Food for thought: formulating away the food effect- a PEARRL Review

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Abstract

Objectives: Co-ingestion of oral dosage forms with meals can cause substantial changes in the rate and extent of drug absorption relative to the fasted state. Food mediated effects on bioavailability can have significant consequences in drug development, regulatory and clinical settings. To date the primary focus of research and analysis has focused on the ability to mechanistically understand the causes and predict the occurrence of these effects.

Key findings: The current review describes the mechanisms underpinning the occurrence of food effects, sheds new insights on the relative frequency that these effects occur in new medicinal products and describes the various methods by which they can be overcome. Analysis of new oral medicines licensed by either the EMA or FDA since 2010 revealed that over 40% of new medicinal products display significant food effects. Due to altered bioavailability, these medicines are often required to be dosed, rather restrictively, in either the fed or the fasted state, which can hinder clinical usefulness.

Conclusions: There are clinical and commercial advantages to predicting the presence of food effects early in the drug development process, in order to mitigate this risk of variable food effect bioavailability. Formulation approaches aimed at reducing variable food-dependent bioavailability, through the use of bio-enabling formulations, are an essential tool in addressing this challenge and the latest state-of-the-art in this field are summarised here

Key words

Food effect; bioavailability; bio-enabling formulations; food-drug interactions; formulation screening; gastrointestinal physiology

Introduction

The concomitant administration of oral dosage forms with food can have a significant impact on drug pharmacokinetics and bioavailability relative to the fasted state. With oral drug delivery continuing to be the method of choice for drug administration, understanding the effects food has on the biopharmaceutical aspects of drug delivery is key to the drug development process as well as the effective and rational use of medicines in the clinical setting [1, 2]. Oral medicines are generally required to be repeatedly administered, often chronically and in multiple daily dosings, so it is inevitable that drugs will be administered in different prandial states. The understanding of the effects food has on pharmacokinetics is consequently a critical factor in assessing the clinical potential of new medicines and designing a food effect resistant formulation early in drug development can both provide a commercial advantage and prevent costly reformulation later in the product lifecycle [1, 3].

It is just over 40 years since the publication of the first major review focusing on the manner by which food affects drug absorption [4], and the topic has been subject to extensive research and review in the interim [5-9, 3, 10, 11]. Despite the abundance of studies examining the predictability, mechanistic understanding, and ability to overcome the effects of food on bioavailability, a universal approach to quantitatively predict food effect does not exist, nor is it a likely prospect. Significant progress has, however, been made in identifying potential drug candidates and drug products that display food effect bioavailability, understanding the mechanisms by which food effects occurs and developing formulations to overcome this effect.

While there has been comprehensive review and analysis of the mechanisms underlying the food effect, and more recently of current approaches to predict food effect (Pentafragka *et al.*, this issue)[12], to date there has been limited analysis of the relative abundance of medicines which display food effect and the systematic approaches utilised to eliminate food mediated changes in bioavailability. The aims of the current review are, therefore, to briefly summarise the main causes of food mediated changes in bioavailability, discuss the clinical and regulatory impact with regard to the types of and abundance of preparations which display significant food effects and to describe the various formulation approaches currently implemented to overcome the food effect. To our knowledge this is the first review to focus primarily on the use of enabling formulations to overcome

food effects on bioavailability in clinical and pre-clinical studies, while it also provides an updated compilation of recently licensed medicines which demonstrate significant food effect.

Food Effects; causes and clinical consequences

What is a food-effect?

In its simplest terms, food effects on drug absorption are observed when the rate and/or extent of drug bioavailability is altered when a drug or drug product is administered in fed state, compared to the fasted state. The clinical effects and significance of food effects on absorption are generally assessed with regard to the rate and extent of bioavailability – as measured by peak plasma concentrations (C_{max}), time to peak plasma concentration (T_{max}) and the total extent of bioavailability (area under the curve; AUC) [1]. Welling classified food drug interactions into five categories causing [5];

- Reduced extent of bioavailability
- Delayed rate of absorption
- Increased extent of bioavailability
- Accelerated rate of absorption
- No effect

With regard to clinical significance, the most crucial aspect of food effect is generally considered to be the extent of bioavailability change, and the terms 'positive food effect' and 'negative food effect' have been coined to describe either an increase or decrease in the overall extent of bioavailability, respectively[1]. While some variation in bioavailability is tolerated, larger deviations in the fed, relative to the fasted state can have clinical implications. It is, thus, necessary to have some guidance on defining what exactly constitutes a significant food effect. Accordingly, the FDA have provided guidelines on how to design clinical trials to investigate food effects, recommending dosing in both fasted and fed states. The FDA guidance defines that a food-effect is established if the 90% confidence intervals for the ratio of population geometric means, based on log-transformed data, for either $AUC_{0\rightarrow\infty}$ or C_{max} fall outside the 80-125% bioequivalence limits relative to the reference, i.e. the same formulation administered in the fasted stated [13]. The fed state represents dosing post ingestion of a high fat, FDA standard breakfast, containing 800 – 1000 kcal with approximately 50% of total calories coming from fat, to maximise potential for demonstrating a food effect [13].

Figure 1 illustrates the key steps in drug absorption and bioavailability and indicates how food influences these processes, while the underlying mechanisms of these processes are described in subsequent sections of this review.

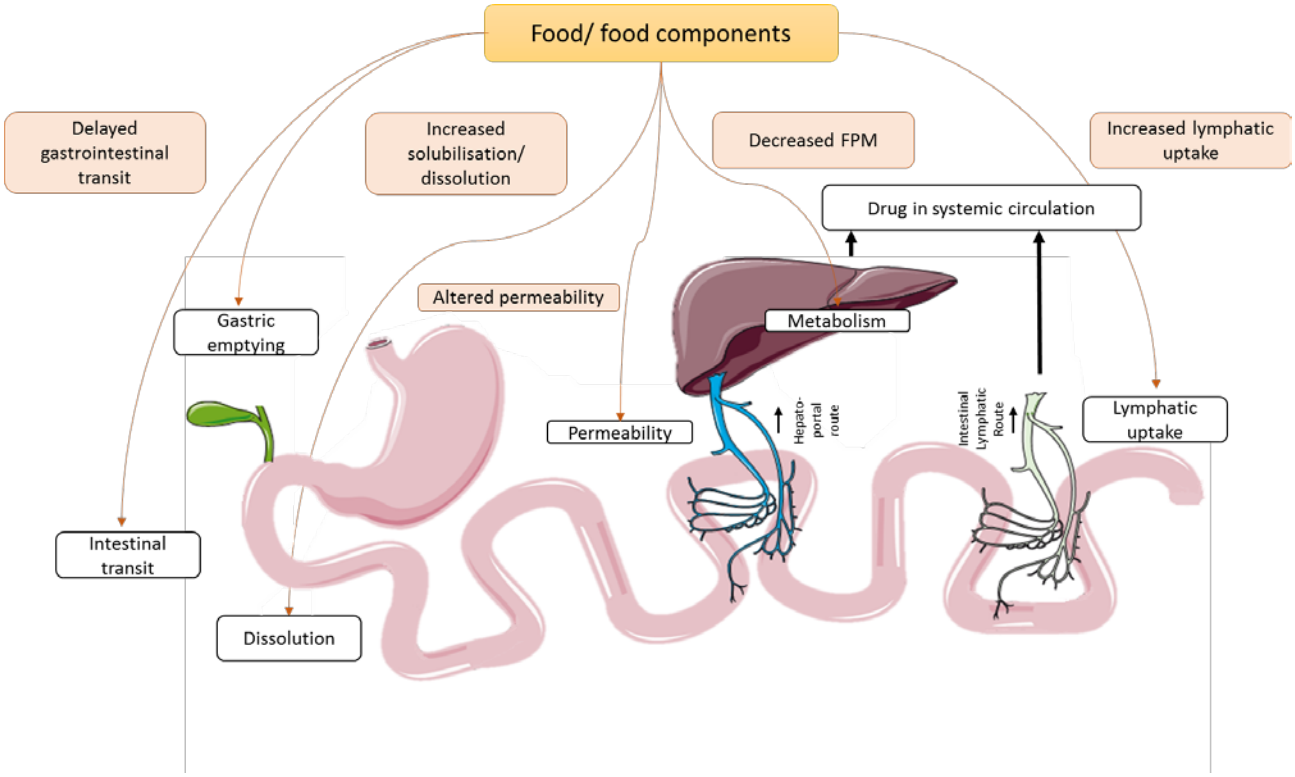

Figure 1 Schematic diagram of critical steps in drug absorption and influence of food and food components; FPM: first pass metabolism

Mechanisms underlying the food effect

Drug absorption via the oral route is a function of the interplay of various complex biopharmaceutical processes, namely (i) drug molecular and physicochemical properties, (ii) formulation characteristics, (iii) the physiological changes of the gastrointestinal tract induced in the fed state and (iv) the physical chemical changes in the composition of the gastrointestinal fluid [1]. The Biopharmaceutical Classification System (BCS) and Biopharmaceutical Drug Disposition Classification system (BDDCS) provide a useful predictor of potential food effects based on drug physicochemical properties, as summarised in figure 2 [14, 15]. The anticipated effects are predicted by the most likely limiting factor for bioavailability, namely solubility or dissolution for BCS/BDDCS class II compounds, permeability for class III compounds, or a combination thereof for BCS class IV compounds. An overall delay in Tmax and reduced Cmax for highly bioavailable compounds can be associated with a delayed gastric emptying [16]. While this tool does not capture all the potential effects of food, it is the most widely utilised simple tool to predict food effect behaviour, and is estimated to be accurate in approximately 70% of cases [17].

