption. The fed state can, however, also influence the route of drug transport from the intestine to the blood circulation (lymph *versus* portal vein), drug distribution to organs and tissues including target and off-target sites, and organs of elimination. This section discusses food-induced changes in drug distribution and their clinical ramifications.

5.1. Lymphatic drug transport

Following absorption, the majority of drugs are transported from the intestine to the systemic blood circulation through the mesenteric capillaries and veins, then *via* the portal vein to the liver before reaching the general circulation. However, the intestinal epithelium also contains a rich network of lymphatic vessels (see Fig. 9) (Bernier-Latmani and Petrova, 2017; Trevaskis et al., 2008, 2015).

Each intestinal villi has one or two blind-ended lacteals through which lymph flows to pre-collecting, then collecting mesenteric lymph vessels and lymph nodes, before eventually joining the thoracic lymph duct. The thoracic lymph empties directly into the systemic circulation *via* the subclavian vein thus avoiding passage through the liver (unlike portal vein blood). Most drugs, however, are not transported in significant quantities *via* the lymphatic vessels as the flow rate of mesenteric lymph fluid is 500–1000 fold lower than the flow rate of blood through the portal vein (Charman and Stella, 1986; Trevaskis et al., 2008, 2015). In contrast, dietary lipids and some highly lipophilic compounds, including highly lipophilic drugs and/or prodrugs (typically those with logP > 5 and long chain triglyceride solubility > 50 mg/kg and/or very high affinity for chylomicrons such as halofantrine (Khoo et al., 2003), testosterone undecanoate (Shackleford et al., 2003) and methylnortestoerone undecanoate (White et al., 2009), moxidectin (Lespine et al., 2006), CP532,623 and CP524,515 (Trevaskis et al., 2010b), Org45697 and Org46035 (Caliph et al., 2009), cannabinoids (Zgair et al., 2017), dexanabinol and PRS-211,220 (Gershkovich et al., 2007a)) may be transported from the intestine *via* the lymphatics (Charman and Stella, 1986; Lawless et al., 2015; Trevaskis et al., 2008, 2010c, 2015). This is mediated by drug association with the lipid-rich lipoproteins (primarily chylomicrons, CMs) that are assembled in the enterocyte from dietary and endogenous lipids. CMs are transported from the intestine *via* the lymphatics as the blood vessel endothelium is less permeable than the lymphatic endothelium, precluding the access of CMs that can be up to 1000 nm in diameter (Dixon, 2010; Randolph and Miller, 2014; Trevaskis et al., 2008, 2015). In contrast, the initial lymphatics and lacteals contains wide gaps between endothelial cells and also potentially active transport pathways that facilitate the entry of large assemblies such as CMs (Dixon, 2010; Randolph and Miller, 2014; Trevaskis et al., 2008, 2015).

The total mass of the drug that is absorbed and transported from the intestine *via* the portal vein and lymphatic system combined can be altered by food induced changes to the rate and/or extent of drug absorption *via* the mechanisms outlined earlier in this review. For highly lipophilic drugs, food may also affect the route of drug transport from the intestine to blood circulation (*i.e.* proportional transport *via* the lymph *vs* portal vein). The lipid component of food (both lipid quantity and type), in particular, influences intestinal lymphatic drug transport as some dietary lipids stimulate intestinal CM formation and thus increases in lymphatic lipid and drug transport (Trevaskis et al., 2008, 2015). For instance, post-prandial administration of highly lipophilic drugs such as halofantrine, methylnortestosterone undecanoate, CP532,623 and CP524,515 to greyhound dogs markedly increases intestinal lymphatic drug transport relative to administration in the fasted state (Khoo et al., 2002; Trevaskis et al., 2010b; White et al., 2009). For these compounds, administration with even a small quantity of lipid (in a formulation or partial meal) is sufficient to support a substantial increase in lymphatic lipid and drug transport, with drug transport in lymph directly related to the quantity of lipid consumed (Khoo et al., 2003; Trevaskis et al., 2010b; White et al., 2009). In addition to quantity, the type of lipid in the meal influences the extent of lymphatic drug transport. This reflects the fact that long chain lipids (such as those found in in olive oil, soybean oil, animal fats *etc.*), but not short or medium chain length lipids (such as those found in higher concentration in coconut oil), are assembled into CMs and transported from the intestine *via* lymph (Caliph et al., 2000; Trevaskis et al., 2013). Differences in lipid saturation can also influence lymphatic lipid and drug transport (Holm et al., 2001). Mono- and poly- unsaturated lipids promote greater increases in CM formation and lymphatic lipid transport than equivalent chain length saturated lipids and may therefore be expected to more efficiently promote lymphatic drug transport.

Overall, intestinal lymphatic transport of highly lipophilic drugs may therefore vary depending on the type and quantity of lipid in ingested food and will be particularly increased when drug is administered around the same time as a long chain lipid-rich meal (Khoo et al., 2002; Trevaskis et al., 2010b; White et al., 2009). Recent studies in animal models have demonstrated that increases in lymphatic drug transport can alter drug metabolism (Shackleford et al., 2003; Trevaskis

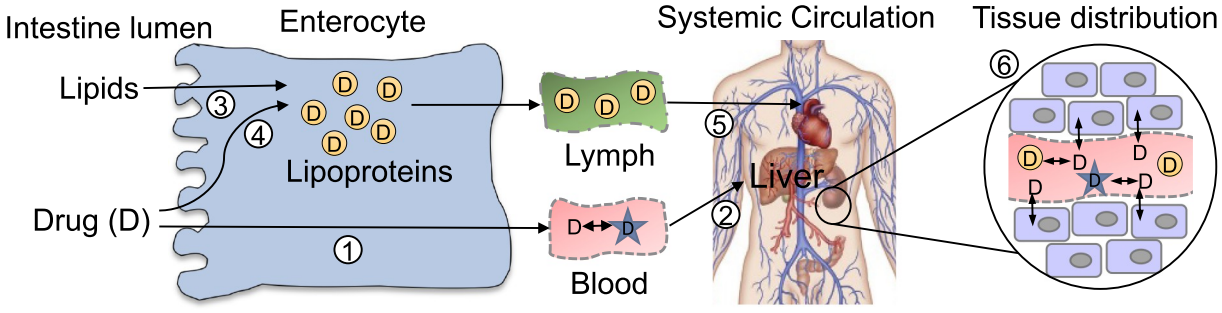

Fig. 9. Following oral administration, the majority of drugs are transported from the intestine to the systemic blood circulation through the mesenteric capillaries and veins (*i.e.* blood vessels) (1), then *via* the portal vein to the liver before reaching the general circulation (2). In contrast, dietary lipids are assembled into lipoproteins (yellow circles) that are transported from the intestine *via* the lymphatic vessels (3). Similarly, highly lipophilic drugs and/or prodrugs can associate with the lipid-rich lipoproteins during passage across enterocytes and subsequently be transported from the intestine *via* the lymphatic vessels (4). Co-administration with food derived lipids tends to increase lymphatic drug transport. The lymphatic vessels draining the intestine flow through one or more lymph nodes before joining the thoracic lymph duct which empties lymph directly into the blood circulation at the subclavian vein above the heart. This avoids passage through the liver and promotion of lymphatic drug transport (*e.g. via* co-administration with food/lipids) can therefore reduce first-pass drug metabolism and enhance drug bioavailability (5). Upon entry into the systemic blood circulation, drugs can reversibly associate with plasma proteins (blue stars) or lipoproteins (yellow circles) (6). Only free drug is readily able to extravasate from the blood vessels and cross cell membranes. Food induced changes in drug binding to plasma proteins and/or lipoproteins can therefore alter drug disposition to organs and tissues, and drug clearance (by affecting drug uptake into clearance organs). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al., 2006, 2009) and drug disposition (Caliph et al., 2013) which can subsequently impact drug bioavailability (Shackleford et al., 2003; Trevaskis et al., 2006, 2009) and potentially drug efficacy/safety profiles (Trevaskis et al., 2010a; Zgair et al., 2017). Promotion of intestinal lymphatic transport reduces first pass hepatic metabolism as the lymph empties directly into the blood circulation without first passing through the liver (as above) (Khoo et al., 2003; Shackleford et al., 2003; Trevaskis et al., 2009; White et al., 2009). First pass metabolism in the enterocyte may also be reduced through drug sequestration into lipoproteins thus reducing drug access to metabolic enzymes (Trevaskis et al., 2006). Overall, the reduction in metabolism will increase drug bioavailability and potentially therefore influence therapeutic effect. Furthermore, emerging evidence primarily in animal models suggests that promotion of drug transport through the lymph can increase the efficacy of drugs with lymph resident targets such as immunomodulators (Trevaskis et al., 2010a; Zgair et al., 2017), anticancer drugs (Kaminskas et al., 2013; Ryan et al., 2014) and anti-infectives (Chan et al., 2017; Fletcher et al., 2014; Trevaskis et al., 2015). By enabling the administration of lower drug doses to achieve similar therapeutic effects this could potentially enable a reduction in drug toxicity. Finally, entry into the systemic blood circulation within lymph lipid-rich lipoproteins can alter drug disposition and clearance (Caliph et al., 2013) thus impacting drug efficacy and toxicity. This is described in the following section.

