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# 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

## 28 **Key words**

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

## 31 **Introduction**

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

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

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

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

61

## 62 Food Effects; causes and clinical consequences

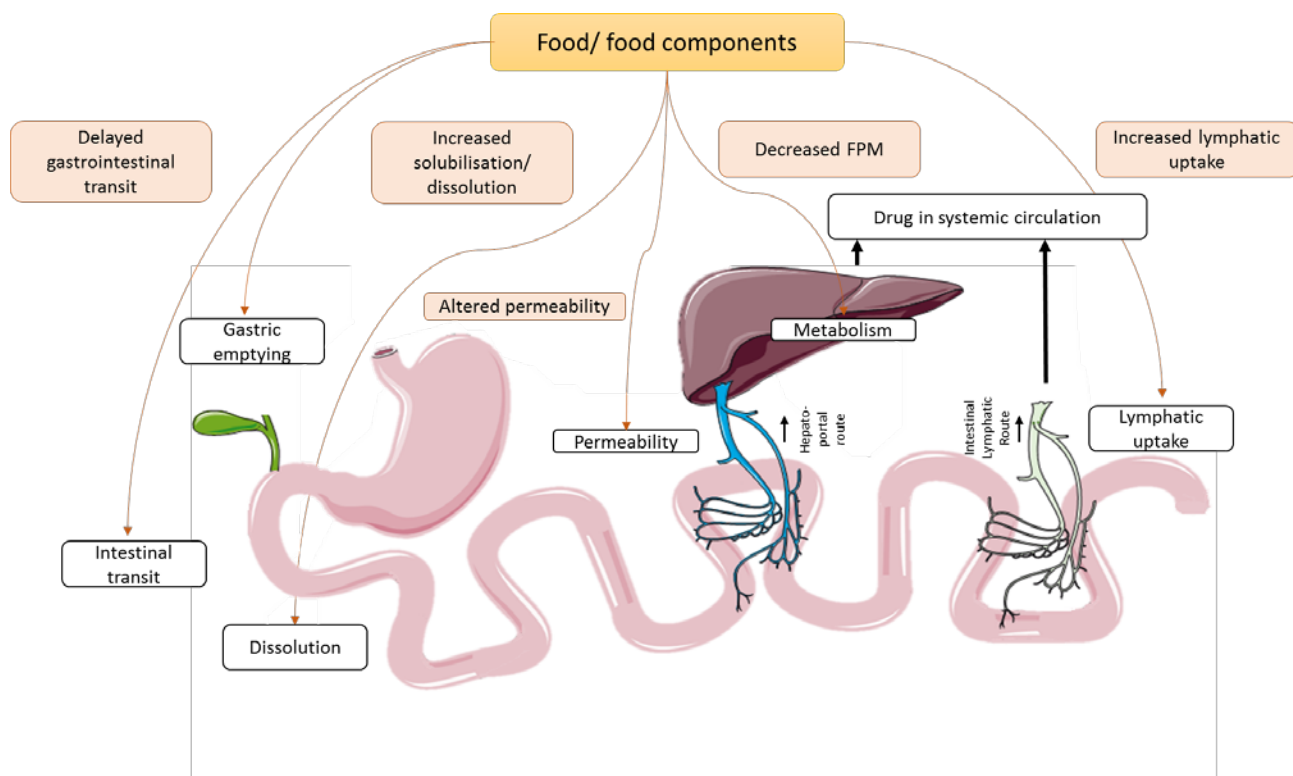
### 63 What is a food-effect?

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

- 71 • Reduced extent of bioavailability
- 72 • Delayed rate of absorption
- 73 • Increased extent of bioavailability
- 74 • Accelerated rate of absorption
- 75 • No effect

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

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



92  
93  
94

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

### 95 Mechanisms underlying the food effect

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

	High Solubility	Low Solubility
High Permeability/Metabolism	<b>Class I</b> $F_{\text{extent}} \leftrightarrow$ $T_{\text{max}} \uparrow$ $C_{\text{max}} \downarrow$	<b>Class II</b> $F_{\text{extent}} \uparrow$ $T_{\text{max}} \uparrow \downarrow \leftrightarrow$ $C_{\text{max}} \uparrow$
Low Permeability/Metabolism	<b>Class III</b> $F_{\text{extent}} \downarrow$ $T_{\text{max}} \uparrow$ $C_{\text{max}} \downarrow$	<b>Class IV</b> $F_{\text{extent}} \uparrow \downarrow \leftrightarrow$ $T_{\text{max}} \uparrow \downarrow \leftrightarrow$ $C_{\text{max}} \uparrow \downarrow \leftrightarrow$