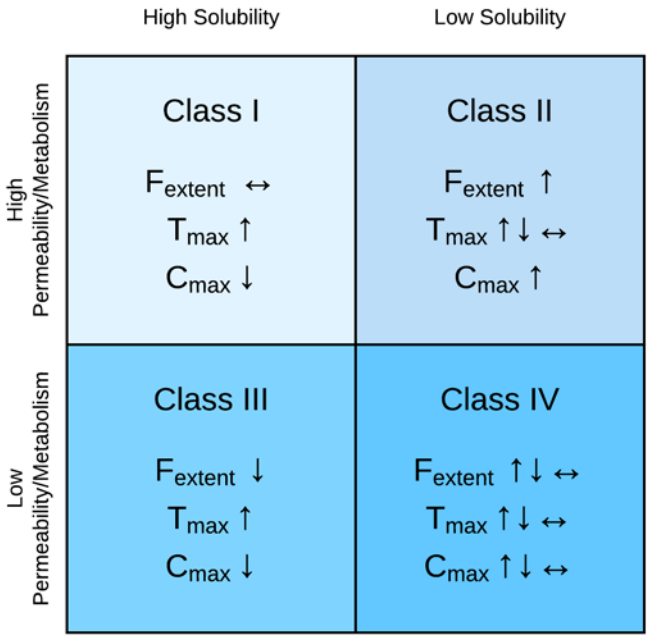

Figure 2 Predicted effect of high fat meals by BCS/BDDCS class. Adapted from Custodio *et al.* (2008)

Drug absorption is inherently variable, owing to both inter- and intra-individual variability in the physiology of the GIT. When considering the gut physiology McConnell *et al.* have stated that there is 'no such thing as an average person'[18], and despite regulatory guidance, equally there is no such thing as a standard meal [13]. The purpose of FDA guidance is to provide a standard for bioavailability and bioequivalence studies, where the likelihood of observing a food effect is maximised. However, this is not always reflective of the fed state for patients, which adds further to the variability and complexity of absorption and drug product performance.

In the fed state the physicochemical composition of the gastrointestinal fluid, including its volume, pH, osmolality, surface tension, hydrodynamics and overall composition change. These changes have been extensively reviewed by Pentafragka *et al.* in the current issue[12]. The reader is directed here for greater detail, specifically with regard to the intraluminal environment after intake of meals similar in composition to that suggested by the FDA and EMA for food effect and fed state bioequivalence studies i.e. a high-fat, high-caloric meal [13, 19]. There are a number of additional factors that may influence GIT absorption from oral dosage forms and the most pertinent aspects are described below, and summarised in figure 3.

Food induced changes on drug absorption

Gastrointestinal fluid composition

With regard to drug absorption of immediate release dosage forms, it is the characteristics of the stomach and upper intestine which are generally most crucial for drug absorption. Relative to the fasted state, the most pertinent changes in the intraluminal environment include the increase in gastric pH to 5 or higher, along with a corresponding increase in buffer capacity[20-22]. The intragastric fluid volume also increases significantly in the fed state, with increases in the presence of dietary lipids and their digestion products along with increased viscosity of the luminal contents[23-26]. The most significant changes in the small intestinal luminal fluid composition is the increase in bile salt concentrations and the presence of lipid digestion products[27, 24, 28-30]. The extensive absorption in the small intestine means that despite the fluid ingested with a meal and significant gastrointestinal secretions, the overall volume of fluid in the small intestine actually decreases in the fed state[23, 25].

Gastrointestinal motility and its impact on transit time of dosage forms

The interplay between GIT motility and intestinal transit of dosage forms can be complex and affected by numerous factors. In the fasted state, emptying of liquid formulations will occur quite rapidly, whereas emptying of solids can be delayed by up to 2 hours [31-34, 10]. In the fed state, liquids and smaller particles (<3-4mm) will empty with food, at a rate controlled by the caloric density of the food, but which is invariably slower than the fasted state [31, 35]. Larger particles (>7mm) can be retained in the fed state, displaying a significant lag time [36]. Fadda *et al.* have estimated the gastric transit of a non-disintegrating tablet in the fasted, fed and pre-fed state with a median (IQR) gastric emptying time of 37 (19-74) minutes, 149 (119-171) minutes and 39 (25-169) minutes in each state, respectively [37]. Small intestinal transit time appears to be remarkably independent of fed state, and mean values are consistently reported to be 3-4 hours [38, 37]. However, this mean value masks considerable inter- and intra-individual variation.

Metabolism and transporter effects

Both dietary components, including monoglycerides, and bile salts have been shown to have an inhibitory effect on both uptake and efflux transporters *in vitro,* regularly leading to suggestions that high fat meals may lead to inhibition of intestinal enzymes, as well as efflux and uptake transporters[16, 39]. While many enteric enzymes are responsible for drug metabolism, it is the cytochrome P450 (CYP450) family, in particular the CYP3A and CYP2C subfamilies, which are most widely implicated in such interactions as they are the most abundant family and play a crucial role in bioavailability of a wide range of molecules [40, 39].The most commonly implicated transporters are

the organic anion transporter polypeptides (OATP) and P-glycoprotein (p-GP) efflux transporters [41, 42, 16, 43, 39]. However, despite the widely cited assertion that food, generally, inhibits intestinal transporter and enzyme function, to date the clinically important interactions of note regarding enzyme and/or transporter inhibition involve specific food components. Most notable among these is the inhibition of CYP450 enzymes by grapefruit juice, while other foods rich in phytochemicals, such as fruits, herbs and red wine have also been implicated [42, 44, 16, 39]. This constitutes a specific, and well characterised phenomenon involving an individual food component, which is not what is typically considered when discussing food effect, which usually refers to the effects of meals generally rather than the impact of individual components.

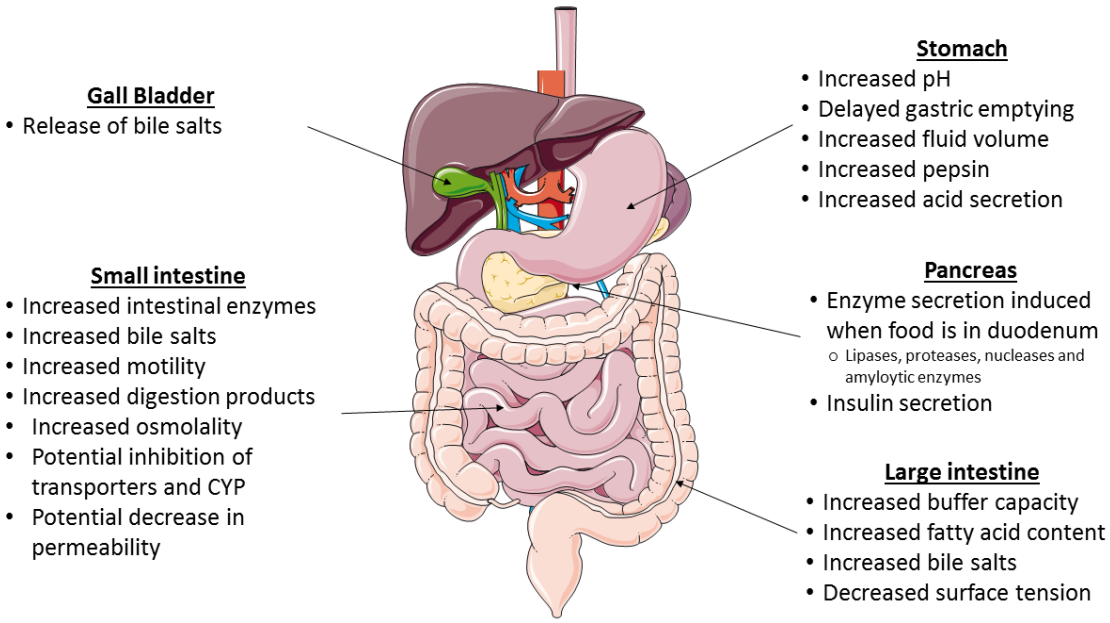

Figure 3 Summary of human physiological changes in the fed state (adapted from Varum *et al.* [3])

Mechanisms of food effect

As has been described above, food has a complex and significant effect on the physiology of the gastrointestinal tract and the physicochemical properties of gastrointestinal fluid, which in turn can have a significant effect on drug absorption. These effects are dependent on both the physicochemical properties of the drug, principally solubility, pKa and LogP/logD, and formulation characteristics, including release and disintegration of solid dosage forms [45, 46, 8]. For the purposes of this review, the focus will predominantly be on immediate release and bio-enabling formulations, the mechanisms by which food causes these changes in bioavailability are discussed here and summarised in table 1. The effect of food on modified release dosage forms can be significantly different to that of immediate release preparations, notably with regard to disintegration and release and the potential for dose dumping. The effects of food on modified release formulations have recently been reviewed by Varum *et al.* (2013)[3], Yasuji *et al.* (2012)[9] and Abuhelwa *et al.* (2017)[10].

Positive food effects

The principal cause of positive food effects is the increase in dissolution and solubilisation of poorly water soluble drugs (PWSD) 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 [28, 47, 30, 48-50]. For drugs which are dissolution rate, rather than solubility limited, the increased gastric residence time also can improve bioavailability, while the increase in gastric pH may result in improved solubility and dissolution of weak acids. In practical terms, it is difficult to isolate the impact of any one of these factors, which work synergistically to increase solubility and dissolution of PWSD.