5.2. Binding to lipoproteins

Lipoproteins are macromolecular vehicles that transport lipids and lipophilic molecules (including some drugs such as halofantrine, cyclosporine A, amiodarone, amphotericin B, nystatin, eritoran, clozapine, haloperidol, paclitaxel *etc.* (Wasan et al., 2008)) through the aqueous environment of the blood circulation and the lymphatic system (Randolph and Miller, 2014; Wasan et al., 2008). There are four main classes of lipoproteins (in order of decreasing size/core lipid content, and increasing density); CMs, very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). CMs are only assembled in the intestine whereas the other lipoproteins are assembled in the liver with lesser amounts released by the intestine. The main role of CM and VLDL is to transport triglycerides to tissues whereas LDL transport cholesterol to tissues, and HDL return cholesterol from tissues to the liver for excretion (Randolph and Miller, 2014; Wasan et al., 2008).

Lipoproteins have a core composed of neutral lipids (triglycerides, cholesterol esters) and a surface composed of amphiphilic lipids (phospholipids, cholesterol) and apo-proteins (Randolph and Miller, 2014; Wasan et al., 2008). Lipophilic drugs can associate with either the core or surface of lipoproteins depending on their physicochemical properties (Wasan et al., 2008). Association may occur during intestinal absorption, as described above for drugs that are lymphatically transported (Gershkovich and Hoffman, 2007; Porter et al., 2007). Alternatively, association may occur upon drug entry into the blood circulation (Gershkovich and Hoffman, 2007; Wasan et al., 2008), in an analogous manner to drug binding to plasma proteins. The association with lipoproteins reduces the free (unbound) fraction of drug present in blood/plasma (Gershkovich and Hoffman, 2007; Wasan et al., 2008). In general, free (unbound) drug is more available to diffuse across cell membranes and to enter organs and tissues. In this way, binding to lipoproteins may reduce the availability of free drug to distribute to tissues thus reducing the volume of distribution (Vd) and also clearance (Cl) by reducing uptake into the liver and/or kidney (Gershkovich and Hoffman, 2007; Mehvar, 2005; Patel and Brocks, 2009). The extent of change to drug Vd and Cl with change in free drug fraction will, however, depend on whether the drug has a low or high Vd or Cl. Generally, a reduction in the free fraction leads to a greater reduction in Vd or Cl for drugs with high Vd or low intrinsic Cl, respectively. The reason for this is well summarised in previous reviews (Huang and Ung, 2013; Mehvar, 2005; Wasan et al., 2008).

Multiple receptors and enzymes facilitate lipid transfer between different lipoprotein types and from lipoproteins into tissues to be stored or used as an energy source (particularly metabolic tissues such as liver, muscle and adipose tissue) (Randolph and Miller, 2014; Wasan et al., 2008). Association with lipoproteins may thus result in increases or decreases in drug disposition to specific tissues by promoting interaction with specific lipoprotein transport pathways (Caliph et al., 2013; Gershkovich and Hoffman, 2007; Patel and Brocks, 2009; Wasan et al., 2008; Yamamoto et al., 2017). Currently these changes cannot be accurately predicted for a given drug and must be determined empirically. For an excellent summary of these effects see reviews by Wasan et al. (2008) and Patel and Brocks (2009).

Following a meal, the distribution of lipids across different lipoprotein subclasses, and the metabolism and tissue uptake of lipoprotein lipids is altered (Wasan et al., 2008). In particular, the concentration of lipid-rich lipoproteins (CM and VLDL) in the blood circulation increases and the lipids in these lipoproteins are directed toward storage tissues such as adipose tissue and to a lesser extent muscle (Gershkovich and Hoffman, 2007; Ooi et al., 2015; Wasan et al., 2008). These changes are dependent on the type of meal and also a range of inter-individual factors such as type of food and diet, race, sex, and presence of health conditions such as dyslipidaemia and metabolic diseases (which can exaggerate meal induced increases in plasma lipids) (Ooi et al., 2015; Wasan et al., 2008). Given that food has a range of effects on lipoprotein metabolism and transport, and that lipoprotein association can increase or decrease drug Vd and Cl, and alter tissue disposition, it is perhaps not surprising that co-administration with food has been found to have a range of different effects on tissue disposition, Vd and Cl of lipoprotein associated drugs (Brocks et al., 2006; McIntosh et al., 2004; Patel and Brocks, 2009; Shayeganpour et al., 2005, 2008; Wasan et al., 2008). Less effort has been directed toward assessment of whether these changes in disposition may impact drug activity, however, a limited number of studies have demonstrated that food induced changes in lipoprotein-drug binding and distribution can impact pharmacodynamics (*i.e.* efficacy and/or safety profiles) (Gershkovich et al., 2007b; McIntosh et al., 2004; Patel and Brocks, 2010).

5.3. Plasma protein binding

Albumin is the most abundant plasma protein (concentration 3.5–5 g/dL) and the most common protein to which drugs bind in plasma (Ascenzi et al., 2014; Yamasaki et al., 2013). Alpha-1 acidic glycoprotein (AAG), although present in much lower concentrations than albumin (0.04–0.1 g/dL), is the second main plasma protein that binds drugs (Huang and Ung, 2013; Israili and Dayton, 2001). Several other proteins have specific affinities for certain endogenous substances and may bind to specific drugs (Ascenzi et al., 2014; Mehvar, 2005).

Albumin has the capacity to bind a range of endogenous and exogenous compounds including fatty acids, metabolites, hormones and many acidic (anionic) drugs. The multi-domain nature of albumin enables it to bind to a large range of molecules including up to the equivalent of nine fatty acid molecules at a time. There are two main binding sites for drugs on albumin – site I (also called the warfarin binding site) and site II (the benzodiazepine binding site). The structure of albumin and the nature of its ligand binding pockets have been excellently reviewed (Ascenzi et al., 2014; Yamasaki et al., 2013).

AAG on the other hand displays a preference for binding lipophilic bases (cationic) and neutral drugs (Huang and Ung, 2013; Israili and Dayton, 2001). AAG is a glycoprotein with a single binding pocket responsible for binding most drugs (Huang and Ung, 2013; Israili and Dayton, 2001). Since AAG is present at much lower concentrations in plasma and displays a single major binding pocket, binding to AAG is more readily saturable with increases in drug concentration than binding to albumin (Ascenzi et al., 2014; Huang and Ung, 2013; Israili and Dayton, 2001). Similarly, there is more likely to be competitive

displacement of drug binding to AAG, when compared with albumin, *via* binding of other endogenous or exogenous molecules (Ascenzi et al., 2014; Huang and Ung, 2013; Israili and Dayton, 2001). For albumin, drug binding can also be altered through allosteric modulation by molecules binding at an alternate site to the drug (Ascenzi et al., 2014; Yamasaki et al., 2013).

As described above for binding to lipoproteins, changes in drug binding to plasma proteins and thus free (unbound) drug concentrations present in the plasma alter drug availability to transfer to tissues as free drug is more readily able to extravasate and cross cell membranes (Ascenzi et al., 2014; Huang and Ung, 2013; Israili and Dayton, 2001; Mehvar, 2005). Increases (or decreases) in drug binding to plasma proteins can thus alter drug tissue disposition patterns, reduce (or increase) drug Vd and Cl. The extent of change to Vd and Cl depends on the properties of the drug as described above for lipoprotein binding (Ascenzi et al., 2014; Huang and Ung, 2013; Israili and Dayton, 2001; Mehvar, 2005). Alterations in drug disposition and Cl may therefore ultimately influence the ability of drugs to access target and off-target sites and thus therapeutic effect.

Food effects on plasma protein binding have not been explored in detail in the literature. Changes in nutrition status can alter albumin and AAG concentrations. Malnutrition and cachexia can reduce albumin and AAG concentrations, whereas a high protein diet may increase plasma protein concentrations (Ascenzi et al., 2014; Huang and Ung, 2013; Israili and Dayton, 2001; Yamasaki et al., 2013). Dietary components and metabolites could also potentially impact drug binding to plasma proteins (Ascenzi et al., 2014; Huang and Ung, 2013; Israili and Dayton, 2001; Yamasaki et al., 2013). For example, fatty acids are highly bound to albumin and increases in fatty acid concentration can allosterically modulate the binding of drugs to albumin (Anguizola et al., 2013; Yamasaki et al., 2017). Changes in blood glucose concentration, as seen in diabetes, also modulate albumin glycosylation and drug binding (Anguizola et al., 2013; Baraka-Vidot et al., 2015). However, the clinical relevance of diet/food induced changes in drug binding has not been clearly demonstrated. In general, despite the influence that plasma protein binding has on the disposition, Cl and effect of drugs, the risk of clinically relevant interactions *via* food-induced changes in drug binding to plasma proteins is considered low (Ascenzi et al., 2014; Huang and Ung, 2013). This is particularly the case because transient increases in drug binding to plasma proteins after a meal typically lead to transient increases in the free drug concentration in plasma followed by a rapid reduction in free drug concentration due to compensatory changes to drug Cl and Vd. Change in plasma protein binding will, however, be most important for highly bound drugs (unbound fraction < 1%) that have a narrow therapeutic window, particularly where Cl is high and therefore changes to free concentration in the plasma do not stimulate significant compensatory changes to clearance.