109

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

111

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

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

127

## 128 Food induced changes on drug absorption

### 129 *Gastrointestinal fluid composition*

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

### 140 *Gastrointestinal motility and its impact on transit time of dosage forms*

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

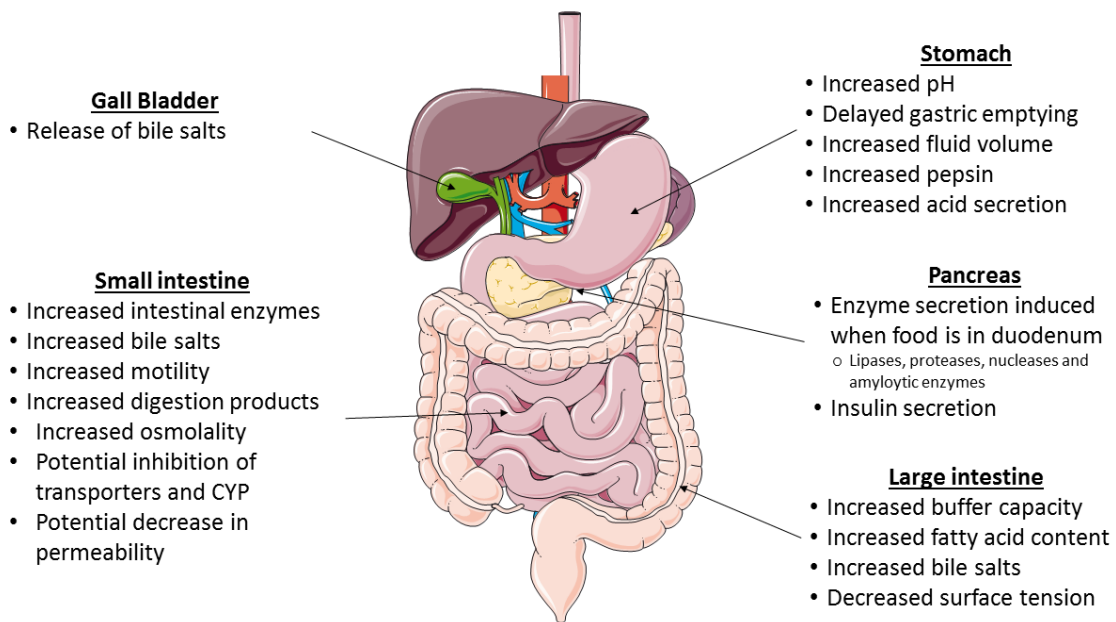
### 152 *Metabolism and transporter effects*

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



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

169  
 170  
 171



172  
 173 **Figure 3 Summary of human physiological changes in the fed state (adapted from Varum *et al.* <sup>[3]</sup>)**

174

## 175 Mechanisms of food effect

176 As has been described above, food has a complex and significant effect on the physiology of the  
177 gastrointestinal tract and the physicochemical properties of gastrointestinal fluid, which in turn can  
178 have a significant effect on drug absorption. These effects are dependent on both the  
179 physicochemical properties of the drug, principally solubility, pKa and LogP/logD, and formulation  
180 characteristics, including release and disintegration of solid dosage forms [45, 46, 8]. For the purposes of  
181 this review, the focus will predominantly be on immediate release and bio-enabling formulations,  
182 the mechanisms by which food causes these changes in bioavailability are discussed here and  
183 summarised in table 1. The effect of food on modified release dosage forms can be significantly  
184 different to that of immediate release preparations, notably with regard to disintegration and  
185 release and the potential for dose dumping. The effects of food on modified release formulations  
186 have recently been reviewed by Varum *et al.* (2013)<sup>[3]</sup>, Yasuji *et al.* (2012)<sup>[9]</sup> and Abuhelwa *et al.*  
187 (2017)<sup>[10]</sup>.