The inhibition of intestinal transporters can play a role in enhancing bioavailability of certain drugs. Wu and Benet have demonstrated that for BCS class II compounds efflux transporters predominate, and that for these compounds transporter inhibition is likely to improve bioavailability [51, 15, 16, 52].

Reduction in first pass metabolism in the fed state can also lead to increases in bioavailability and this can occur through numerous mechanisms including altered blood flow, increased lymphatic uptake and reduced enteric metabolism. Food intake is associated with an increase in splanchnic blood flow by as much as 60% depending on the volume and nature of the meal. This allows drug to bypass the liver, while the increase in hepatic blood flow may also reduce the first pass effect for drugs which display low to moderate clearance [53-55]. Co-administering lipophilic drugs with food allows efficient absorption of these molecules with dietary lipids, via lipid absorption pathways, while particularly lipophilic drugs (logP>5) can also show significant lymphatic uptake [56, 30, 57]. This

can increase the systemic absorption by both increasing the fraction escaping the gastrointestinal lumen and reducing the first pass effect.

The inhibitory effect of meal components on CYP3A4 is also a significant contributor to the reduction of enteric drug metabolism and increased bioavailability in the fed state. Inhibition of CYP3A metabolism by grapefruit juice has been widely associated with increases in bioavailability and subsequent increases in adverse events for a wide range of pharmacologically diverse compounds [40, 16]. While both dietary monoglycerides and bile salts have been demonstrated to have an inhibitory effect on enzymatic activity *in vitro*, and it has regularly been asserted that this inhibition leads to clinically relevant enzyme inhibition by high fat meals such interactions have not yet been extensively characterised *in vivo* [42, 16, 39, 3].

Negative food effects

Negative food effects encompass both reduced and delayed drug absorption. With regard to delayed absorption in the fed state, this often occurs for immediate release preparations without a corresponding reduction in overall bioavailability. The main mechanism by which this occurs is delayed gastric transit in the fed state. This manifests itself as a prolonged T_{max}, which may or may not be accompanied by a reduction in C_{max} or a significant lag time. For medicines which are chronically dosed and where overall exposure, rather than peak plasma levels, mediate pharmacodynamic action, this is unlikely to result in clinically meaningful effects [7].

Decreased absorption in the fed state results in a reduction in AUC, along with a reduction in C_{max}, and can lead to sub-therapeutic plasma levels and loss of efficacy. The most common causes of reduced bioavailability in the fed state are 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 GIT. The increased viscosity can result in either inhibition of disintegration of a dosage form, preventing drug release, or hindering diffusion of drug to the absorptive membranes of the GIT [58-61]. 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 [62-64]. A second direct mechanism by which food can hinder drug absorption is by binding of drug with food components [65, 7]. This is prevalent in the case of polyvalent cations, which are abundant in dairy products [66-68, 7, 69].

Physiological factors can also play a role in negative food effects, especially in the case of drugs displaying instability and possibly acid lability in the GIT. Prolonged gastric residence can result in increased degradation of these molecules, though in the case of acid labile drugs the effect may be

somewhat mitigated by the increase in gastric pH [70]. Food can also result in alterations in absorption through altering both passive permeability and active transport. The presence of increased lipids and bile salts in the fed state can result in micellar entrapment, with the consequent decrease in free drug causing a reduction in permeability [45, 71-73, 49]. While for poorly soluble drugs, this is generally more than compensated for by increases in solubility, highly soluble and poorly permeable compounds may display reduced absorption in this case.

The inhibition of uptake transporters may also result in negative food effects. For poorly permeable drugs, the inhibition of these transporters may result in a reduction in absorption, as these compounds are often reliant on the action of uptake transporters. The general inhibition of intestinal transporters observed in the fed state is therefore likely to reduce the bioavailability of BCS class III compounds. Care is needed, however, when applying this rule of thumb, as class III compounds may be candidates for both uptake and efflux transporters and the relative inhibition of either uptake or efflux transporters, or the extent to which a specific molecule will be a substrate for each particular class can determine the overall effect of bioavailability [16]. Fexofenadine is a BCS class III compound which displays a negative food effect, as predicted by its BDDCS class. Fexofenadine is a substrate for both OATP uptake transporters and P-gp efflux transporters. In the fed state, principally when taken with fruit juices, the inhibition of OATP transporters predominates and absorption is decreased [74-77]. Fruit juice related inhibition of OATP uptake has also been implicated in a reduction in AUC for other drugs, including aliskiren and celiprolol[74, 78-80]. The inhibition of PAT1 has been suggested as a possible reason for the reduced rate of absorption of vigabatrin, though this is most likely due to a reduction in the rate of gastric emptying [81, 82].

The events described here are summarised and examples of drugs affected by the various mechanisms are provided in table 1.

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265 **Table 1 Summary of physiological mechanisms and biopharmaceutical aspects underpinning the food effect**

Physiological mechanism	Biopharmaceutical aspects	Effect on Drug exposure	Example(s)
Increased pH in stomach	Solubility and dissolution of ionisable compounds can be altered	Increases AUC and Cmax for weak acids	Cefuroxime
		Decreases AUC and Cmax for weak bases	Dipyridamole, indinavir
Increased concentration of solubilising species e.g. bile salts, lipid digestion products	Solubilisation of poorly water soluble drugs increases	Increases AUC and Cmax	Fenofibrate Alectinib Danazol
Increased splanchnic blood flow	Saturation of liver enzymes and avoidance of FPM	Increases AUC and Cmax	Propranolol Tacrine Dronedarone
Inhibition of gastrointestinal Cytochrome P450 – e.g. with Grapefruit juice	Fraction of drug escaping gut metabolism increases	Increases AUC and Cmax	Felodipine Ciclosporin Atorvastatin
Inhibition of intestinal absorptive and efflux transporters	Fraction of drug subject to either absorptive or efflux transport is reduced	Increases AUC and Cmax for drugs subject to efflux	Ganciclovir
		Decreases AUC and Cmax for drugs which require uptake transporters	Fexofenadine Talinolol

Delayed gastric emptying	Presence of food in stomach delays transit of drug to small intestine	Increases T_{max}, can decrease C_{max}, may cause T_{lag}	Widespread NSAIDs Paracetamol
Increase in viscosity of intestinal fluid	Reduction in water diffusivity, increase in luminal viscosity, slower water penetration of dosage form, increased disintegration time	Increases T_{max}, may reduce C_{max} and F, may cause T_{lag}	Chlorothiazide, Metformin

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Clinical significance

Most medicines contain instructions to take the medication with a glass of water and often gives specific instructions to either take with food, occasionally specifying the size or content of the meal, or in the fasted state. These recommendations are generally designed either to improve safety and tolerability or to maximise the oral absorption. For example, it is recommended to take Fampyra® (fampridine) without food in order to reduce the risk of adverse events as 'there is a clear relationship between C_{max} and dose related adverse reactions', and taking Fampyra® with food is associated a 15-23% increase in C_{max}[83]. Similarly, the reduction in C_{max} of trifluridine observed in the fed state when taking Lonsurf® may prevent a reduction in neutrophils[84]. Conversely, it is recommended to take both Orkambi® and Kalydeco® with fat containing meals to improve bioavailability and clinical efficacy, as there a 2-4 fold increase in exposure of both lumacaftor and ivacaftor are anticipated when these medicines are administered with fat containing food[85, 86]. Other considerations may include the slower rate of absorption widely observed in the fed state. While there is no overall effect on bioavailability, the orexin receptor antagonist suvorexant (Belsomra®) should not be administered with or soon after a meal, as this may delay sleep onset[87].

However, occasionally there may be contradictory advice or a lack of evidence for justifying these recommendations and occasionally the justification can seem counter-intuitive. For example, it is often recommended to take non-steroidal anti-inflammatory drugs (NSAIDs) with food, with the justification that this can reduce the incidence of gastric side effects, though the extent to which this is effective is questionable. Rainsford and Bjarnason (2011) have stated that 'there are no specifically claimed benefits from these recommendations and their origins have not been made clear', while Moore *et al.* (2015) have said that the evidence that taking NSAIDs with food achieves its objectives is non-existent[88, 89]. Taking NSAIDs with food has been shown to delay T_{max} and reduce C_{max} with no overall effect on bioavailability. Considering that early, high plasma drug concentrations produce better and longer lasting analgesia in acute pain, and reduce the frequency of re-medication, it appears that the recommendation to take NSAIDs with food is misguided [90, 89].

Another implication of significant food effect is the potential implications for the clinically efficacy. Ziprasidone (Geodon®) is an orally active atypical antipsychotic used in the treatment of bipolar affective disorder, which displays non-linear pharmacokinetics in the fasted state, while its absorption is approximately doubled by taking with a meal containing at least 500 kcal. Despite the significant food effect observed and label instructions to take Geodon® with food, about 40% of patients do not consistently take the medication with sufficient food and physicians have suggested that it is less effective in patients displaying poor compliance to the dose instructions [91].