6. Food effects on drug metabolism and elimination

Numerous studies indicate that constituents of food can modulate the activity of drug-metabolising enzymes and drug transporters (Won et al., 2012). However, translation of *in vitro* data to the clinic is not always clear (Farkas and Greenblatt, 2008; Harris et al., 2003; Sprouse and van Breemen, 2016). Probably the most prominent example of proven clinical relevance is the inhibition of the metabolism of CYP3A substrates by grapefruit juice, which is also reported later in this review. Other foods which have been reported to inhibit CYP3A metabolism include Seville orange juice (Edwards et al., 1999) and red wine, although in the latter case the extent of the interaction is smaller than that due to grapefruit juice (Offman et al., 2001). Clinically relevant interactions *via* CYP3A may also result from the consumption of food constituents which are inducers of CYP3A enzymes. For example, St John's wort is a herbal dietary supplement that results in decreased bioavailability of CYP3A substrates and can lead to the need for dosage adjustments in certain drugs such as cyclosporine and indinavir. In addition, garlic has been shown to reduce exposures of saquinavir (Piscitelli et al., 2002), a drug which is highly extracted by first pass metabolism in the gut. Indeed, the modulation of pharmacokinetics of CYP3A4 substrates by food constituents is largely linked to the high intestinal expression of this enzyme which can result in potential for significant impact on bioavailability as well susceptibility to modulation by food constituents. Intestinal expression of other CYP enzymes is lower relative to CYP3A, however certain UDP-glucuronosyltransferases (UGT) isoforms are also highly expressed and play a role in reducing oral bioavailability of drugs such as raloxifene (see chapter 4.4) (Nakamori et al., 2012). Therefore, the potential for food drug effects when raloxifene is taken with potent inhibitors of UGT exists and has been explored *in vitro* (Gufford et al., 2015) although clinical evidence is so far lacking. In addition, inhibition of drug transporters, including P-gp and OATPs, has been identified as a potential cause of food effects. Again the magnitude and clinical importance remains to be clarified (Farkas and Greenblatt, 2008). A recent review collates the numerous fruit juices and herbal supplements which can lead to clinical changes in the oral bioavailability of drugs (Stieger et al., 2017).

Another potential mechanism of food effect exists for drugs which are subject to high first pass extraction because in such cases, bioavailability is sensitive to the changes in hepatic and splanchnic blood flow which occur after ingestion of food. Food intake was reported to increase bioavailability of propranolol (McLean et al., 1981) and pharmacokinetic modelling indicated that this could be due to decreased first-pass liver extraction (McLean et al., 1978). More recently, physiologically based pharmacokinetic models for propranolol and ibrutinib, another drug with high hepatic extraction, were applied and a positive food effect was simulated (Rose et al., 2017). In the case when first pass metabolism is saturable, it is possible that an increase in hepatic blood flow with food reduces the concentrations of drug during first pass and desaturation of metabolism. This would then result in an increase in first-pass extraction and thus, a negative food effect. Such a case was reported for tacrine which showed a significant decrease in systemic exposure when taken with food (Welty et al., 1994).

Food can also cause changes in urinary pH by processes like alkalinisation due to milk intake or due to a pure vegetarian diet or conversely acidification caused by a very protein rich diet. Since mainly the non-ionised form of acids or bases are reabsorbed after glomerular filtration or secretion, changes in urine pH can lead to a change in pharmacokinetics of drugs eliminated by the kidneys. Thus it has been recommended that diet should be kept stable during treatment with memantine as its pharmacokinetic profile is considerably affected by urine pH (Freudenthaler et al., 1998).

7. Specific food-drug interactions

Most often, the chemical composition of oral drug products is relatively simple as they are based on a single drug or a mixture of only a few drugs. However, the presence of various excipients can lead to more complex chemical composition. Usually, excipient selection is based on their chemical and pharmacological inactivity and, absence of pharmacokinetic and pharmacodynamics interactions with the drug(s). In certain cases, the addition of excipients preserves the drug from pharmacokinetic problems such as pH degradation, or improves patient compliance (*e.g.* colourants, taste masking agents). Analogous to drug products, food is also a mixture of different chemical entities endowed with a determinable structure and specific (re)active moieties. Nonetheless, it is clear that food is a very complex chemical system, in which low and high molecular weight components are mixed together and all of them can, in principle, cause specific food-drug interactions that can be classified in terms of binding properties. Adducts could be typically generated by covalent bonds between drugs and food components such as proteins (Liebler, 2008). Conversely, non-covalent complexes, can occur when weak interactions such as salt bridges,

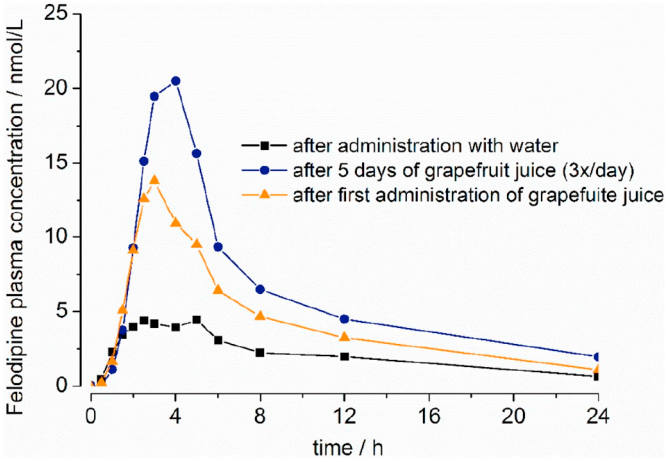

Fig. 10. Effect of grapefruit juice on mean felodipine plasma concentrations. Felodipine plasma concentrations were measured after the oral administration of 10 mg felodipine with either water, after the first glass of grapefruit juice (8 oz.), or after 5 d of thrice daily administration of grapefruit juice. Adapted from Lown et al., 1997.

hydrogen bond or hydrophobic contacts (Neel et al., 2017) are established between them. In order to have an effect on oral drug absorption, these interactions must generate adducts or complexes with chemical physical properties significantly different from the original reactants. In particular, parameters such as molecular weight and logP are relevant to control the absorption *via* biological membranes by means of passive diffusion (Duffy and Jorgensen, 2000). In recent years, *in silico* methods have been further optimised to also predict ADME properties (Hou and Wang, 2008).

Some well-known examples of specific food-drug interaction are detectable especially in the field of chelating compounds, *i.e.* those able to form stable complexes preferably with bivalent cations such as calcium or magnesium widely present in many foods, stable complexes. The chemical structure of these chelating drugs can easily explain the reasons of the complexing properties because they expose heteroatoms such as oxygen and nitrogen in the correct conformation for the metal coordination. Tetracyclines (Ziółkowski et al., 2016) and quinolones (Stojkovic et al., 2014; Uivarosi, 2013) have been demonstrated to create complexes with cations of foods or antacids (Ogawa and Echizen, 2011) with absorption characteristics dramatically different from the free drug. An exhaustive specific food-drug interaction analysis for other kind of non-metal coordination is not available in literature. However, the advent of novel *in silico* and *in vitro* approaches will hopefully speed up the progress of knowledge and provide new insights into this topic.

In the following chapter, various specific food-drug interactions occurring primarily on a pharmacokinetic level will be discussed. Apart from well-known and highly relevant examples such as grapefruit juice, milk and ethanol, we will also address specific effects of functional foods on oral drug delivery.

7.1. Grapefruit juice

In the following section, an overview will be provided related to the specific interactions between grapefruit juice and metabolising enzymes. In a second part, the interactions between grapefruit juice and uptake/efflux transporters will be discussed. The clinical relevance of these interactions will be demonstrated by literature examples for drug compounds that are depending on these enzymes/transporters for metabolism or absorption, respectively.