## 188 Positive food effects

189 The principal cause of positive food effects is the increase in dissolution and solubilisation of poorly  
190 water soluble drugs (PWSD) in the fed state. The release of bile salts and the presence of exogenous  
191 solubilising species, such as ingested lipids and their digestion products serve to enhance solubilising  
192 capacity of gastrointestinal fluid [28, 47, 30, 48-50]. For drugs which are dissolution rate, rather than  
193 solubility limited, the increased gastric residence time also can improve bioavailability, while the  
194 increase in gastric pH may result in improved solubility and dissolution of weak acids. In practical  
195 terms, it is difficult to isolate the impact of any one of these factors, which work synergistically to  
196 increase solubility and dissolution of PWSD.

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

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

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

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

### 218 *Negative food effects*

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

226 Decreased absorption in the fed state results in a reduction in AUC, along with a reduction in  $C_{max}$ ,  
227 and can lead to sub-therapeutic plasma levels and loss of efficacy. The most common causes of  
228 reduced bioavailability in the fed state are direct physicochemical interactions between drugs, or  
229 drug products, and food. One potential cause of this effect is the reduced diffusivity of drug in the  
230 viscous postprandial upper GIT. The increased viscosity can result in either inhibition of  
231 disintegration of a dosage form, preventing drug release, or hindering diffusion of drug to the  
232 absorptive membranes of the GIT <sup>[58-61]</sup>. This can be problematic for poorly permeable drugs,  
233 particularly those with narrow absorption windows, as by the time viscosity has reduced in the distal  
234 gut, the absorption window has been transited and absorption will be reduced <sup>[62-64]</sup>. A second direct  
235 mechanism by which food can hinder drug absorption is by binding of drug with food components  
236 <sup>[65, 7]</sup>. This is prevalent in the case of polyvalent cations, which are abundant in dairy products <sup>[66-68, 7,</sup>  
237 <sup>69]</sup>.

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

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

247 The inhibition of uptake transporters may also result in negative food effects. For poorly permeable  
248 drugs, the inhibition of these transporters may result in a reduction in absorption, as these  
249 compounds are often reliant on the action of uptake transporters. The general inhibition of  
250 intestinal transporters observed in the fed state is therefore likely to reduce the bioavailability of  
251 BCS class III compounds. Care is needed, however, when applying this rule of thumb, as class III  
252 compounds may be candidates for both uptake and efflux transporters and the relative inhibition of  
253 either uptake or efflux transporters, or the extent to which a specific molecule will be a substrate for  
254 each particular class can determine the overall effect of bioavailability <sup>[16]</sup>. Fexofenadine is a BCS  
255 class III compound which displays a negative food effect, as predicted by its BDDCS class.

256 Fexofenadine is a substrate for both OATP uptake transporters and P-gp efflux transporters. In the  
257 fed state, principally when taken with fruit juices, the inhibition of OATP transporters predominates  
258 and absorption is decreased <sup>[74-77]</sup>. Fruit juice related inhibition of OATP uptake has also been  
259 implicated in a reduction in AUC for other drugs, including aliskiren and celiprolol<sup>[74, 78-80]</sup>. The  
260 inhibition of PAT1 has been suggested as a possible reason for the reduced rate of absorption of  
261 vigabatrin, though this is most likely due to a reduction in the rate of gastric emptying <sup>[81, 82]</sup>.

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

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

<b>Physiological mechanism</b>	<b>Biopharmaceutical aspects</b>	<b>Effect on Drug exposure</b>	<b>Example(s)</b>
Increased pH in stomach	Solubility and dissolution of ionisable compounds can be altered	Increases AUC and C <sub>max</sub> for weak acids	Cefuroxime
		Decreases AUC and C <sub>max</sub> 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 C <sub>max</sub>	Fenofibrate Alectinib Danazol
Increased splanchnic blood flow	Saturation of liver enzymes and avoidance of FPM	Increases AUC and C <sub>max</sub>	Propranolol  Tacrine  Dronedarone
Inhibition of gastrointestinal Cytochrome P450 – e.g. with Grapefruit juice	Fraction of drug escaping gut metabolism increases	Increases AUC and C <sub>max</sub>	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 C <sub>max</sub> for drugs subject to efflux	Ganciclovir
		Decreases AUC and C <sub>max</sub> 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