The impact of food on drug bioavailability is pertinent for new molecularly targeted therapies in oncology, particularly in the case of the kinase inhibitors [92]. While FDA drug label instructions are generally designed to maximise the bioavailability of the drug, there is a distinct reversal of this situation for oncological preparations, where there is a noticeable trend towards label instructions to take medication in the fasted state despite significant increases in bioavailability in the fed state [93]. This appears to run contrary to established understanding of basic biopharmaceutical principles, which would suggest that bioavailability may be enhanced, while variability can be reduced by co-administering these drugs in the fed state [94]. This has resulted in suggestions of wastefulness, with some clinicians proposing that by ignoring the label recommendations and administering some of these antineoplastic agents with food that significant savings may be made such as $1,700 per month in the case of lapatinib or $3,750 per month in the case of abiraterone acetate [95, 96]. While the case for taking these medicines with food in an off-label manner seems to stand to reason, other factors are important and warrant consideration, not least of which is conditions under which the drug product is licensed. While food effect studies are most often carried out as single dose studies in healthy subjects, the pivotal phase 3 clinical studies, which establish safety and efficacy in patients, may have been initiated in different prandial conditions, leading to a licensed dosing recommendation which reflects that of the relevant clinical study [97, 98]. Dosing in differing prandial conditions runs to that recommended in the drug product label constitutes off-label administration, and risks administration under conditions which have not definitively been demonstrated as safe and effective, while patient adherence to label recommendations is a major concern for oncologists and their ability to manage dosage regimens [99, 98]. The role of inter- and intra-individual variation, regarding meal composition and timing of taking medication with food is also a pertinent consideration [100, 98]. For example, while lapatinib exposure can be increased greater than four-fold when taken with a high fat meal relative to the fasted state, this increase is only two fold when administered with a low fat meal. Considering the high fat and caloric content of the FDA high fat breakfast, it is not realistic to replicate the controlled environment of a food effect trial in the clinical setting, and variations in meal composition from day to day can result in large intra-individual variation [101, 102]. In these cases it may be more reproducible, easily understood and easier to promote patient and clinician adherence where medicines are dosed in the fasted state [97].

In cases where a specific type of meal is explicitly detailed, this can add further to the complexity. With regard to the multi-kinase inhibitor regorafenib (Stivarga®), the type of meal is particularly important, not only for the magnitude but, in fact, for the direction of the food effect. A significant increase in bioavailability was observed with a low fat breakfast, while a high fat meal causes a reduction in bioavailability with the resultant recommendation to ‘take Stivarga® with food (a low-

fat breakfast)' [84]. Specifying a particular meal further adds to the risk associated with clinical use of medicines which display significant food mediated alterations in bioavailability, and risks reducing compliance with dosage regimens. It must be acknowledged that, with regard to oncological products, there may be specific challenges for fed state administration when considering the side effect profiles, such as nausea and vomiting, along with reduced appetite of patients undergoing certain chemotherapeutic regimens. While the debate continues as to whether these medications are best administered in the fed or fasted state, one thing which is abundantly clear is that a method of delivering these drugs in a reproducible, bio-enhanced manner, independent of prandial state would be advantageous.

Overall, establishing the clinical implications of food effect can be difficult, from the point of view of development scientists, clinicians and, indeed, regulators. The FDA bioequivalence criteria are deliberately conservative, ensuring maximal opportunity to observe a food effect, and do not take into account the variability and therapeutic window of the drug being assessed. A modest increase or decrease in bioavailability in the fed state will mean that bioequivalence is not demonstrated, however, if this drug displays large variability in bioavailability and/or possesses a wide therapeutic window, a modest change in variability, such as the 30% increase in exposure observed for gefitinib, is unlikely to be clinically significant [98]. This is notable among some of the recently licensed polymerase and protease inhibitors licensed in the treatment of the hepatitis C virus (HCV), in both individual and combination products, including Zepatier® (elbasvir and grazoprevir), Epclusa® (sofosbuvir and velpatasvir) and Daklinza® (daclatasvir). These products all display modest variations in bioavailability in the fed compared to the fasted state, though these minor changes are not deemed clinically relevant, allowing dosing independent of meal intake (table 2).

Another factor to consider is that while food effect studies are most often single dose studies, often this effect is lessened with multiple dosing, where variability in the patient population pharmacokinetics and the therapeutic window of the drug in question are important considerations Such an example is that of Syndros® (dronabinol) where, despite a 2.5 fold, increase in exposure in a single dose fed state pharmacokinetic study, only the first dose is recommended to be taken with food, with subsequent dosing taken without regard to meals (table 2).

Yan *et al.* have recently identified numerous cases where there are label differences with regard to food effect between the US product information (PI) and European summary of product characteristics (SPC) [11]. This demonstrates the difficulties in interpretation of food effect data, which may be subjective and not entirely dependent on pharmacokinetic considerations, but also on the clinical pharmacodynamic response. It is also interesting to note that there does not appear to

be a consistent trend in these differences and of the products they identified, two-thirds displayed significant pharmacokinetic food effects. In the case of the anticoagulant Xarelto® (rivaroxaban), the clinical recommendation in fact varies between product strength, where the 10mg and 15mg preparations can be taken with or without a meal, while the 20mg strength should be taken with a meal[103]. It is easy to envisage difficulties for clinicians in advising patients where dosing instructions vary for the same products between jurisdictions, but also between dose strengths.

Table 2 provides a summary of the food effects of newly licensed drugs or formulations approved in the US and/or EU over the last seven years which have, demonstrated significant food effect, or have been designated with a label restriction with regard to the administration of drug with regard to food. A food effect was considered significant if the ratio of AUC and/or C_{max} in the fed and fasted states fell outside 80-125%. We have also included products with a specific label claim regarding dosing with food. In cases where it was stated that a product showed no change or a non-significant change in either AUC or C_{max} in the fed or fasted state, but no values or ratios were obtained, a value of 1 was assigned.

Interestingly, our estimates have suggested that approximately 40% (67 of 157 products identified; 42.68%) of medicines licensed by the EMA and FDA since January 1st 2010 display a significant food effect or have been licensed with a label restriction with regard to dosing with or without food. Included in this analysis were new chemical entities, new combination products and previously marketed active pharmaceutical ingredients which have been reformulated. Excluded from our analysis were generic medicines/ abbreviated new drug applications (ANDAs), parenteral, topical, transdermal and other non-oral preparations (including buccal and sublingual preparations and orally disintegrating tablets), extended/ controlled release preparations and oral medicines designed for local administration within the GIT, i.e. those not subject to appreciable levels of absorption. In a competitive market place, the ability to take a medicine without regard to the timing of meals presents a clear commercial advantage for developing dosage forms that can be administered independent of food [104].

393 **Table 2 Recently licenced medicines displaying significant food effect and/or food specific dosage instructions**
394 **Data obtained from FDA Drug Label (from Drugs@FDA database) or European Summary of Pharmaceutical Characteristics (SPC) unless otherwise stated**

Year licensed	Drug Name	Commercial Name	Clinical Recommendation regarding timing of food	Food Effect	AUC_{Fed}/ AUC_{Fasted}	$Cmax_{Fed}$/ $Cmax_{Fasted}$
2017	Spironalactone	Carospir®	CAROSPIR can be taken with or without food, but should be taken consistently with respect to food	Positive	1.9	-
2017	Glecarprevir Pibrentasvir	Mavyret®	Take orally once daily with food	Positive	1.83-2.63[a] 1.4-1.53[a]	-
2017	Sofosbuvir Velpatasvir Voxilaprevir	Vosevi®	Taken orally once daily with food	Positive	1.64-2.44[b] 1.4-2.66[b] 2.12-5.35[b]	-
2017	Deutetrabenazine	Austedo®	Administer with food	Positive	1[c]	1.5
2017	Betrixaban	Bevyxxa®	Take at the same time each day with food	Negative	0.39[d] 0.52[e]	0.3[d] 0.5[e]
2017	Telotristat ethyl	Xermelo®	Take with food	Positive	3.64[f] 1.33[g]	2.12[f] 1.47[g]
2016	Tenofovir alafenamide	Vemlidy®	Take with food	Positive	1.65	-
2016	Cabozatinib	Cabometyx®	Take at least 2 hours before and at least one hour after food	Positive	1.57	1.41
2016	Elbasvir Grazoprevir	Zepatier®	Taken with or without food	Neutral; Elbasavir Positive; Grazoprevir	0.89 1.5	0.85 2.8
2016	Migalastat hydrochloride	Galafold®	Take on an empty stomach, at least 2 hours before or after food intake	Negative	0.6	-
2016	Dronabinol	Syndros®	Because food delays the absorption of SYNDROS, administer the first dose on an empty stomach at least 30 minutes before eating. Subsequent doses can be taken without regard to meals.	Positive	2.5	0.8
2016	Emtricitabine Rilpivirine	Odefsey®	Take with a meal	Positive	Emtricitabine 0.91[h], 0.88[e]	-