7.1.1. Interactions with metabolising enzymes

Inhibition of intestinal first-pass metabolism may increase the absorption of drug substrates of the corresponding enzymes. A well-known example is an inhibition of the intestinal cytochrome P450 (CYP) 3A enzymes by grapefruit juice (*Citrus paradisi* Macfad) (Ameer and Weintraub, 1997; Dresser et al., 2000; Murray, 2006). Furanocoumarins (such as bergamottin and 6′,7′-dihydroxy-bergamottin) have been identified as the potential constituents in grapefruit inhibiting these intestinal CYP3A enzymes, resulting in an increase in systemic exposure for defined substrates (Dresser et al., 2000). A significant effect of grapefruit juice on the absorption of CYP3A4 metabolised drugs has been demonstrated in humans (Fleisher et al., 1999; Glaeser et al., 2007; Wagner et al., 2001). This interaction was discovered by chance in an interaction study between felodipine (dihydropyridine, Ca^{2+} antagonist) and ethanol. Grapefruit juice was used to mask the taste of ethanol. Felodipine undergoes high presystemic (first-pass) CYP3A4-mediated metabolism in the gut and liver resulting in a low bioavailability (15%). Subsequent studies showed that grapefruit juice reduced pre-systemic felodipine metabolism *via* an interaction with CYP3A4 present in the intestinal wall. The effect of grapefruit juice can, therefore, lead to an increase in felodipine in the systemic circulation (systemic AUC and C_{max}) and this effect can last longer than 24 h. An amount of 250 mL of grapefruit juice increases the AUC and C_{max} to 267% and 345%, respectively (Fig. 10) (Lown et al., 1997). The combination of grapefruit juice and felodipine resulted in lower blood pressure and more often orthostatic hypotension.

The magnitude of the effect of food on the activity of metabolising enzymes and intestinal transporters varies greatly from person to person, depending on the intrinsic differences in the activity of metabolising enzymes and transporters in the intestine so that individuals with, for example, higher CYP3A4 levels also have a higher proportional increase. The decreased expression of CYP3A4 with concomitant intake of grapefruit juice indicates that it is not just a competitive interaction. Since the mRNA for CYP3A4 is unchanged, the interaction between diet and CYP3A4 is likely to be in the post-translational mechanism, *e.g.*, by accelerated CYP3A4 degradation by means of down-regulation. In order to recover the enzymatic activity, a completely new *de novo* synthesis is needed, which explains the long effect of grapefruit juice (Bailey et al., 1998; Glaeser et al., 2007).

7.1.2. Interactions with uptake/efflux transporters

Recently, it has been discovered that the P-gp can limit the bioavailability of many orally administered drugs by transporting the substrate back into the intestinal lumen. In an *in vitro* study of flavonoid components from grapefruit juice, it was discovered that the efflux of the P-gp substrate vinblastine decreased. There was a concentration-dependent nutritional interaction of grapefruit juice on the permeability of vinblastine across the Caco-2 cells. Higher concentrations of grapefruit juice resulted in a lower efflux permeability of vinblastine (Wagner et al., 2001).

Besides P-gp, grapefruit juice also inhibits uptake transport by the organic anion transporter peptide 1A2 (OATP1A2). In a study by Glaeser et al., it was shown that the administration of grapefruit juice can lower the plasma levels of fexofenadine in humans without fexofenadine undergoing significant metabolism. Based on *in vitro* studies, it was shown that grapefruit juice can inhibit the transporter OATP1A2. The proof-of-concept was clearly demonstrated when fexofenadine was used in a human PK study to evaluate the function OATP1A2. The plasma concentration of fexofenadine was measured in healthy volunteers who were administered 300 mL of grapefruit juice at 0, 2 or 4 h prior to the intake of fexofenadine. Concomitant administration of grapefruit juice and fexofenadine resulted in an $AUC_{0-8\ h}$ that had dropped by 52% compared to the test condition when fexofenadine was co-administered with water. Drinking grapefruit juice 2 h before taking fexofenadine reduced the average AUC by 38% and drinking grapefruit juice 4 h in advance had no effect on drug absorption (Bailey et al., 1998; Glaeser et al., 2007).

7.2. Milk

Whole fat cow's milk contains has a total caloric content of 65 kcal/100 mL and contains 3.7 g of fat, 4.6 g of carbohydrates, and 3.4 g of protein per 100 g, which contribute to approximately 50%, 30% and 20% of the total caloric content, respectively (Jensen, 1995). In comparison to the meal proposed by EMA and FDA (EMA, 2012; FDA, 2002), milk is a homogenous liquid with up to 20% more calcium (Walstra et al., 2006). Based on the similarities between milk composition and the reference meal (Guimarães et al., 2018), milk-based biorelevant media to simulate composition of gastric contents in the fed state have been proposed (Diakidou et al., 2009). Intragastric drug solubility has been estimated in milk-based biorelevant media digested with pepsin and lipase to simulate the digestion and lipolysis in the fed state. Solubility measurements in these media resulted in solubility values that were similar to the solubility values estimated *ex vivo* in gastric contents aspirated from healthy adults in the fed state (Diakidou et al., 2009).

Positive food effects on the absorption of the lipophilic drug lumefantrine have been observed when the drug was administered with milk and a fat-enriched meal, due to solubilisation effects (Mwebaza et al., 2013). However, food effects were not captured when milk was used instead of the meal proposed by the regulatory agencies. Data with milk could deviate from data with the meal due to milk-specific drug interactions, such as chelate formation and drug protein binding (Singh, 1999).

Multivalent ions present in milk (*e.g.* Ca^{2+}, Mg^{2+}) can chelate with drugs belonging to several classes (*e.g.* bisphosphonates, tetracyclines) and the resulting complexes are not available for absorption. Tetracyclines should be taken without milk or dairy products to avoid decrease in exposure due to formation of insoluble chelates of tetracyclines in the presence of calcium (Singh, 1999). Recent studies in healthy humans showed that even a relatively small volume of milk which contains an extremely low amount of calcium can severely impair the absorption of this drug (Jung et al., 1997). The oral bioavailability of demeclocycline decreased by 83% when taken with milk, while drug administration after a dairy-free meal resulted in a positive food effect, as shown in Fig. 11 (Neuvonen, 1976).

When compared with the fasted state, drug exposure in humans for minocycline and tetracycline was also lowered by 27% and 65%, respectively, when co-administered with milk. The administration of minocycline and tetracycline after dairy-free food, however, reduced drug plasma levels to a lesser extent when compared with milk; the AUC after milk compared to meal consumption decreased by 17% and 36%, respectively (Leyden, 1985). In contrast, doxycycline experienced no food effects when administered with milk or diverse nutrient-specific meals (Neuvonen, 1976; Welling et al., 1976). Based on data from healthy adults, the exposure to ciprofloxacin, an antibiotic drug belonging to the class of fluoroquinolones, is reduced with milk by 30–36% when compared with its administration with water because of chelate formation with calcium (Hoogkamer and Kleinbloesem, 1995; Neuvonen et al., 1991). However, ciprofloxacin plasma levels remained unchanged when the drug was administered with water or after a standard meal without milk (Ledergerber et al., 1985; Neuvonen et al., 1991), or when administered with a high-fat high-calcium breakfast (Frost et al., 1989). The lack of a negative food effect in the presence of chelating ions in the high-fat high-calcium breakfast was explained by unavailability of free calcium ions for drug chelation due to possible trapping of calcium in the mixed meal components (Frost et al., 1989). Although most fluoroquinolones chelate with multivalent ions (Läer et al., 1997), interactions between milk and fluoroquinolones are not always observed; *e.g.* the enoxacin and ofloxacin extent of absorption in humans was scarcely affected after administration with milk compared to a milk-containing and milk-free standard breakfast (Dudley et al., 1991; Lehto and Kivisto, 1995; Singh, 1999). The antiarrhythmic drug sotalol chelates with multivalent ions (Läer et al., 1997) and exhibits a negative food effect when administered with milk (AUC decreased by 27% and C_{max} by 33%) and milk-containing meals (AUC decreased by 37% and C_{max} by 40%); herein it should be noted that the drug levels achieved for sotalol taken with milk were greater compared to a milk-containing meal (Kahela et al., 1979). A critical milk-related food-drug interaction was shown for estramustine due to a formation of a poorly absorbable calcium-complex (Gunnarsson et al., 1990). Drug absorption was significantly decreased with milk compared to low-calcium water and to a low-calcium breakfast with an AUC reduction of 63% and 43%, respectively (Gunnarsson et al., 1990).

Another mechanism for milk-related drug interactions is the specific protein content of milk when compared with the reference meal, with casein being the major contributor to the total milk protein content by approximately 85%. However, its relative content in the protein fraction of the standard meal is considerably lower (18%). Drug binding to proteins in milk is mainly dictated by drug binding to casein and a linear correlation between drug binding to casein solutions and to milk was found for several drugs (Stebler and Guentert, 1990). *In vitro* drug binding studies performed using skimmed and full-fat milk associated the bound to free drug concentration ratio to drug lipophilicity (Macheras et al., 1990). In line with *in vitro* studies showing that up to 52% of phenytoin was bound to skimmed milk components, administration of phenytoin in healthy adults resulted in a reduction of the AUC by half when ingested with milk (Macheras et al., 1991). In accordance to these findings, clinical investigations aiming at identifying the influence of carbohydrates, fats, or proteins in phenytoin exposure revealed that drug absorption was reduced only after protein intake (Johansson et al., 1983).

A rather unusual drug-milk interaction concerning the cytostatic drug 6-mercaptopurine and its metabolism *via* the enzyme xanthine oxidase might lead to reduced drug exposure (de Lemos et al., 2007). Due to high concentrations of xanthine oxidase in milk, the co-administration might lead to an increased inactivation of the drug; thus, separation of the timing of 6-mercaptopurine intake and milk was proposed by the authors (de Lemos et al., 2007).

