Assessment of food effects during clinical development

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Abstract

Food-drug interactions frequently hamper oral drug development due to various physicochemical, physiological and formulation-dependent mechanisms. This has stimulated the development of a range of promising biopharmaceutical assessment tools which, however, lack standardized settings and protocols. Hence, this manuscript aims to provide an overview of the general approach and the methodology used in food effect assessment and prediction. For *in vitro* dissolution-based predictions, the expected food effect mechanism should be carefully considered when selecting the level of complexity of the model, together with its drawbacks and advantages. Typically, *in vitro* dissolution profiles are then incorporated into physiologically based pharmacokinetic models, which can estimate the impact of food-drug interactions on bioavailability within 2-fold prediction error, at least. Positive food effects related to drug solubilization in the GI tract are easier to predict than negative food effects. Preclinical animal models also provide a good level of food effect prediction, with beagle dogs remaining the gold standard. When solubility-related food-drug interactions have large clinical impact, advanced formulation approaches can be used to improve fasted state pharmacokinetics, hence decreasing the fasted/fed difference in oral bioavailability. Finally, the knowledge from all studies should be combined to secure regulatory approval of the labelling instructions.

Keywords

Food-drug interactions; *in vitro*; *in silico*; *in vivo*; formulation

Introduction

Food-drug interactions often present a significant challenge during the development of oral medicines, due to their influence on drug pharmacodynamics and pharmacokinetics (PK). In particular, food may have a substantial impact on drug absorption and metabolism, which will be reflected in the measured PK parameters. The high degree of complexity when dealing with food effects on oral bioavailability arises from the diversity of underlying mechanisms (**Figure 1**), which can originate from the drug physicochemical properties, the formulation technology or the physiology (for details see the review of Koziolek *et al.*, 2019a) and the difficulties in predicting such food effects at the pre-clinical stage (Bennett-Lenane *et al.*, 2022; Koziolek *et al.*, 2019a).

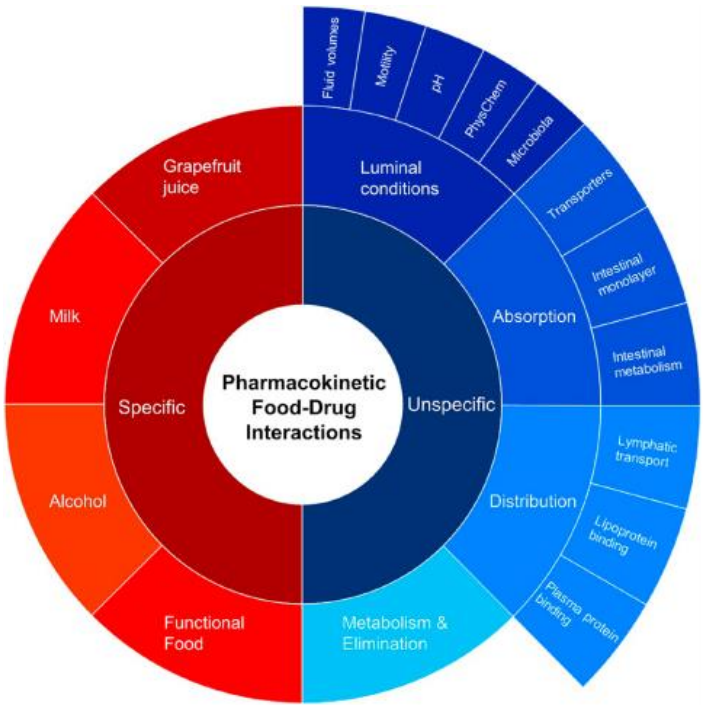


Figure 1. Summary of specific and unspecific pharmacokinetic food-drug interactions. Reprinted from Koziolek *et al*. 2019a, Creative Commons CC-BY license.

As a result, regulatory agencies generally require submission of pharmacokinetic data after food intake from the pharmaceutical industry to support labelling instructions (FDA, 2002, 2022). Hence, the study of food effects, their mechanisms and their impact on drug safety and efficacy has attracted considerable interest. A wide variety of *in silico*, *in vitro* and *in vivo* methods (**Figure 2**) have been developed to assess the various mechanisms and implications of food effects (Chen *et al.*, 2018; Koziolek *et al.*, 2019a; Koziolek *et al.*, 2018; Veerman *et al.*, 2020). Some of those methods have been described in a recent review (Wilson *et al.*, 2022).