	Tenofovir alafenamide				Rilpivirine 1.13[h], 1.72[e] Tenofovir alafenamide 1.45[h], 1.53[e]	
2016	Rucaparib	Rubraca®	Take with or without food	Positive	1.38	1.2
2016	Sofosbuvir Velpatasvir	Epclusa®	Take with or without food	Positive; sofosbuvir Positive; velpatasvir	1.6[h] 1.78[e] 1.21[h] 1.34[e]	- -
2016	Venetoclax	Venclexta®	Take with a meal and water	Positive	3.4[d] 5.1[e]	-
2015	Elvitegravir Cobicistat Emtricitbine Tenofovir alafenamide	Genvoya®	Take Once Daily with Food	Positive	Elvitegravir 1.34[d] 1.87[e]	-
2015	Alectinib	Alecensa®	Administer with food	Positive	3.1	-
2015	Daclatasvir	Daklinza®	With or without food, with sofosbuvir	Negative	0.77	0.72
2015	Eluxadoline	Viberzi®	Taken twice daily with food	Negative	0.4	0.5
2015	Flibanserin	Addyi®	No instructions with regard to food intake	Positive	1.18[d] 1.43[h] 1.56[e]	1.02[d] 1.13[h] 1.15[e]
2015	Idebenone	Raxone®	Administer with food	Positive	5-7	-
2015	Ivabradine	Corlanor®/ Procoralan®	Take with meals	Positive	1.2-1.4	-
2015	Ixazomib	Ninlaro®	Taken at least one hour before or 2 hours after food	Negative	0.72	0.31
2015	lumacaftor ivacaftor	Orkambi®	Take with fat containing food	Positve; Lumacaftor Positive; Ivacaftor	2 3	- -
2015	Palbociclib	Ibrance®	Take with food	Positive	1.12[d] 1.13[h]	1.27[d] 1.24[h]

					1.21[e]	1.38[e]
2015	Sonidegib	Odomzo®	Take on an empty stomach	Positive	7.4-7.8	7.4-7.8
2015	Tasimelteon	Hetlioz®	Taken without food	Negative	-	0.56
2015	Trifluridine Tipiracil	Lonsurf®	Within One hour after completion of meal	Negative	1[c]	0.6
			Take with food, as decrease in Trifluridine C_{max} can prevent decrease in neutrophils	Negative	0.6	0.6
2014	Ceritinib	Zykadia®	Administer ZYKADIA on an empty stomach (i.e., do not administer within 2 hours of a meal)	Positive	1.58[d] 1.73[e]	1.43[d] 1.41[e]
2014	Delamanid	Deltyba®	Delamanid should be taken with food	Positve	2.7	-
2014	Droxidopa	Northera®	Take consistently with or without food	Negative	0.8	0.65
2014	Idelalisib	Zydelig®	Zydelig can be taken with or without food	Positive	1.4	-
2014	Ledipasvir	Harvoni®	Taken daily with or without food	None; ledipasvir	1[c]	1[c]
	Sofosbuvir			Positive; sofosbuvir	2	1[c]
2014	Naloxegol	Movantik®	Take on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal	Positive	1.45	1.3
2014	Nintedanib	Ofev®	Take with food	Positive	1.2	-
2014	Pirfenidone	Esbriet®	Three times daily taken with food.	Negative	0.84	0.51
2014	Suvorexant	Belsomra®	Suvorexant may be taken with or without food; however for faster sleep onset, suvorexant should not be administered with or soon after a meal	None	1[c]	1[c]
2014	Tasimelteon	Hetlioz®	Take without food	Negative	-	0.56
2013	Afatinib	Gilotrif®	Take at least 1 hour before or 2 hours after a meal	Negative	0.61	0.5
2013	Dabrafenib	Tafinlar®	Taken at least 1 hour before or at least 2 hours after a meal	Negative	0.69	0.49
2013	Dimethyl fumarate	Tecfidera®	Take TECFIDERA with or without food	Negative	1[c]	0.6

2013	Dolutegravir	Tivicay®	May be taken without regard to meals	Positive	1.33[d] 1.41[h] 1.66[e]	1.46[d] 1.52[h] 1.67[e]
2013	Obrutinib	Imbruvica®	No instructions with regard to food intake	Positive	2	-
2013	Nalmefene hydrochloride dihydrate	Selincro®	Selincro can be taken with or without food	Positive	1.3	1.5
2013	Ospemifene	Osphena®	One tablet taken orally once daily with food	Positive	1.7	2.3
2013	Simeprevir	Olysio®	One 150 mg capsule taken once daily with food	Positive	1.69[e]	-
2013	Trametinib	Mekinist®	Take at least 1 hour before or at least 2 hours after a meal	Negative	0.76	0.3
2012	Bedaquiline	Sirturo®	Bedaquiline should be taken with food to enhance its oral bioavailability	Positive	2	-
2012	Bosutinib	Bosulif®	Taken once daily with food.	Positive	1.7	1.8
2012	Cabozantinib	Cometriq®	Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking COMETRIQ.	Positive	1.57	1.41
2012	Elvitegravir Cobicistat Emtricitabine Tenofovir disoproxil fumarate	Stribild®	The recommended dose of STRIBILD is one tablet taken orally once daily with food	Positive Neutral Neutral Positive	1.34[d] 1.87[e] 1[c] 1[c] 1.24[d] 1.23[e]	- - - -
2012	Ivacaftor	Kalydeco®	Taken orally every 12 hours with fat-containing food	Positive	2 to 4	-
2012	Mirabegron	Myrbetriq®/ Betmiga®	Taken once daily with or without food	Negative	0.49[d] 0.83[e]	0.25[d] 0.55[e]
2012	Regorafenib	Stivarga®	Take Stivarga with food (a low-fat breakfast)	Positive	1.48[e] 0.8[e,g] 0.49[e,g] 1.36[d]	-

					1.4[d,g] 1.23[d,g]	
2012	Isotretinoin	Absorica®/ Epuris®	Recommended dosage of 0.5 to 1 mg/kg/day given in two divided doses without regards to meals for 15 to 20 weeks	Positive	1.5	1.26
2011	Abiraterone acetate	Zytiga®	ZYTIGA must be taken on an empty stomach	Positive	5[d] 10[e]	7[d] 17[e]
2011	Boceprevir	Victrelis®	800 mg administered orally three times daily (every 7 - 9 hours) with food (a meal or light snack).	Positive	1.65	-
2011	Gabapentin enacarbil	Horizant®	Once daily taken with food at about 5 PM	Positive	1.24[d] 1.34[h] 1.44[e]	-
2011	Piperaquine tetraphosphate Artenimol	Eurartesim®	Eurartesim should be administered with water no less than 3 hours after the last food intake, and no food should be taken within 3 hours after each dose	Positive	Piperaquine; 3 Artenimol; 1.43	-
2011	Rilpivirine hydrochloride	Edurant®	Taken once daily with a meal	Positive	1.666667	-
2011	Rivaroxaban	Xarelto®	10mg and 15mg; With or without food 20mg; Take with food	10mg and 15mg; Neutral 20mg Positive	1[c] (10mg) 1.39 (20mg)	-
2011	Telaprevir	Incivek®	INCIVEK tablets is 750 mg (two 375-mg tablets) taken orally 3 times a day (7-9 hours apart) with food (not low fat)	Positive	2.17[d] 3.37[h] 4.3[e]	-
2011	Vemurafenib	Zelboraf®	Take with or without a meal	Positive	4.6-5.1	2.5
2011	Vilazodone hydrochloride	Viibryd®	VIIBRYD should be taken with food.	Positive	1.64 - 1.85	2.47 - 2.6
2010	Dronedarone	Multaq®	Take twice a day with morning and evening meals	Positive	3.75	-
2010	Fampridine	Fampyra®	Since there is a clear relationship between Cmax and dose related adverse reactions,	Positive	0.93-0.98	1.15-1.23

			it is recommended to take Fampyra without food			
2010	Lurasidone HCl	Latuda®	Latuda should be taken with food	Positive	2	3

[a] Mean systemic exposures with moderate to high fat meals
[b] Values refer to geometric mean systemic exposure.
[c] Where no numerical values for food effect were obtained but no significant food effect was observed a value of 1 was assigned
[d] Low fat fed
[e] High fat fed
[f] Parent compound
[g] Active metabolite
[h] Moderate fat meal

Strategies to overcome food effect bioavailability in drug development

Where food effects are identified, there is generally three choices facing drug development and/or regulatory scientists: (1) consider an alternative lead drug molecule that will not display food effects, (2) apply specific instructions for how a medicine is taken with regard to food or (3) design a formulation which overcomes to food effect. With an increasing desire to improve R&D efficiency in drug development, and the 'quick win, fast fail approach' now favoured in drug development, there is an increasing desire to predict food effects earlier in the drug development process [105, 106]. This will also allow potential to identify a food-independent formulation, approaches to which are described here. The primary focus is on the clinical performance observed with such formulation approaches, while notable studies in preclinical studies, principally in beagle dogs are also reviewed. While pre-clinical animal models, including the dog model, are not always representative of human bioavailability, they remain a cornerstone of pre-clinical formulation development, particularly with regard to food effect [105, 107]. Dogs are indeed the most widely characterised animal model in food effect studies, and dog specific food effect models are widely available, with a general tendency to be over-predictive of human food effect [108, 109].

Lead candidate modification and optimisation

Once a potential lead compound has been identified during the drug development process, the final drug discovery phase involves modifying the molecular structure or physicochemical properties of the potential drug candidate to improve biopharmaceutical performance. The two guiding principles are the maintenance of favourable properties in lead compounds, retaining the motifs identified as crucial to the structure activity ratio (SAR), while also improving deficiencies in drug structure, often with the aim of improving the deliverability of the drug [110]. While it is unlikely that development scientists will specifically focus on food effect at this stage, identification and selection of appropriate lead candidates can lead to a reduction in food effect bioavailability later in the development process. While studies focussing on modifying the structure and physiochemical properties of a lead candidates specifically with the aim of reducing the impact of food are sparse, there are numerous examples of marketed drugs with related chemical and clinical properties, but differing food effects.