7.3. Ethanol

Ethanol (alcohol) is one of the most widely used legal drugs in the world and therefore, specific interactions with certain drugs can occur. However, it should always be considered that alcohol intake also leads to several changes of human GI physiology and thus, unspecific interactions with drug administration may also occur contribute to the observed effect.

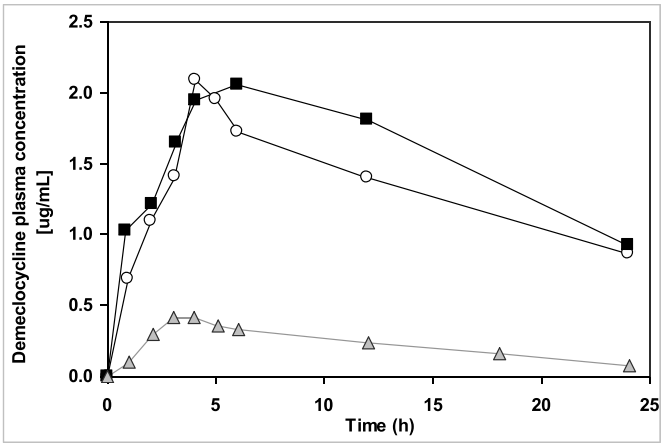

Fig. 11. Mean serum concentrations [μg/mL] after administration of 300 mg demeclocycline with water (○), after a dairy-free meal (■), and after administration with 240 mL of milk (△).
Adapted from Neuvonen, 1976.

7.3.1. Interactions with drugs

The consumption of alcohol can affect the processes of dissolution and absorption, but can also have downstream effects on metabolism and elimination.

When compared with intake with water, the solubility of lipophilic compounds (BCS class II/IV) in luminal fluids can be higher in the presence of ethanol (Amidon et al., 1995; Fagerberg et al., 2015), which leads to a higher concentration gradient between luminal fluid and plasma. As a result, higher plasma concentrations arise due an accelerated and more effective intestinal uptake of the drug.

Different groups have studied the effect of alcohol on the apparent solubility (S_{app}) and the absorption of nine lipophilic compounds in fasted state simulated gastric fluid (FaSSGF) in the presence of 0% and 20% ethanol (pH 2.5). These experiments showed that ethanol causes a significant increase in solubility for non-ionised compounds (up to 14 times higher) and for several weak acids (up to 13 times higher). For the non-ionised compounds such as felodipine or griseofulvin, intestinal absorption was also increased. In case of felodipine, even a two-fold higher intestinal uptake was observed (based on *in silico* compartmental absorption simulations in GI-Sim). In contrast, the increased solubility of the weak acids such as indomethacin or ibuprofen did not result in an increased absorption. This effect was explained by the authors by the high solubility of these compounds in the intestine where weak acids are ionised. Consequently, the drugs were too polar to cross the biological membrane. The solubility of weak bases (dipyridamole, cinnarizine) was not affected by the presence of ethanol since they are completely ionised at the acidic pH of the stomach (Fagerberg et al., 2015).

The same authors also studied the effect of ethanol on the apparent solubility of 22 poorly soluble compounds in fasted state simulated intestinal fluid (FaSSIF), to which they added 0%, 5% and 20% ethanol (pH 6.5). The effect of 5% ethanol on the solubility was negligible for most compounds. In contrast, for 13 of the 22 compounds, a three-fold increase in solubility was observed in the presence of 20% ethanol. The increase in solubility was greater for neutral and acidic compounds compared to the basic compounds which exhibited a more compound-specific influence. The authors indicated that an increase in solubility of compounds in the small intestine is probably temporary because of the

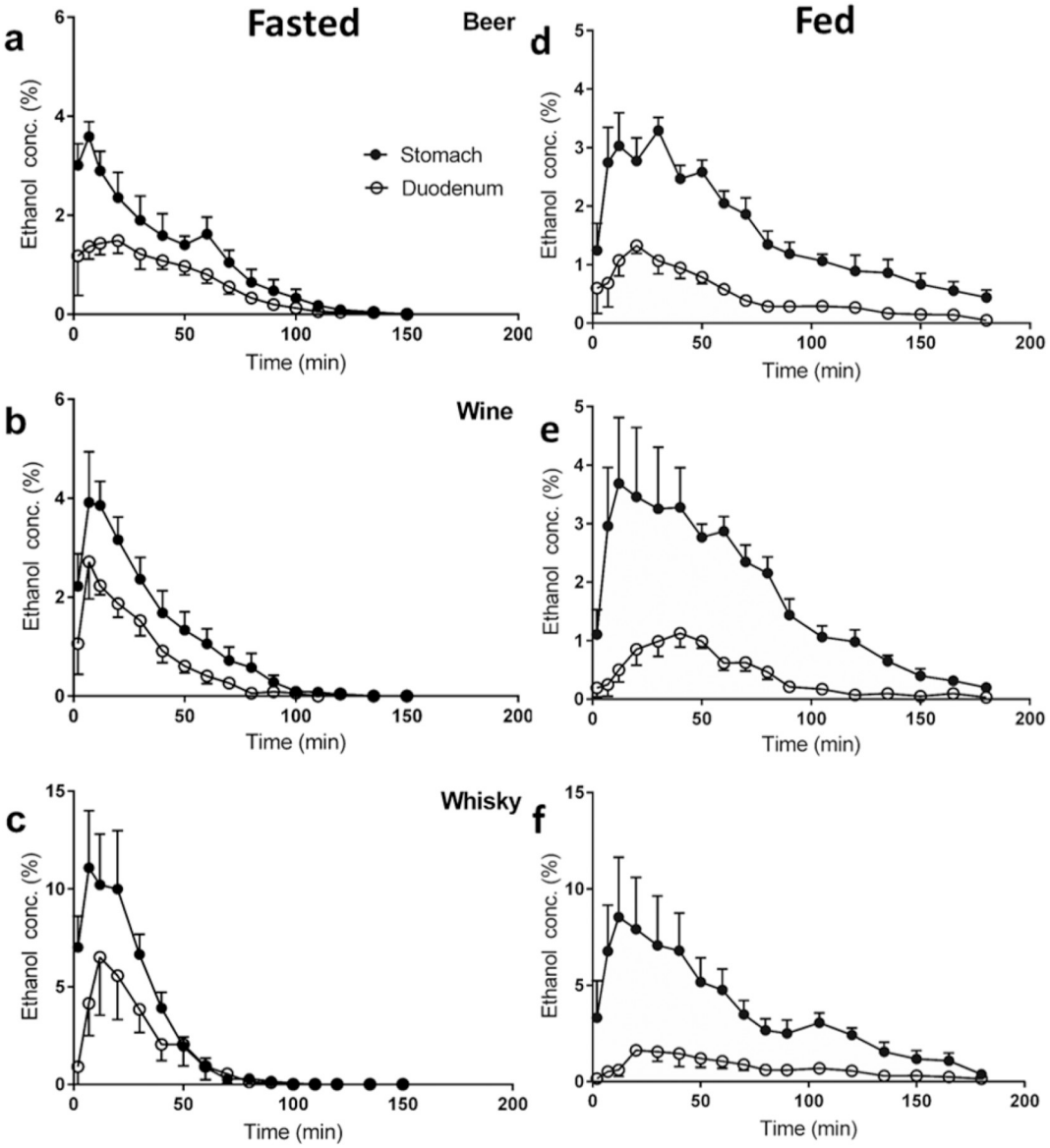

Fig. 12. Alcohol concentration in the stomach and the small intestine after intake of 500 mL of beer, 200 mL of wine and 80 mL of whisky. The different alcoholic drinks were given under fasted (left) and fed (right) conditions.
Adapted from Rubbens et al., 2016.

rapid dilution and absorption of ethanol in the small intestine (Fagerberg et al., 2012). This suggestion is in line with the study by Rubbens et al. who investigated intraluminal ethanol concentrations in fasted and fed healthy volunteers after the consumption of alcohol beverages (Fig. 12) (Rubbens et al., 2016). Following the consumption of beer, wine or whisky, low and rapidly declining intestinal ethanol concentrations were observed. Intraduodenal ethanol concentrations did not reach levels high enough to affect local drug solubility as was previously stated by Fagerberg et al. (Fagerberg et al., 2012).

Ethanol does not only increase the absorption of BCS class II drugs but also those belonging to BCS class I (highly soluble, highly permeable) (Amidon et al., 1995). This was demonstrated by a study by Hayes et al. in seven subjects where the mean plasma C_{max} of diazepam almost doubled after drinking 30 mL of a solution consisting of 50% ethanol and 50% distilled water (Hayes et al., 1977). Fagerberg et al. commented that despite this drug belongs to BCS class I, diazepam does not show a very high solubility in the intestinal media (compared to the administered dose). Therefore, in the presence of alcohol, diazepam may rapidly dissolve and will be quickly absorbed (Fagerberg et al., 2015). This fact is not unimportant since diazepam is often combined with alcohol. The National Institute on Drug Abuse reported 40 years ago that alcohol was the most common cause of emergency admissions by taking drugs. If the cause was the intake of alcohol with drugs, diazepame was the most common drug (Hayes et al., 1977).