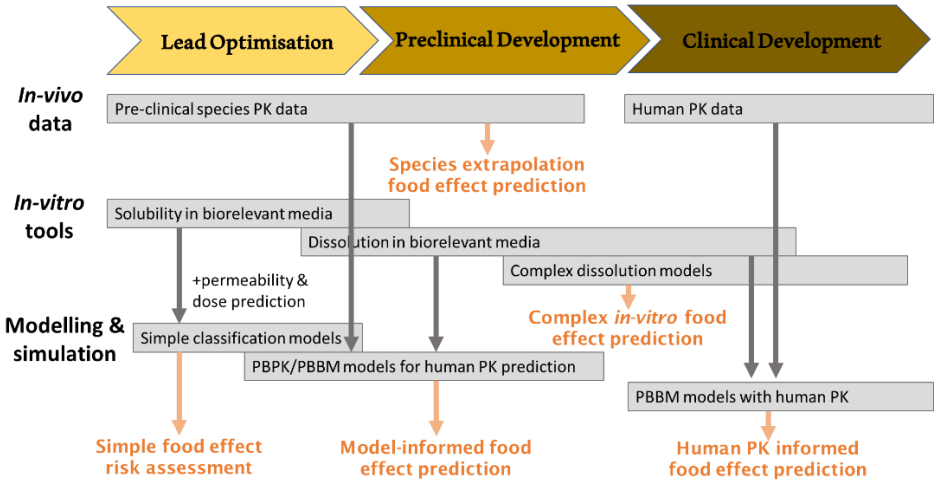


Figure 2. Food effect prediction workflow in pharmaceutical development.

At the same time, method selection depends on the goal of food effect evaluation and on the stage of drug development: for example, early assessment protocols serve to estimate the risk of significant food effects in the clinic, largely based on drug properties alone. Recently, physiologically based pharmacokinetic (PBPK) modelling has gained larger attraction also for food effect prediction at preclinical stages. As a project approaches first-in-human dosing, pre-clinical *in vivo* data and formulation specific *in vitro* data can be used to attempt to prospectively predict clinically relevant effects of food intake on drug PK in humans. Finally, once clinical PK data is available, this can be used to guide further formulation development (*e.g.* to develop a

formulation with a reduced food effect) and to further refine *in silico* and *in vitro* methods (Figure 1).

Although the recently published Food and Drug Administration (FDA) guidance for assessing the food effects provides an updated regulatory perspective on the topic (FDA, 2022), it does not include an overview of the various methodologies that are actually being used to assess the impact of food by the pharmaceutical industry. Hence, this review aims to describe the current practices in the application of *in vitro*, *in vivo* and *in silico* tools for food effect assessment in the context of the drug development stage and to provide an overview of the respective regulatory and clinical development considerations.

In vitro **prediction tools**

In vitro prediction tools can be used to predict the *in vivo* performance of a drug product in humans after administration of food, relative to fasted state, especially when the dissolution of the drug in the gastrointestinal (GI) lumen is the primary driver for a food effect. In practice, this means that food effect prediction via *in vitro* tools commonly focuses on drugs with poor aqueous solubility, which often display positive food effects on oral drug bioavailability. Such drugs belong to class 2 or 4 of the biopharmaceutical classification systems (BCS). This area of focus is logical as poorly water-soluble drugs are very common in modern pharmaceutical company portfolios, and as they are also more likely to display clinically significant food effects. For BCS 1 and 3 drugs, clinically significant food effects are somewhat less frequently encountered, and due to high drug solubility, may be related to the impact of the fed state environment on aspects beyond the dissolution of the drug product. In the following sections, we will address the some of the most frequently used in vitro tools, which can vary greatly in their complexity and ability to mimic the real situation in the human gastrointestinal tract, see **Figure 3**.