Pithavala *et al.* examined the effect that crystal habit may have on absorption and food-effect, and demonstrated the importance of screening drug polymorphs. Initial first in human (FIH) trials suggested a negative food effect for axitinib form IV in a film-coated, immediate release tablet. A 23% reduction in absorption in the fed state was demonstrated. Subsequent investigations identified

a more stable polymorph, form XLI. Food effect studies carried out with form XLI demonstrated an increase in the overall bioavailability of 19% with a high fat meal, and a 10% reduction with a moderate fat meal compared to fasting, which were not considered to be clinically significant changes [111].

Modifying the chemical structure by means of producing prodrugs can also be used to eliminate food effect, as demonstrated by the development of fosamprenavir, a prodrug of the previously marketed protease inhibitor amprenavir. Due to its poor solubility, amprenavir was originally formulated as a lipid based formulation (Agenerase®) which demonstrated reduced bioavailability (AUC decreased by 23%) when taken with a high fat meal. Fosamprenavir, a phosphate ester prodrug with improved solubility, was originally developed with a view to reduce the significant daily pill burden associated with Agenerase® (eight capsules, twice daily). Successful formulation of fosamprenavir (Telzir®) not only reduced the dosing schedule to one tablet twice daily, but also eliminated the negative food effect seen with amprenavir, allowing dosing independent of prandial state [112].

The prodrug approach has also been used to produce the gabapentin ester, gabapentin enacarbil. The original aim of such an approach was to increase the poor and saturable bioavailability of gabapentin. The ester prodrug is completely hydrolysed to gabapentin by esterase enzymes in the gut and liver [113, 114]. While gabapentin bioavailability is greater from the prodrug when dosed in equimolar concentrations, Horizant® (gabapentin enacarbil) is required to be dosed with a meal, while Neurontin® (gabapentin) can be dosed with or without food. Numerous studies have demonstrated increases in exposure to gabapentin after oral dosing as gabapentin enacarbil [113, 115, 114]. Mean increases in AUC_{inf} of 23% for low fat, 31% for moderate fat and 40% for high fat meals have been observed in one study [115]. Meanwhile exposure to gabapentin from Neurontin® is not significantly different in the fasted and fed states with an increase of 14% in AUC and C_{max} in the fed state [116]. Direct comparison in these cases is, however, difficult as gabapentin enacarbil is only utilised in extended release preparations, while gabapentin is an immediate release formulation and both compounds are utilised for different indications. A similar approach, using an ester prodrug, has also been demonstrated to improve the bioavailability and eliminate the food effect for the direct thrombin inhibitor melagatran [117].

Formulation approaches to enhance bioavailability

Numerous formulation approaches have been utilised to overcome food effects on bioavailability and the type of formulation chosen will depend on the nature and mechanism of the food effect, the drugs physiochemical properties and the intended therapeutic profile. To date, the majority of

studies aimed at overcoming food effect have focused on poorly water soluble, BCS class II compounds. This is both due to these molecules being the most commonly observed class in drug development pipelines, and the fact that these molecules are the most amenable to formulation approaches designed to overcome their biopharmaceutical limitations. This has provided a focus for the development of bio-enabling formulations to improve dissolution and bioavailability, ultimately with the aim of ensuring BCS class II compounds will behave more like BCS class I compounds *in vivo*. It is widely stated that by maximising dissolution *in vivo* in the fasted state it may also be possible to prevent the postprandial increases in solubilisation and mitigate or eliminate a positive food effect entirely, though as we will discuss below, this may be an oversimplification. While each of the formulations discussed in this article have indeed been well characterised elsewhere, they are discussed here specifically in the context of their use in eliminating food effects on bioavailability.

Nanosized preparations

The term nanocrystal has emerged to describe drug particles with a crystalline structure in the nanoscale range [118]. Nanosizing refers to the reduction of API particle size to the sub-micron range, typically <500nm, and with modern production techniques it is possible to achieve particle size in the 100-200nm range [119]. The reduction in particle size leads to an increase in surface area available for solvation and increases the rate of dissolution. The formation of nanoparticles may not only enhance dissolution, but evidence exists that solubility may also be increased through changes in the particle curvature and introduction of defects into the crystal lattice, while the thickness of the diffusion layer surrounding the particle may also be reduced [120-122, 118]. Nanonisation of API has proven useful in enhancing the bioavailability of PWSD, and numerous commercial examples exist, and many of these commercial preparations have been shown to eliminate a positive food effect previously seen with marketed preparations or in the drug development process.

Fenofibrate has been widely investigated as a model PWSD displaying positive food effect bioavailability. Originally marketed as a co-micronized capsule, with an API particle size of 5-15 µm, which required dosing with food to achieve maximal absorption of a 200mg dose, it has repeatedly been reformulated using different bio-enabling approaches. Two nanonized preparations of fenofibrate have so far reached market, namely Tricor® (also marketed as Lipantil® Supra; prepared using NanoCrystal® milling technique developed by Elan Nanosystems) and Triglide™ (prepared via high pressure homogenisation). Comparison of absorption from 145 mg nanosized Tricor® formulation in the fasted and fed state to that of the 160 mg microcoated tablets demonstrated similar exposure in the fed state, while absorption from the nanonized tablet was increased in the fasted state and resulted in the elimination of a food effect [123, 124].

Aprepitant is a BCS class IV compound which was formulated as a nanoparticle, using NanoCrystal® technology, during drug development to enhance fasted state dissolution. The final preparation was marketed as EMEND® and was found to improve fasted state exposure and eliminate the positive food effect seen with early tablet formulations in clinical development [125, 126].

Megestrol acetate is a steroidal progestin which is licensed for use as an appetite stimulant in anorexia and cachexia. Thus, the positive food effect seen with the original Megace® oral suspension, along with the 800mg dose in the relatively large volume of 20 mL suspension was seen as problematic in patients with decreased appetite. Reformulation as the nanocrystalline Megace® ES demonstrated a reduction of food effect, but also allowed dose reduction to 625mg administered in 5 mL of the new formulation [127, 128].

The advantages of nanonized API compared to other methods of particle size reduction, specifically micronization through hammer- or jet-milling was demonstrated by Jinno *et al.* [129]. Here, a spray dried nanocrystalline suspension of cilostazol not only improved bioavailability approximately 5 fold in fasted beagle dogs relative to two different micronized preparations, but also eliminated the positive food effect seen with the micronized formulations. This was attributed to improved dissolution, as demonstrated in biorelevant FaSSIF media [129].

Several other nanocrystalline preparations have also demonstrated enhanced fasted state bioavailability in the fasted state and elimination of food effect in pre-clinical animal models, including ziprasidone [91, 130], lurasidone [131] and the novel gamma secretase inhibitor ELND006 [132]. Table 4 contains numerous examples of commercially available nanocrystalline preparations where food effect has been studied. In all cases a significant food effect observed with previous formulations has been mitigated or eliminated, demonstrating that nanosizing is an effective approach to eliminating food effect bioavailability.

Amorphisation and solid dispersion

The term solid dispersion describes a wide range of different, but related formulations which are designed to maintain drug in an amorphous or phase-separated crystalline state [133]. By reducing the drug particle size to the molecular level rapid dissolution can be facilitated, and production of an amorphous form will improve the apparent solubility, while solid dispersion can also confer improved wettability, increased porosity and, ultimately, improved biopharmaceutical performance [134-136]. Solid dispersions are being used increasingly often as bio-enabling formulations for PWSD to enhance oral bioavailability and numerous commercial preparations exist [137]. These preparations most often exist as amorphous drug dispersed in an inert carrier matrix, and this narrow definition has been used to describe their behaviour [138].

One such example is that of Kaletra®, a combination product of lopinavir and ritonavir produced using solid dispersion technology, specifically hot melt extrusion, using PVP/VA as a carrier [139]. Having originally been formulated as a soft gelatin capsule containing lipid excipients, the capsule formulation of Kaletra® were required to be taken with food, with a 48% increase in bioavailability observed in the fed state. The poor solubility of the API also meant that the capsule dose was limited to an 80mg/20mg strength capsule. Reformulation as a solid dispersion allowed production of a 200mg/50mg tablet, reducing the pill burden from 10 capsules daily to four tablets daily. The amorphous solid dispersion formulation also displayed only insignificant changes in bioavailbility in the fed compared to the fasted state, allowing food independent dosing [139].

Similarly, Lynparza® (olaparib) has been reformulated from a lipid-based, crystalline solid dispersion of micronised olaparib in Gelucire®, to a hot-melt extrusion based dispersion using copovidone as a carrier [140]. While the original formulation was developed after significant pre-clinical development, and displayed a 2-fold increase relative to a standard immediate release tablet, relatively low drug loading (10%) led to a significant pill burden for patients (16 capsules daily) [141]. The development of the melt extrusion tablet formulation both increased olaparib bioavailability and drug loading, allowing a dose reduction from 400mg to 300mg twice daily, and reduced the pill burden to four tablets daily. The food effect was also reduced, with a 20% increase in exposure observed for the capsule compared to a 9% increase with the tablet formulation [142, 143, 140].

Banarjee *et al.* developed a ziprasidone solid dispersion via hot melt extrusion, which retained crystalline characteristics of ziprasidone while suspending the drug in a hydrophilic matrix to improve wettability and dissolution, resulting in a nearly 10-fold increase in solubility. The enhanced dissolution translated to improved bioavailability in fasted healthy volunteers, while simultaneously eliminating the positive food effect observed with the commercial Zeldox® formulation [144].