After systemic absorption, ethanol is metabolised by alcohol dehydrogenase (ADH) and the CYP2E1, an enzyme that is also responsible for the biotransformation of xenobiotics and fatty acids. Therefore, clinically significant pharmacokinetic interactions with ethanol can also occur when drugs are administered that are substrates of these enzymes. Fortunately, this includes only a limited number of drugs such as paracetamol or theophylline.

7.3.2. Interactions with oral drug products

The drug release profile of certain drug products can be strongly influenced by the co-administration of alcohol. A change in release of the drug in the presence of alcohol can be caused by the drug itself (*e.g.*, solubility changes of the drug or excipients) and/or by the environment in which the drug is released (*e.g.*, stimulation of acid secretion). The extent to which alcohol has an impact on drug release depends on (i) the duration of exposure and (ii) the volume and concentration of alcohol that is administered. The volume and concentration of the present alcohol in the gastrointestinal (GI) tract is mainly determined by the rate of drinking and the nature of the alcoholic beverage (Lennernäs, 2009).

In daily life, alcohol is often combined with drugs and especially with analgesic drugs such as opioids (synergistic effect). Ethanol ensures that patients are less aware of the pain or reduce the stress associated with pain (Johnson et al., 2012). Since the worldwide consumption of analgesics and following a recently reported and possibly fatal interaction of ethanol with Palladone™ (Murray and Wooltorton, 2005), a lot of literature studies focus on the interactions between alcohol and drug products. The incident of Palladone™ has aroused the interest of industry and academia to perform more research related to alcohol and controlled-release (CR) formulations.

Dissolution tests are essential to investigate whether CR preparations are sensitive to ethanol or not. Simultaneous intake with ethanol can influence the bioavailability of the CR formulation and, in a worst-case scenario, alcohol can cause dose dumping (ADD). *In vitro* tests can be useful to predict the effects of certain alcohol-drug product interactions *in vivo* (EMA, 2019b). Human PK studies involving ethanol are rarely performed because of the potential risk for dangerous side effects in patients.

7.4. Functional food

Food is usually considered functional if it affects beneficially one or more target functions in the body, beyond adequate nutritional effects, in the way that is relevant to either an improved state of health and/or reduction of risk of disease ("Scientific Concepts of Functional Foods in Europe Consensus Document", 1999). Functional foods must remain foods and must demonstrate their effects when consumed as a part of normal dietary pattern. A functional food can be; a natural whole food,

Table 2
Major classes of bioactive ingredients in functional foods.
(Abuajah et al., 2015; Hasler, 2002)

Bioactive ingredient	Sources	Health benefit[a]
Probiotics (*Lactobacillus*, *Bifidobacterium*)	Dairy products	Modification of intestinal microflora, Improvement of gastrointestinal health
Polyphenols (*anthocyanidins*, *catechins*, *flavonoids*, *tannins*)	Fruits, vegetables, plant extracts, fortified foods	Antioxidant effect, Anticancer properties, Reduced risk of cardiovascular diseases
Carotenoids (*β-carotene*, *α-carotene*, *lycopene*, *lutein*, *astaxantine*)	Fruits, vegetables, plant extracts, fortified foods	Antioxidant effect, Anticancer effects
Dietary fibre (*soluble*, *insoluble*, *fructo-oligosaccharides*)	Cereals, fruits, vegetables, mushrooms	Anticancer effects, Reduced risk of cardiovascular diseases, Immunomodulatory effects, Cholesterol-lowering effects, Laxative effect, Prebiotic effect
Plant sterols and stanols	Cereals, fortified foods	Cholesterol-lowering effect,
Soy isoflavones (*daidzein*, *genistein*)	Soy-based foods	Reduction of menopause symptoms, Anticancer effects, Reduced risk of cardiovascular diseases
(n-3) fatty acids (*linolenic*, *eicosapentaenoic acid*, *docosahexaenoic acid*)	Fatty fish, fortified foods	Reduced risk of cardiovascular diseases, Reduced triglyceride levels, Improved neurological functions
Conjugated linoleic acid	Meat and dairy products	Anticancer effect (breast cancer)
Glucosinolates and indols	Cruciferous vegetables	Anticancer effect
Organosulfur compounds	Garlic	Immunomodulatory effects, Anticancer effect, Cholesterol-lowering effect

[a] Listed health benefits refer to consummation of listed bioactive ingredients in their natural form as part of regular nutrition and are corroborated by large epidemiological studies or interventional human trials.

a processed food to which a bioactive (*e.g.* minerals and vitamins or other biologically active compounds) has been added (fortified food) and food where the level of naturally occurring bioactive has been modified (Gul et al., 2016). Examples of the major categories of bioactives that can be found in functional foods, their sources and potential health benefits are summarised in Table 2.

Significant efforts are currently being made to reach consensus on scientific concepts of functional foods by using science-based supporting evidence on positive effects on physiological functions, for example, by the FUFOSE concerted action in Europe ("Scientific concepts of functional foods in Europe: Consensus document", 1999). On the other hand, additional actions are needed in order to adequately consider certain safety aspects of functional foods. Major safety issues are related to functional foods containing complex plant extracts and bioactives not normally present in foods or present in significantly lower concentrations. Safety considerations should take into account their acute/chronic toxicity, allergenic potential as well as their potential to increase the risk for food-drug interactions. This chapter will specifically focus on potential functional food-drug interactions. Thereby, we will focus on different classes of bioactive ingredients that are either exclusively present in certain types of functional foods or are present in functional foods in significantly higher amounts in comparison to natural (basic) foods.

7.4.1. Polyphenolic compounds

Polyphenolic compounds are naturally present in a variety of foods, however, their content and diversity are additionally increased in functional foods enriched with plant extracts. They can be added to conventional food to exert its potential health-promoting properties, but can also be used as natural food additives (preservatives and

Table 3
Examples of possible drug interactions with polyphenols/plant extracts used as functional foods.

Plant extract	Major active ingredient/s	Effect/s	Clinical evidence for interactions with	Refs
Green tea (*Camellia sinensis*)	Catechins (epigallocatechin-3-gallate) *etc.*	Antiplatelet activity, Inhibition of drug transporters (OATP1A1), Inhibition of CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4, UGT1A1 and UGT1A4	Caffeine Tizanidine Topical cocaine Nasal cocaine	[a,b]
Grape seed (*Vitis* sp.)	Resveratrol	Inhibition of intestinal CYP3A4, Inhibition of CYP2C9 and CYP2D6, Weak induction of CYP1A2	Not reported	[c]
Turmeric (*Curcuma longa*)	Curcuminoids (*e.g.* curcumin)	Anticoagulant effect, Hypoglycaemic effect, Antiestrogenic effect, Inhibition of CYP1A1, CYP1A2 and CYP3A4, Inhibition of drug transporters (p-gp)	Talinolol	[d,e,f]
Soy (*Glycine max*)	Isoflavons (genistein, daidzein)	Binding to estrogen receptors, Diuretic effect, Hypoglycaemic effect, Inhibition of CYP1A, CYP1B and CYP2 enzymes, Biotransformation (activation) by gastrointestinal microflora	Anti-aromatase agents CYP3A4-inducing drugs: encorafenib, venetoclax, guanfacine	[g,h]
	Tyramine (in fermented soy products)	Metabolization by monamine oxidase (MAO)	MAO inhibitors: phenelzine, tranylcypromine	
Milk thistle (*Silybum marianum*)	Silymarin	Glucose lowering effect in diabetes type 2 patients, Inhibition of UGT, Inhibition of CYP2C9 and CYP3A4	Not reported	[i,j,k,l]
St. John's wort (*Hypericum perforatum*)	Hypericin, hyperforin	Induction of CYP3A4, Induction of CYP1A2, CYP2C9, CYP3A4, Serotonin agonist	Various CYP3A4 substrates, *e.g.* digoxin, nifedipine, talinolol, verapamil, indinavir, ciclosporine, tacrolimus, Amytriptilin CYP2C9 substrates: omeprazole	[j,m,n,o]
Rosemary (*Rosmarinus officinalis*)	Caffeic acid derivatives, rosmarinic acid *etc.*	INHIBITION of platelet aggregation, Induction of CYP1A1 and CYP1A2	Not reported	[p,q]
Thyme (*Thymus vulgaris*)	Thymol, carvacrol, apigenin, luteolin, caffeic acid *etc.*	Inhibition of acetylcholinesterase, Anticoagulant effect	Not reported	[r,s]