## 267 Clinical significance

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

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

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

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

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



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

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

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

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

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

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

381 Interestingly, our estimates have suggested that approximately 40% (67 of 157 products identified;  
382 42.68%) of medicines licensed by the EMA and FDA since January 1<sup>st</sup> 2010 display a significant food  
383 effect or have been licensed with a label restriction with regard to dosing with or without food.  
384 Included in this analysis were new chemical entities, new combination products and previously  
385 marketed active pharmaceutical ingredients which have been reformulated. Excluded from our  
386 analysis were generic medicines/ abbreviated new drug applications (ANDAs), parenteral, topical,  
387 transdermal and other non-oral preparations (including buccal and sublingual preparations and  
388 orally disintegrating tablets), extended/ controlled release preparations and oral medicines designed  
389 for local administration within the GIT, i.e. those not subject to appreciable levels of absorption. In a  
390 competitive market place, the ability to take a medicine without regard to the timing of meals  
391 presents a clear commercial advantage for developing dosage forms that can be administered  
392 independent of food<sup>[104]</sup>.

393  
394

**Table 2 Recently licenced medicines displaying significant food effect and/or food specific dosage instructions**  
 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 <sub>Fed</sub> /AUC <sub>Fasted</sub>	C <sub>max</sub> <sub>Fed</sub> /C <sub>max</sub> <sub>Fasted</sub>
2017	Spironalactone	Carospir®	CAROSPIR can be taken with or without food, but should be taken consistently with respect to food	Positive	1.9	-
2017	Glecaprevir Pibrentasvir	Mavyret®	Take orally once daily with food	Positive	1.83-2.63 <sup>a</sup> 1.4-1.53 <sup>a</sup>	-
2017	Sofosbuvir Velpatasvir Voxilaprevir	Vosevi®	Taken orally once daily with food	Positive	1.64-2.44 <sup>b</sup> 1.4-2.66 <sup>b</sup> 2.12-5.35 <sup>b</sup>	-
2017	Deutetrabenazine	Austedo®	Administer with food	Positive	1 <sup>c</sup>	1.5
2017	Betrixaban	Bevyxxa®	Take at the same time each day with food	Negative	0.39 <sup>d</sup> 0.52 <sup>e</sup>	0.3 <sup>d</sup> 0.5 <sup>e</sup>
2017	Telotristat ethyl	Xermelo®	Take with food	Positive	3.64 <sup>f</sup> 1.33 <sup>g</sup>	2.12 <sup>f</sup> 1.47 <sup>g</sup>
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; Elbasvir 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 <sup>h</sup> , 0.88 <sup>e</sup>	-

Tenofovir alafenamide

Rilpivirine  
1.13<sup>h</sup>, 1.72<sup>e</sup>  
Tenofovir  
alafenamide  
1.45<sup>h</sup>, 1.53<sup>e</sup>

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

					1.21 <sup>e</sup>	1.38 <sup>e</sup>
2015	Sonidegib	Odomzo <sup>®</sup>	Take on an empty stomach	Positive	7.4-7.8	7.4-7.8
2015	Tasimelteon	Hetlioz <sup>®</sup>	Taken without food	Negative	-	0.56
2015	Trifluridine Tipiracil	Lonsurf <sup>®</sup>	Within One hour after completion of meal	Negative	1 <sup>c</sup>	0.6
			Take with food, as decrease in Trifluridine C <sub>max</sub> can prevent decrease in neutrophils	Negative	0.6	0.6
2014	Ceritinib	Zykadia <sup>®</sup>	Administer ZYKADIA on an empty stomach (i.e., do not administer within 2 hours of a meal)	Positive	1.58 <sup>d</sup> 1.73 <sup>e</sup>	1.43 <sup>d</sup> 1.41 <sup>e</sup>
2014	Delamanid	Delytba <sup>®</sup>	Delamanid should be taken with food	Positive	2.7	-
2014	Droxidopa	Northera <sup>®</sup>	Take consistently with or without food	Negative	0.8	0.65
2014	Idelalisib	Zydelig <sup>®</sup>	Zydelig can be taken with or without food	Positive	1.4	-
2014	Ledipasvir	Harvoni <sup>®</sup>	Taken daily with or without food	None; ledipasvir	1 <sup>c</sup>	1 <sup>c</sup>
	Sofosbuvir			Positive; sofosbuvir	2	1 <sup>c</sup>
2014	Naloxegol	Movantik <sup>®</sup>	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 <sup>®</sup>	Take with food	Positive	1.2	-
2014	Pirfenidone	Esbriet <sup>®</sup>	Three times daily taken with food.	Negative	0.84	0.51
2014	Suvorexant	Belsomra <sup>®</sup>	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 <sup>c</sup>	1 <sup>c</sup>
2014	Tasimelteon	Hetlioz <sup>®</sup>	Take without food	Negative	-	0.56
2013	Afatinib	Gilotrif <sup>®</sup>	Take at least 1 hour before or 2 hours after a meal	Negative	0.61	0.5
2013	Dabrafenib	Tafinlar <sup>®</sup>	Taken at least 1 hour before or at least 2 hours after a meal	Negative	0.69	0.49
2013	Dimethyl fumarate	Tecfidera <sup>®</sup>	Take TECFIDERA with or without food	Negative	1 <sup>c</sup>	0.6