However, while these approaches have successfully reduced food effect using solid dispersion technology, table 4 contains numerous examples where this is not the case. For the marketed solid dispersion formulations and amorphous drug preparations for which food effect data could be found (n = 21) almost half (n = 10) display positive food effect, while four preparations displayed a negative food effect. The fact that two thirds of these bio-enabled formulations display food effect bioavailability suggests that while solid dispersions may well improve dissolution in the fasted state, quite often solubility limitations remain.

Lipid Based Formulations

The original rationale for the investigation of the use of lipid-based formulations (LBF) to increase bioavailability of PWSD was the observation of positive food effects for many of these compounds

[145]. The ability of food to enhance the absorption of PWSD has long been attributed to the ability of meal components, and in particular lipids, to enhance drug solubilisation, dissolution and absorption. Thus, the addition of exogenous lipids to pharmaceutical preparations was proposed and investigated as a viable option to enhance the bioavailability of PWSD. LBFs have thus become one the most widely investigated and characterised formulation types for bioavailability enhancement and the elimination of a positive food effect, and have become 'renowned for their potential to reduce the impact of food on drug absorption [146]. One of the earliest studies to specifically focus on the utility of LBF to eliminate food effect bioavailability was that of Charman *et al.* (1993). This study demonstrated that the approximately 3 fold increase in C_{max} and AUC observed for a commercial danazol capsule formulation (Danocrine®) was elimninated using a lipid emulsion of danazol in glycerol mono-oleate [147].

However, eliminating food effect using LBF is not always straightforward, and can require significant formulation development, as is the case for lipid-based formulations of cyclosporine. The commercial success of self-emulsifying drug delivery system (SEDDS) formulation of Neoral® owing principally to its elimination of the food effects and reducing inter-subject variability relative to the crude lipid emulsion formulation of Sandimmune® [148, 149]. Delivery as a crude emulsion was not sufficient to overcome the food effect, which required a more elaborate SEDDS formulation.

Similarly, Roaccutane® is a soft gelatin capsule, which contains isotretinoin solubilised in water-insoluble solvents, namely beeswax, soya bean oil and hydrogenated soya bean oil, which displays an approximately 2.7 fold increase in bioavailbility in the fed compared to fasted state. Absorica® is a novel isotretinoin formulation developed using Lidose® technology, which enhanced the fasting state bioavailbility and reduced the food effect to a 1.5 fold increase, which is not considered to be clinically significant and allows food independent dosing [150].

While the use of LBF to eliminate food effect has been widely acknowledged, it is interesting to look more critically at this claim. The use of LBF to enhance the fasted state bioavailability has been the major focus of formulation development over the last five decades, and it is a logical inference that by enhancing the solubility limited bioavailability in the fasted state, the post-prandial increase in absorption mediated by increased solubility can be reduced or avoided. However, as presented in table 4, of the 29 LBFs for which food effect data was gathered, 17 of these formulations displayed significant positive food effect, while only 9 formulations demonstrating truly food independent dosing.

This can be exemplified by the case study of Fortovase®, a SEDDS formulation designed to improve the oral bioavailability of saquinavir, relative to the conventional capsule formulation, Invirase®.

While bioavailability was enhanced approximately three fold by Fortovase®, a significant food effect was still evident, with a similar increase in the fed state to that observed with Invirase® (6.7 fold increase).

Perlman *et al.* have examined the food effect of torcetrapib in dogs using a range of different SEDDS formulations, finding that the composition of the formulation can be crucial in determining the food effect, with a food effect ranging from complete absence to 3.8 fold increase in beagle dogs. It should be noted, however, that all formulations reduced the food effect seen with aqueous (18 fold increase) and lipid (5 fold increase) suspensions used in early drug development [151]. Thus, while simply administering PWSD with lipids may reduce the magnitude of the food effect, true elimination may require more extensive formulation optimisation [8]. Christiansen *et al.* have similarly demonstrated a reduction of food effect for cinnarizine tablets when co-administered with placebo SNEDDS, relative to administration without this placebo lipid formulation in healthy volunteers, though complete elimination of food effect was not possible [152].

Various other lipid-based formulations have also been investigated in pre-clinical species with varying levels of success, and with a general trend towards reducing rather than eliminating food effects [153-163]. While the assertion that LBF are excellent candidates to eliminate food effect is widespread, the evidence from the literature, and from product literature in particular is underwhelming and a more systematic investigations are required to fully elucidate the potential for LBF to overcome food effects [164].

Cyclodextrins

Cyclodextrins have been widely used to enhance the oral bioavailability of lipophilic and poorly water-soluble drugs, in both pre-clinical animals and in humans. The bioavailability enhancing effects are mainly due to enhanced dissolution kinetics, increased solubility and potential reduction in degradation as well as increased permeability [165]. Experience with cyclodextrins with a specific focus on elimination of food effect is, however, limited.

Sporanox® (itraconazole) has been formulated both as an amorphous solid dispersion, which displayed significant, positive food effect and as an oral solution solubilised by hydroxypropyl-β-cyclodextrin inclusion complex. Sporanox® cyclodextrin solution has demonstrated higher bioavailability than Sporanox capsules in the fed state, and has also been demonstrated to show enhanced bioavailbility in the fasted state, eliminating the need for fed state dosing [166-168].

Along with the commercial itraconazole preparataion, cyclodextrin complexes have also been investigated in pre-clinical food effect studies. Thombre *et al.* have demonstrated that a sulfobutyl

ether- β-cyclodextrin (SBE-β-CD) inclusion complex enhanced fasted bioavailability and eliminated food effect for ziprasidone relative to the commercial preparation (Geodon®) in beagle dogs [91, 169]. Wang *et al.* have recently demonstrated similar results with an SBE-β-CD complex of amiodarone [170].

While the experience with cyclodextrin preparations for eliminating food effect is limited, these examples show promise for this formulation method to eliminate food effect, though overall clinical acceptability may be limited as the relatively large intake volume (up to 20 mL for Sporanox® solution) may be problematic for some patients.

Guiding formulation selection

With the range of formulations available, identification of the biopharmaceutical risks for a particular drug candidate is essential in order to ensure the most appropriate formulation is chosen. While it may be possible that different types of formulation may achieve improved solubilisation for a particular drug candidate, identification of the most beneficial formulation can be advantageous in the industrial setting where developing parallel formulation portfolios can put a strain on the limited timelines and resources. Kuentz *et al.* have recently reviewed the various methods by which formulations are selected in the pharmaceutical industry [171]. The key elements of formulation screening involve identifying the critical physiochemical and biopharmaceutical properties that are likely to play a role in drug bioavailability and generating a target product profile (TPP). Ideally, formulation decision trees based on a basic set of drug properties, such as that proposed by Rabinow *et al*. [172], or those based on identifying the biopharmaceutical limitations, such as the BCS based decision trees suggested by Ku *et al.* [173], can be implemented and will provide a relative simple strategy to formulation choice. There is an abundance of such decision trees in the literature, with focus on enhancing bioavailability and manufacturability of drug candidates. However, given the lack of a clear consensus on the appropriate prediction of food effect bioavailability and the contradictory evidence of the various formulation options at eliminating food effect, it is no surprise that no decision tree exists specifically focus on eliminating the food effect. In the absence of a specific decision tree, choice is best guided by analysing BCS/BDDCS class assignment and utilisation of existing decision trees for each appropriate class. Formulation approaches suitable for each class are summarised in figure 4.

While significant experience, no doubt, exists within the pharmaceutical industry, this data is often not published in the literature. The paucity of data regarding the systematic and structured development of formulations with the intention of eliminating food effect means that, initially, the decision to focus on one particular formulation approach to eliminate a food effect remains largely empiric. More thorough formulation development and characterisation, however, can benefit from a more mechanistic approach, using a range of *in vitro*, *in vivo* and *in silico* tools. A recent example of such an approach is that of Pandey *et al.* [174]. In this work, the group first identified a large food effect in an early stage clinical trial in healthy volunteers. This food effect was subsequently investigated mechanistically using biorelevant *in vitro* screening tools along with *in silico* modelling using the GastroPlus® ACAT model. This biorelevant screening identified that the key mechanism governing the observed positive food effect was the enhanced solubilisation by dietary lipids, while *in silico* modelling suggested that other contributory factors were involved, including the changing pH and the impact of gastrointestinal transporters and metabolism. The integration of the early

clinical data with the biorelevant measurements with the *in silico* model allowed development of a bio-predictive *in vitro* dissolution method, which enabled rapid formulation screening. Formulation screening led to the development of a surfactant containing, wet-granulated tablet formulation. The approximately 3.5-fold increase in fed state bioavailability observed for the dry granulated formulation was reduced to an approximately 1.5-fold increase, which was deemed not to be clinically significant for this compound [174].