[a] Albassam and Markowitz, 2017.
[b] Momo et al., 2004.
[c] Detampel et al., 2012.
[d] Adiwidjaja et al., 2017.
[e] Bahramsoltani et al., 2017.
[f] Lee et al., 2018.
[g] Ronis, 2016.
[h] Shulman et al., 1989.
[i] Di Pierro et al., 2012.
[j] Markowitz, 2003.
[k] Sridar et al., 2004.
[l] Woodbury and Sniecinski, 2016.
[m] Henderson et al., 2002.
[n] Murphy et al., 2005.
[o] Mouly et al., 2017.
[p] Debersac et al., 2001.
[q] Naemura et al., 2008.
[r] Jukic et al., 2007.
[s] Tognolini et al., 2006.

antioxidants). As aforementioned, the complexity of their chemical composition and concentration levels above those normally present in food, increase the possibility of the occurrence of clinically significant functional-food drug interactions. Due to antidiabetic, anticoagulant, hypotensive and other health-promoting properties of polyphenols used as functional food ingredients, pharmacodynamic-type interactions are possible with respective drug classes. However, most of the known interactions involve drug metabolising enzymes (phase I and phase II) and transport proteins. Polyphenols undergo extensive biotransformation and show high affinity for efflux transporters in the gut; therefore, their bioavailability is limited but the potential for pharmacokinetic interactions with drugs at gut level is high (Lambert et al., 2007). Among phase I enzymes, CYP3A4 is known to be the main enzyme involved in intestinal and hepatic metabolism of drugs and data on food-drug interactions involving CYP3A4 are accumulating. In majority of cases, dietary polyphenols inhibit CYP3A4 activity and increase the actual dose of the drug, although quercetin, genistein and certain flavons produce opposite effects by activating the enzyme (Basheer and Kerem, 2015). Soy isoflavons and methoxylated flavonoids (apigenin) are extensively metabolised by CYP1A and 1B isoforms, accounting partially for their anticancer activity but also increasing their drug interaction potential (Lambert et al., 2007). Green tea catechins inhibit the activity of numerous CYP enzymes, but also undergo extensive methylation, glucuronidation and sulfation affecting the activity of phase II enzymes (Albassam and Markowitz, 2017). Significant interactions also occur at the level of transport proteins (ABC) that play a key role in determining drug absorption, elimination as well as drug entry into some pharmacologically important compartments. These transporters interact significantly with dietary flavonoids and in such way affect the bioavailability of anti-cancer agents, cardiac drugs, HIV protease inhibitors, immunosuppressants, steroids and many other drugs (Montanari and Ecker, 2015; Morris and Zhang, 2006). Table 3 lists some examples of polyphenols/plant extracts commonly used in functional food production and their possible interactions with drugs.

7.4.2. Organosulfur compounds

Organosulfur compounds (OSC) are functional compounds mainly present in two groups of vegetables: garlic and onion (that contain *S*-alk(en)yl-L-cysteine sulfoxides) and cabbage, cauliflower and kale (that contain *S*-methyl L-cysteine sulfoxide) (Munday, 2012). Epidemiological studies indicate positive associations of their consumption with decreased risk of cancer and other diseases (Nicastro et al., 2015). Due to antiplatelet, glucose lowering and antihypertensive properties, garlic and onion might enhance (adverse) effects of anticoagulants, antidiabetics and antihypertensive drugs (Eldin et al., 2010; Hou et al., 2015; Hubbard et al., 2006; Woodbury and Sniecinski, 2016; Xiong et al., 2015). Garlic (extracts) inhibits CYP2E1 and induces CYP3A4 and should be used cautiously in patients taking drugs metabolised by these enzymes (paracetamol, chlorzoxazone, and anaesthetics; calcium channel blockers, chemotherapeutic agents, antifungals, glucocorticoids and others) (Gurley et al., 2002; Ho et al., 2010). Evidence from *in vivo* research suggests that broccoli consumption induces CYP1A2 and CYP2A6 enzymes so theoretically, broccoli might increase the metabolism and reduce the levels of certain drugs (Hakooz and Hamdan, 2007).

7.4.3. Non-starchy and sulphated polysaccharides

Non-starchy and sulphated polysaccharides such as fucoidan are present in medicinal mushrooms and some seaweeds. Due to their health-promoting properties, they are increasingly used as novel functional food ingredients, mainly in the form of medicinal mushroom extracts. Given that clinical research shows that taking maitake mushroom polysaccharide can theoretically lower blood glucose, combining maitake mushroom with antidiabetic drugs might increase the risk of hypoglycaemia (Konno et al., 2001). In one case report, maitake mushroom increased the anticoagulant effects of warfarin probably due to polysaccharide constituent of maitake mushroom that caused warfarin dissociation from protein (Hanselin et al., 2010). Since *in vitro* evidence suggests that shiitake mushroom extracts might stimulate immune function, theoretically, taking shiitake mushroom might decrease the effects of immunosuppressive therapy (Dai et al., 2015).

7.4.4. Probiotics

Probiotics are major functional components of yogurt, although nowadays are also present in other types of foods. As mentioned in Section 7.2 dairy products (including yogurt) should not be administrated with certain antibiotics such as ciprofloxacine or tetracycline since they significantly reduce drug absorption (McEvoy, 1998; Neuvonen et al., 1991). This effect is related to divalent cations but not to probiotics. However, certain bacterial strains in yogurt can cause infections in patients taking medications that suppress the immune system (Kalima et al., 1996; Rautio et al., 1999), while concomitant administration of certain antibiotics or antifungals might decrease the effectiveness of probiotics (Lewis and Freedman, 1998; Xiao et al., 2010). However, the potential of probiotics to alter the bioavailability of drugs might be far more significant as obvious from the increasing amount of scientific data stating that drug metabolism by the gut may cause significant alterations in drug-induced pharmacodynamics and toxicities (Noh et al., 2017; Wilson and Nicholson, 2017). Therefore, probiotic-induced changes of the host microbiome must be considered as the potentially important source of clinically significant interactions and should be more closely studied in the future (see Section 3.5).

8. Contribution of the formulation to food-drug interactions

Food intake induces dynamic changes in the composition and volumes of luminal fluids as well as the patterns of GI motility which ultimately affect the behaviour of orally administered drug products. The main changes induced by food consumption are comprehensively described in the earlier sections of this review, however, the main strategies to overcome food effects by formulation will be discussed herein. The consequences of food effects can be complex and problematic, therefore, an orally administered drug product should ideally have the same bioavailability irrespective of the fed or fasted state. Where food effects are identified, there are generally three approaches that drug development or regulatory scientists can implement to mitigate against a food effect including: 1) to consider an alternative lead drug molecule that will not display food effect, however, this method is complicated, expensive and can delay the drug development process; 2) to apply specific instruction for how a drug is taken with regards to food, although this is restrictive and may interfere with the patient's daily life or to; 3) design a formulation which overcomes the overall food effect. When compared with the other available strategies, the latter is considered to be the most practical solution to circumvent potential food effects (O'Shea et al., 2018; Varum et al., 2013).

Food-drug interactions can lead to a positive food effect whereby food consumption increases drug bioavailability such as for poorly soluble drugs that are presented as immediate release formulations. In addition, food can delay the disintegration of immediate release products in the stomach including tablets (Kelly et al., 2003), two-piece capsules (Jones et al., 2012; Tuleu et al., 2007) and one-piece capsules (Wilson and Washington, 1988). The principal cause of positive food effects is the increase in dissolution and solubilisation of poorly water-soluble drugs in the fed state. The release of bile salts and the presence of exogenous solubilising species such as ingested lipids and their digestion products, serve to enhance solubilising capacity of gastrointestinal fluid (O'Shea et al., 2018; Varum et al., 2013).

In order to mitigate positive effects, formulation strategies can be implemented to boost drug bioavailability in the fasted state in order to match that of the fed state, thereby eradicating a food effect. Such approaches include amorphous and solid dispersions, lipid-based formulations and nano-sized preparations (O'Shea et al., 2018).

In other cases, food-drug interactions can contribute to a negative food effect which decrease drug bioavailability. The most common causes of reduced bioavailability in the fed state are the direct physicochemical interactions between drugs (or drug products) and food. One potential cause of this effect is the reduced diffusivity of drug in the viscous postprandial upper GI tract. The increased viscosity can result in either inhibition of disintegration of a formulation which prevent drug release or hinder the diffusion of drug to the absorptive membranes of the GI tract. This can be problematic for poorly permeable drugs, particularly those with narrow absorption windows as by the time viscosity has reduced in the distal gut, the absorption window has been transited and absorption will be reduced. A second direct mechanism by which food can hinder drug absorption is by binding of drug with food components (O'Shea et al., 2018).

To overcome negative food effects, the drug product can be formulated to release further down the GI tract to minimise the interaction of the drug with the ingested meal. Such an approach includes the use of modified release formulations, particularly delayed release (*e.g.* enteric coated) systems. These formulations, however, may also be subject to food effects in relation to delayed gastric emptying and have the potential for dose dumping.