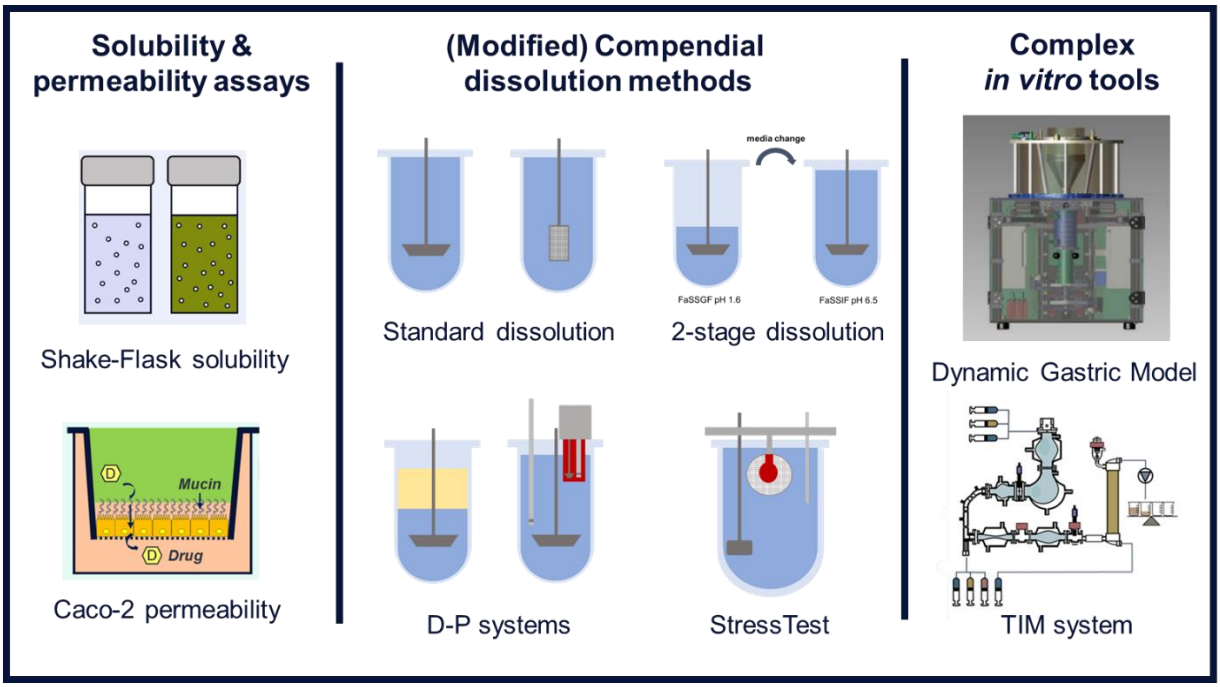


Figure 3. Schematic representation of the types of in vitro models used to study food effects. D-P denotes "dissolution-permeation" and TIM denotes "TNO Gastro-Intestinal Model". The sketch of the Caco-2 permeability setup was obtained from Ye *et al*. 2022, the Dynamic Gastric Model sketch was obtained from Mann and Pygall 2014 and the TIM sketch was obtained from López Mármol *et al.* 2022.

Simple solubility- and permeability-based models for food effect prediction

Solubility in biorelevant media is often used as a starting point for food effect prediction for poorly water-soluble drugs when new drug candidates are identified. Solubility in fasted and fed state simulated intestinal fluids (FaSSIF/FeSSIF) has been shown to reflect that observed in human aspirates reasonably well, in both the fasted and fed state (Augustijns *et al.*, 2014). However, it is only if a drug's absorption is incomplete (due to low solubility and/or slow dissolution) when differences in FaSSIF/FeSSIF solubility potentially translate to a meaningful difference in bioavailability. The BCS (Fleisher *et al.*, 1999; Ku, 2008; O'Shea *et al.*, 2019) and the related

Biopharmaceutics Drug Disposition Classification System (BDDCS) (Benet, 2013) have been proposed as tools for use in the prediction of food effects. The typical assumptions for how food effects vary with BCS class are shown in **Figure 4A**.

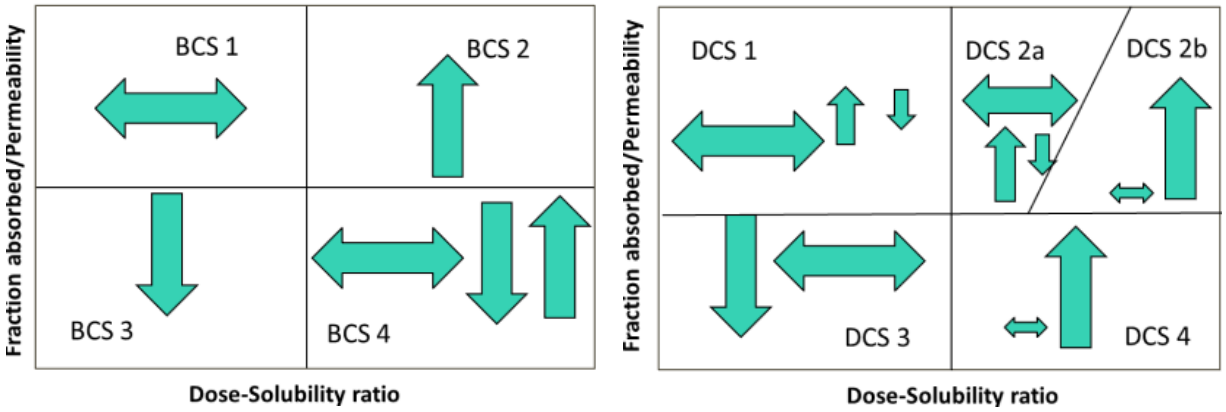


Figure 4. (A) Postulated direction of food effect (fed/fasted ratio) on the bioavailability of orally administered drugs based on the Biopharmaceutical Classification System (BCS). (B) Postulated direction of food effect on the bioavailability of orally administered drugs based on the Developability Classification System (DCS). The size of the arrows represents the approximate frequency of a positive, negative, or no food effect being observed based upon a set of 131 oral drugs approved by the FDA between 2011 and 2017. A significant food effect was classified as a change in AUC of 15% or greater, irrespective of whether this was deemed a clinically significant difference.