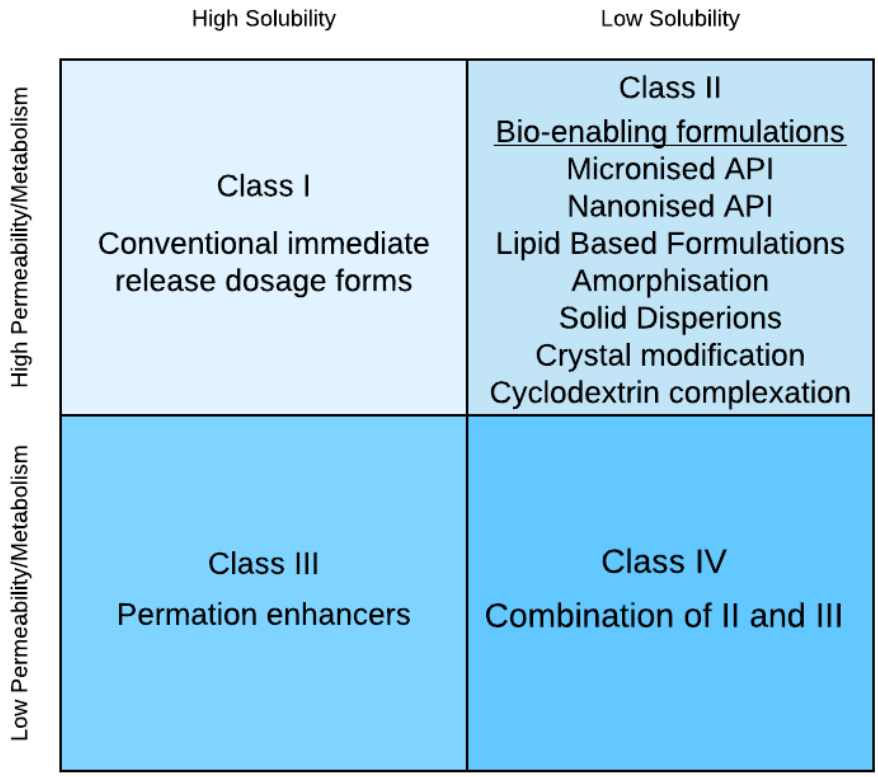

Figure 4 Approaches to formulation design based on BCS/BDDCS classification

685 **Table 3 Approved bio-enabling formulations with clinical food effect data**
686 **Data obtained from FDA Drug Label (from Drugs@FDA database) or European Summary of Pharmaceutical**
687 **Characteristics (SPC) unless otherwise stated**

	Trade name	API	Clinical recommendation	AUC$_R$
Amporhous solid dispersions	Cesamet®	Nabilone	No specific instructions	
	Sporanox® (capsule)/ Onmel®	Itraconazole	Sporanox is for oral administration and must be taken immediately after a meal for maximal absorption.	
	Prograf®	Tacrolimus	Administer capsules consistently with or without food	
	Kaletra®	Ritonaivr/lopinavir	Kaletra tablets can be taken with or without food.	
	Intelence®	Etravirine	Taken following a meal	
	Zortress®/ Certican®	Everolimus	Administer consistently with or without food at the same time as cyclosporine.	
	Norvir®	Ritonavir	Take Norvir with meals	
	Zelboraf®	Vemurafenib	Administer ZELBORAF approximately 12 hours apart with or without a meal	
	Incivek®	Telaprevir	Take with food (not low fat)	
	Kalydeco®	Ivacaftor	With fat containing food	
	Viekirax®	Ombitasvir Paritaprevir Ritonavir	Viekirax tablets should be taken with food, without regard to fat and calorie content	
	Fenoglide®	Fenofibrate	Should be taken with meals	
	Rezulin®	Troglitazone	Rezulin should be taken with a meal	1.1
	Noxafil®	Posaconazole	Taken with food	
Pure Amorphous Drug	Ceftin®	Cefuroxime axetil	Administer tablets with or without food	
	Viracept®	Nelfinavir mesylate	VIRACEPT should be taken with a meal	

	Accupril®	Quinapril HCl	No specific instructions
	Victrelis®	boceprevir	Take three times daily with food (a meal or light snack)
	Crestor®	Rosuvastatin Calcium	CRESTOR can be administered as a single dose at any time of day, with or without food
	Zepatier®	elbasavir grazoprevir	One tablet taken orally once daily with or without food
	Accolate®	Zafirlukast	ACCOLATE should be taken at least 1 hour before or 2 hours after meals.
Lipid Based Formulations	Agenerase®	Amprenavir	AGENERASE may be taken with or without food, however, a high fat meal decreases the absorption of amprenavir and should be avoided
	Neoral®	Cyclosporin A/I	Neoral be administered on a consistent schedule with regard to time of day and relation to meals.
	Accutane®/ Roaccutane®	Isotretinoin	Accutane should be administered with a meal
	Kaletra®	Lopinavir Ritonavir	Kaletra capsules must be taken with food
	Norvir®	Ritonavir	Take with food
	Restandol®/ Andriol® Testocaps	Testosterone undecanoate	Restandol Testocaps must be taken with a normal meal
	Targretin®	Bexarotene	Targretin® capsules should be taken as a single oral daily dose with a meal.
	Lamprene®	Clofazimine	Administer 100 mg LAMPRENE daily with meals
	Sandimmune®	Cyclosporin A	To be administered on a consistent schedule with regard to time of day and relation to meals.
	Marinol®	Dronabinol	Take twice daily , before lunch and supper
	Avodart®	Dutasteride	May be administered with or without food
	Procardia®	Nifedipine	No specific instructions

	Rapamune®	Sirolimus	Oral solution; Administer once daily by mouth, consistently with or without food
	Fortovase®	Saquinavir	FORTOVASE should be taken within 2 hours after a full meal
	Amitiza®	Lubiprostone	Take with food to reduce nausea
	Aptivus®	Tipranavir	Always take APTIVUS with food.
	Hycamtin®	Topotecan HCl	May be administered with or without food
	Akynzeo®	Netupitant Palonsetron	Can be taken with or without food
	Prometrium®	Progesterone	No specific instructions
	Utrogestan®	Progesterone	Utrogestan 100mg Capsules should not be taken with food and should be taken at bedtime.
	Absorica®	Isotretinoin	Recommended dosage of 0.5 to 1 mg/kg/day given in two divided doses without regards to meals for 15 to 20 weeks
	Lipofen®	Fenofibrate	LIPOFEN™ capsules should be given with meals, thereby optimizing the absorption of the medication.
	Ofev®	Nintedanib	Take with food
	Navelbine®	vinorlebine tartrate	Administer the capsule with some food, as this has also been shown to reduce the incidence of nausea and vomiting
	Zemplar®	Paricalcitol	Without regard to meals
	Toctino®	Alitretinoin	With a main meal
	Vyndaqel®	Tafamidis meglumine	With or without food
	Rayaldee®	calcifediol	Once Daily at bedtime
	Xtandi®	Enzalutamide	XTANDI can be taken with or without food
Nanocrystal	Lipantil Supra®	Fenofibrate	Without regard to meals
	Megace® ES	megestrol acetate	No specific instructions

	Emend®	aprepitant	With or without food
	Triglide®	Fenofibrate	TRIGLIDE may be administered with or without food
	Rapamune®	sirolimus	To minimise variability, Rapamune should consistently be taken either with or without food
Cyclodextrin	Sporanox® (Oral solution)	Itraconazole	Oral solution; Taking SPORANOX® Oral Solution under fasted conditions improves the systemic availability of itraconazole. Instruct patients to take SPORANOX® Oral Solution without food, if possible
Crystalline Solid Dispersion	Lynparza® (capsule)	Olaparib micronised in Gelucire; manufactured as a suspension of drug in molten excipient	No specific instructions
	Lynparza® (tablet)	Hot melt extruded olaparib in co-povidone carrier matrix	Taken orally twice daily with or without food

[a] Where no numerical values for food effect were obtained but no significant food effect was observed a value of 1 was assigned
[b] Moderate fat meal
[c] High fat meal
[d] Low fat meal
[e] With Breakfast
[f] 2 hours post breakfast
[g] 4 hours post breakfast
[h] Active metabolite

Conclusion

This review has investigated the causes and impact of food mediated changes in drug bioavailability. While our mechanistic understanding of the causes of food effects, and our ability to predict when and why it might occur have developed significantly since Welling first reviewed this topic 40 years ago, food effects still pose significant problems with regard to both development and regulatory scientists.

Despite the increased awareness of the negative clinical impact of food effects on bioavailability and the strict regulatory guidance regarding the appropriate testing of new medicinal products in the fed and fasted states there appears to be an ever-increasing challenge of food mediated alterations in drug bioavailability, likely reflecting the increasing prevalence of PWSD in drug development

pipelines. While there has been increasing understanding and development of improved drug delivery technologies, there remains an overall lack of appreciation of the scale of the food effect challenge, as evidenced by the fact that over 40% of new medicines display significant food effects, or possess a label claim in respect of dosing with regard to food intake. This has had a knock-on effect in the clinic, where the success or commercial advantage of compounds can be affected, particularly with antipsychotic and oncological preparations.

While this review has summarised the various formulation approaches that have been utilised to mitigate food effect, it is still difficult to definitively suggest a method of choice for formulating new compounds to overcome significant food effects. The major focus of formulation approaches to mitigate food effects to date has focused on compounds displaying positive food effects mediated by poor dissolution or solubility, while relatively limited approaches exist for drugs displaying negative food effects, where permeability, diffusivity or metabolism related limitations occur. It is interesting to note that despite significant improvements in formulation design and characterisation with regard to supersaturable and bioenabling formulations that many of these marketed formulations still appear to behave sub-optimally *in vivo*, specifically with regard to food effects.

Formulating compounds to overcome food effect remains largely empirically driven, with only sporadic case studies for individual compounds published. While the presence or absence of food effects is unlikely to be a key driving factor in early formulation development, it can be a critical factor when entering the clinic. In the absence of large databanks of formulation design studies in easily obtainable literature, greater use of mechanistic and in silico approaches will be central to enhancing our ability to discriminate between formulations likely to overcome food-mediated alterations in drug bioavailability.

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