2013	Dolutegravir	Tivicay®	May be taken without regard to meals	Positive	1.33 <sup>d</sup> 1.41 <sup>h</sup> 1.66 <sup>e</sup>	1.46 <sup>d</sup> 1.52 <sup>h</sup> 1.67 <sup>e</sup>
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 <sup>e</sup>	-
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	Stribild®	The recommended dose of STRIBILD is one tablet taken orally once daily with food	Positive	1.34 <sup>d</sup> 1.87 <sup>e</sup>	-
	Cobicistat			Neutral	1 <sup>c</sup>	-
	Emtricitabine			Neutral	1 <sup>c</sup>	-
	Tenofovir disoproxil fumarate			Positive	1.24 <sup>d</sup> 1.23 <sup>e</sup>	-
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 <sup>d</sup> 0.83 <sup>e</sup>	0.25 <sup>d</sup> 0.55 <sup>e</sup>
2012	Regorafenib	Stivarga®	Take Stivarga with food (a low-fat breakfast)	Positive	1.48 <sup>e</sup> 0.8 <sup>e,g</sup> 0.49 <sup>e,g</sup> 1.36 <sup>d</sup>	-

					1.4 <sup>d,g</sup> 1.23 <sup>d,g</sup>	
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 <sup>d</sup> 10 <sup>e</sup>	7 <sup>d</sup> 17 <sup>e</sup>
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 <sup>d</sup> 1.34 <sup>h</sup> 1.44 <sup>e</sup>	-
2011	Piperaquine tetraphosphate Artemimol	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 Artemimol; 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 <sup>c</sup> (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 <sup>d</sup> 3.37 <sup>h</sup> 4.3 <sup>e</sup>	-
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
395	<sup>a</sup> Mean systemic exposures with moderate to high fat meals					
396	<sup>b</sup> Values refer to geometric mean systemic exposure.					
397	<sup>c</sup> Where no numerical values for food effect were obtained but no significant food effect was observed a value of 1 was assigned					
398	<sup>d</sup> Low fat fed					
399	<sup>e</sup> High fat fed					
400	<sup>f</sup> Parent compound					
401	<sup>g</sup> Active metabolite					
402	<sup>h</sup> Moderate fat meal					
403						



## 404 Strategies to overcome food effect bioavailability in drug development

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

## 419 Lead candidate modification and optimisation

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

432 Pithavala *et al.* examined the effect that crystal habit may have on absorption and food-effect, and  
433 demonstrated the importance of screening drug polymorphs. Initial first in human (FIH) trials  
434 suggested a negative food effect for axitinib form IV in a film-coated, immediate release tablet. A  
435 23% reduction in absorption in the fed state was demonstrated. Subsequent investigations identified

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

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

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

#### 465 **Formulation approaches to enhance bioavailability**

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

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

#### 480 [Nanosized preparations](#)

481 The term nanocrystal has emerged to describe drug particles with a crystalline structure in the  
482 nanoscale range <sup>[118]</sup>. Nanosizing refers to the reduction of API particle size to the sub-micron range,  
483 typically <500nm, and with modern production techniques it is possible to achieve particle size in the  
484 100-200nm range <sup>[119]</sup>. The reduction in particle size leads to an increase in surface area available for  
485 solvation and increases the rate of dissolution. The formation of nanoparticles may not only enhance  
486 dissolution, but evidence exists that solubility may also be increased through changes in the particle  
487 curvature and introduction of defects into the crystal lattice, while the thickness of the diffusion  
488 layer surrounding the particle may also be reduced <sup>[120-122, 118]</sup>. Nanonisation of API has proven useful  
489 in enhancing the bioavailability of PWSD, and numerous commercial examples exist, and many of  
490 these commercial preparations have been shown to eliminate a positive food effect previously seen  
491 with marketed preparations or in the drug development process.