Food-mediated interactions of a modified-release formulation are significantly reduced for multiparticulate systems (Varum et al., 2010). Moreover, the small size and divided nature of multiparticulate formulations reduce the risk of dose dumping. For example, enteric coated erythromycin pellets resulted in lower variability and higher bioavailability when compared with enteric coated tablets following food intake (Graffner et al., 1986). A similar outcome was achieved for the oral bioavailability of acetylsalicylic acid when administered as enteric coated granules which was shown to be less variable and unaffected by the presence of food in contrast to enteric coated tablets (Bogentoft et al., 1978). In general, the greater the size of the formulation, the more prolonged the period of gastric emptying in the fed state and also the greater the variability (Davis et al., 1986).

Adding further to the complication of the presence of food, the timing of the meal further influences the transit of oral modified release formulations. For example, a study which investigated the administration of a multiple-unit formulation 30 min before food consumption showed faster gastric emptying when compared with the fasted state (Digenis et al., 1990). This suggest that food consumption contributes to increase gastric motility and subsequently, gastric emptying. Small intestinal transit is also accelerated following food intake which can further affect oral bioavailability; for instance, erythromycin, which is optimally absorbed in the small intestine, was lower in the fed state in comparison to the fasted (Edelbroek et al., 1993). This was further confirmed by a gamma scintigraphy study which investigated the transit of formulations in the small intestine in three different feeding conditions; 1) under the fasted state (tablet administered on an empty stomach), 2) fed state (tablet administered after food) and 3) pre-feed (tablet administered 45 min before food). Under the pre-feed regimen, small intestinal transit time was significantly shorter (100 min) when compared with the fasted (204 min) or fed conditions (210 min) (Fadda et al., 2009).

As aforementioned, delayed release systems can be used to mitigate a negative food effect. For instance, it has been shown that targeting trientine to the middle or lower part of the small intestine by means of an enteric coating abolished the negative food effects observed when given as an oral solution in the fed state (Tanno et al., 2008). This has been attributed to the delayed gastric emptying of the enteric coated formulation and the distal release of the drug, thus, avoiding physicochemical food-drug interactions. Similarly, when administered as a capsule, the bioavailability of DX-9065 was reduced in the fed state. Designed as a modified release enteric coated tablet, however, oral drug bioavailability was successfully increased 5-fold by limiting interactions with bile salts, negating negative food effects (Fujii et al., 2011). More recently, an enteric coated risedronate product has been reported which offers the possibility of being safely administered with food. Currently registered drug products with risedronate are required to be taken on an empty stomach to prevent the drug from chelating with food components. The reformulated tablet containing the drug and ethylenediaminetetraacetic acid (EDTA) was coated with a layer of an enteric polymer which released its contents in the small intestine, thereby circumventing the segments of the GI tract where food-drug interactions significantly occur. At this level, EDTA can act as a scavenger for food components such as calcium ions which consequently allow the drug to be freely absorbed (Pazianas et al., 2013).

9. Real-life dosing conditions – regulatory considerations

The extent of food-drug interactions may depend on the way in which a drug substance is manufactured into the drug product. Thus, user instructions (warnings or recommendations) in the product information (in Europe: SmPC/PL) can either be drug substance-specific or product-specific. The rationale for the warnings on food-drug interactions in user instructions in the product information can also be quite diverse and may vary from rather strict to soft (Medicines Bank, Netherlands, 2019; Paśko et al., 2017). For example, a well-known and strict warning is that the product should not be used with certain types of food, *e.g.* for the iron supplement ferrous fumarate it is stated that milk, tea or coffee should not be taken within 2–3 h after intake as this reduces absorption. A less strict warning is included for the calcium antagonist nifedipine, where it is stated that the use of grapefruit juice is *discouraged* as concurrent use of nifedipine and grapefruit juice results in an increased plasma concentration and prolonged effect. For levothyroxine, a softer warning is included by stating that the absorption from the intestine *may* decrease by soy and fibre containing food, and that dose adjustments *may* be needed, especially when starting or discontinuing soy containing products (Medicines Bank, Netherlands, 2019). In all cases, the strictness of the advice in the SmPC is dependent on the PK/PD relationship and the clinical consequences with respect to efficacy and safety. It should also be acknowledged that warnings may fail to be included in the user instruction because of lack of data or just because the SmPC/PL is outdated (San Miguel et al., 2005).

The user instruction may also indicate that the product should on purpose be taken with food or drink, which actually implies an instruction. This is commonly done to intentionally alter absorption or to mitigate side effects. For example, non-steroidal anti-inflammatory drugs such as diclofenac or the antibiotic amoxicillin/clavulanic acid should be taken prior or during a meal to reduce the risk for gastric complaints. Acamprosate, a drug used in alcohol treatment therapies, is another drug that should be taken with food (Medicines Bank, Netherlands, 2019). Increasingly, the intake of drugs with antioxidants that are naturally occurring in food is investigated to protect the side effects of mutagenic drugs like cisplatin or methotrexate (Famurewa et al., 2017; Said Salem et al., 2017).

In real world settings, many patients and health-care professionals consider that the lack of a warning or an advice on the joint intake of a drug product with food or drink implies that there is none. They commonly use this understanding to consider that it is no problem to co-administer a drug product with (semi-solid) food or drink on a spoon or to mix the product through the whole meal or a full glass of any drink other than water. Likewise, it is often not considered a problem to modify the product first, *e.g.* crushing tablets or opening capsules. All these methods of administration are commonly adopted to ease or to ensure safe swallowing, *e.g.* in young children, patients who are severely ill, or in patients who are facing cognitive problems like dementia for example. In children, these methods are also commonly used to improve taste, however this reason is less important in (older) adults (Haw and Stubbs, 2010; Stegemann et al., 2012). When product modifications and/or co-administration or mixing with food or drink is no longer possible to ensure easy and safe swallowing, or for ease of work, drug products may also be administered through a feeding tube

(Demirkan et al., 2017). In rare situations, food or drink may also be used to cover the intake of the drugs (Haw and Stubbs, 2010; Kala, 2012).

Patients and health care professionals do not often take into account that mixing should only be used when co-administration is unavoidable, as it runs the risk that the patient will not swallow the whole meal or drink the full glass and thus, not take the full dose. Patients also run a greater risk of developing a resent to the food when the taste of the whole meal is affected rather than one spoonful of food or drink (van Riet-Nales et al., 2015). More importantly, from a regulatory perspective, the lack of an instruction means that the product should be taken on its own or just with some water. This is because the co-administration or mixing implies a direct contact between the drug product and the food, which may either have an effect on the drug substance itself (*e.g.* stability or changes in particle size) or the specific characteristics of the formulation (*e.g.* coating, liposomes *etc.*). For this reason, co-administration is to be preferred over mixing, as the contact time and area significantly increases in case of mixing. The risk of tube blockage should also be considered in cases where food is used to administer a drug product through an enteral feeding tube (EMA, 2019a; Demirkan et al., 2017).

Companies may accept that in real world settings the co-administration of a drug product with food or drink is sometimes unavoidable. As such, pharmaceutical companies should aim to consider the development of new drug products with the co-administration of food in mind, specifically for use in children or the geriatric population (EMA, 2013, 2017). Thus, companies may voluntarily decide to provide a user instruction for an alternative administration approach involving the joint intake of their product with (semi-solid) food or drink. Such instructions on co-administering and mixing of the drug product with food or drink should be clearly differentiated from the standard instruction to take the product on its own or with some water during a meal. For example, the standard instruction for CREON 25.000 capsules indicate that it can be taken during or immediately after any meal. However, the capsules may also be opened to ease swallowing. The capsule content (*i.e.* coated granules) should be then mixed with acidic food (pH $\leq$ 5.5) such as apple sauce, yogurt or fruit juice to not affect the enteric coating. The same instruction applies for many other gastro-resistant formulations if co-administered or mixed with food or drink as there is a need to ensure gastro-resistance (Medicines Bank, Netherlands, 2019).

10. Conclusion

This review has revealed that the co-administration of food or drink can affect drug release (volume and composition of luminal fluids, transit times, motility), absorption (uptake and efflux transporters), distribution (lymphatic drug transport, lipoprotein and plasma protein binding), metabolism and elimination (drug-metabolising enzymes and drug transporters). Moreover, animal studies have suggested that the microbiome can be another integral factor for oral drug bioavailability and pharmacokinetics. With regards to specific food-drug interactions, the effects of grapefruit on drug metabolising enzymes and uptake and efflux membrane transporters; of milk on drug absorption and; of ethanol on drug absorption, distribution, metabolism and elimination are just the tip of the iceberg. Moreover, the administration of functional foods and food supplements can also impact drug activity and thus, there is a need of science-based supporting evidence not only on positive effects and safety, but also on potential food-drug interactions. However, many mechanistic studies are still based on *in vitro* and animal models and *in vivo* studies in humans which confirm whether these food-induced changes are relevant for drug activity are often lacking. To advance the pharmaceutical arena, a better knowledge of the food-induced changes affecting drug activity is required to understand whether the design of a formulation which overcomes the overall food effect could represent a successful strategy for future drug development.

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Conflicts of interest

Diana van Riet-Nales and Marc Maliepaard are experts of the European Medicines Agency (EMA) and Diana van Riet-Nales is a member of the MEB Committee on Clinical Practice.

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