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

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

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

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

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

#### 525 **Amorphisation and solid dispersion**

526 The term solid dispersion describes a wide range of different, but related formulations which are  
527 designed to maintain drug in an amorphous or phase-separated crystalline state [133]. By reducing the  
528 drug particle size to the molecular level rapid dissolution can be facilitated, and production of an  
529 amorphous form will improve the apparent solubility, while solid dispersion can also confer  
530 improved wettability, increased porosity and, ultimately, improved biopharmaceutical performance  
531 [134-136]. Solid dispersions are being used increasingly often as bio-enabling formulations for PWSD to  
532 enhance oral bioavailability and numerous commercial preparations exist [137]. These preparations  
533 most often exist as amorphous drug dispersed in an inert carrier matrix, and this narrow definition  
534 has been used to describe their behaviour [138].

535 One such example is that of Kaletra<sup>®</sup>, a combination product of lopinavir and ritonavir produced  
536 using solid dispersion technology, specifically hot melt extrusion, using PVP/VA as a carrier <sup>[139]</sup>.  
537 Having originally been formulated as a soft gelatin capsule containing lipid excipients, the capsule  
538 formulation of Kaletra<sup>®</sup> were required to be taken with food, with a 48% increase in bioavailability  
539 observed in the fed state. The poor solubility of the API also meant that the capsule dose was limited  
540 to an 80mg/20mg strength capsule. Reformulation as a solid dispersion allowed production of a  
541 200mg/50mg tablet, reducing the pill burden from 10 capsules daily to four tablets daily. The  
542 amorphous solid dispersion formulation also displayed only insignificant changes in bioavailability in  
543 the fed compared to the fasted state, allowing food independent dosing <sup>[139]</sup>.

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

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

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

## 565 Lipid Based Formulations

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

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

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

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

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

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

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

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

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

## 620 Cyclodextrins

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

626 Sporanox<sup>®</sup> (itraconazole) has been formulated both as an amorphous solid dispersion, which  
627 displayed significant, positive food effect and as an oral solution solubilised by hydroxypropyl- $\beta$ -  
628 cyclodextrin inclusion complex. Sporanox<sup>®</sup> cyclodextrin solution has demonstrated higher  
629 bioavailability than Sporanox capsules in the fed state, and has also been demonstrated to show  
630 enhanced bioavailability in the fasted state, eliminating the need for fed state dosing <sup>[166-168]</sup>.

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

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

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

641



## 642 Guiding formulation selection

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

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

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

	High Solubility	Low Solubility
High Permeability/Metabolism	<p>Class I</p> <p>Conventional immediate release dosage forms</p>	<p>Class II</p> <p><u>Bio-enabling formulations</u></p> <p>Micronised API</p> <p>Nanonised API</p> <p>Lipid Based Formulations</p> <p>Amorphisation</p> <p>Solid Dispersions</p> <p>Crystal modification</p> <p>Cyclodextrin complexation</p>
Low Permeability/Metabolism	<p>Class III</p> <p>Permeation enhancers</p>	<p>Class IV</p> <p>Combination of II and III</p>

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683

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

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

	Trade name	API	Clinical recommendation	AUC
Amorphous 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.
	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
Vitreolis®	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.
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®	vinorelbine tartrate	Administer the capsule with some food, as this has also been shown to reduce the incidence of nausea and vomiting
Zemlar®	Paricalcitol	Without regard to meals
Toctino®	Alitretinoin	With a main meal
Vyndaqel®	Tafamidis meqlumine	With or without food
Royaldee®	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

688 <sup>a</sup> Where no numerical values for food effect were obtained but no significant food effect was  
689 observed a value of 1 was assigned  
690 <sup>b</sup> Moderate fat meal  
691 <sup>c</sup> High fat meal  
692 <sup>d</sup> Low fat meal  
693 <sup>e</sup> With Breakfast  
694 <sup>f</sup> 2 hours post breakfast  
695 <sup>g</sup> 4 hours post breakfast  
696 <sup>h</sup> Active metabolite

## 697 Conclusion

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

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

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

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

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

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