However, as BCS is primarily designed to identify risks of bio-inequivalence in a regulatory setting, it is therefore by nature conservative when determining if an actual *in vivo* effect is likely. For instance, the common assumption that BCS 2 drugs are likely to have positive food effects does not necessarily hold true, as many BCS 2 drugs can be formulated in a manner that allows almost completely absorption even in fasted state, thus eliminating the potential for a solubility-related food effect.

The Developability Classification System (DCS) system (Butler and Dressman, 2010), which was developed with early development biopharmaceutics questions in mind, including the propensity for food effects, is a more discriminative tool than BCS in predicting solubility-related food

effects. It uses solubility in FaSSIF as the arbiter of whether a drug is high or low solubility, and subdivides BCS class 2 drugs into class 2a (dissolution rate-limited) and class 2b (solubility-limited) drugs. As shown in **Figure 4B**, the solubility-limited drugs (DCS class 2b and 4) have the highest propensity to show positive food effects.

The true picture of how food effect relates to BCS/DCS class is complex, due to the multiple, and sometimes poorly understood factors involved, some of which are inadequately captured in a simple solubility/permeability framework. It is worth noting that whilst BCS/DCS class 3 drugs have a greater risk of negative food effects, they are equally likely to display no significant food effect. As could be expected, BCS/DCS class 1 drugs rarely show meaningful food effects.

Compendial dissolution methods to predict food effects for poorly water-soluble compounds

When evaluating formulations for food effects, comparative dissolution generated in a compendial apparatus, such as the paddle (USP apparatus 2) method in FaSSIF/FeSSIF can be used at initial stages. The dissolution profiles can be used directly to indicate a food effect by the difference between the fasted and fed states. Alternatively, the dissolution profiles may be incorporated into a PBPK or a physiologically-based biopharmaceutics model (PBBM) to account for other factors potentially influencing the actual food effect. Working with the first widely applied versions of bile salt micelle-containing biorelevant media, Galia *et al.* demonstrated that dissolution in FaSSIF/FeSSIF (version 1) could broadly predict the observed food effect in humans for the neutral, low solubility drug danazol (Galia *et al.*, 1998), whilst Nicolaides *et al.* demonstrated that differences in human bioavailability in fasted/fed state for four low solubility neutral/weak acid drugs were also predicted from the *in vitro* data (Nicolaides *et al.*, 1999). In addition, human pharmacokinetic data in the fasted and fed state has been shown to be reasonably well correlated

to FaSSIF/FeSSIF dissolution profiles for a wider set of poorly water soluble compounds (Mathias *et al.,* 2015).

Since the publication of the original biorelevant media recipes in the late 1990's, modified intestinal media (version 2), plus media for the fed state gastric environment (Jantratid *et al.*, 2008) were proposed. In addition, newer versions incorporate the products of lipid digestion into simulated intestinal media (Fuchs *et al.*, 2015; Jantratid *et al.*, 2008). Subsequent to the introduction of biorelevant dissolution media, the incorporation of dissolution data into PBPK models has been demonstrated to be an invaluable approach with numerous publications advocating their use (Kushwah *et al.*, 2021; Otsuka *et al.*, 2013; Shono *et al.*, 2009; Shono *et al.*, 2010).

For modified and extended-release oral products, attempts have been made to predict fasted and fed state performance using flow-through (USP apparatus 4) and reciprocating cylinder (USP apparatus 3) set ups. Both set ups allow multiple biorelevant media changes to mimic the transit of a dosage form through the GI tract. Andreas *et al.* demonstrated that for two nifedipine ER formulations, the reciprocating cylinder method was shown to qualitatively predict the positive food effect, although the flow-through method was less predictive (Andreas *et al.*, 2016). Both these compendial set ups have also been used with success to predict the impact of food on mesalamine formulations (Andreas *et al.*, 2015). As well as being used for extended-release formulations, the flow-through apparatus with biorelevant media has also been shown to predict the food effect of immediate release formulations (Kushwah *et al.*, 2021; Sunesen *et al.*, 2005). However, these compendial methods, even with multiple media changes, miss many motility-related events *in vivo*, especially the strong peristaltic movements associated with gastric emptying of residual solids and meal components (Koziolek *et al.*, 2018).

Modified compendial set ups

Whilst FaSSIF/FeSSIF dissolution comparisons may be useful, and certainly add physiological relevance in terms of micellar solubilization over simple buffer solutions, there are caveats in their use which can lead to under- or over-prediction of an *in vivo* food effect, especially if the fasted/fed ratio is estimated directly from the *in vitro* data. These include:

a) Differences in dissolution rate and/or solubility *in vitro* in FaSSIF/FeSSIF will not translate directly into *in vivo* differences for drugs where suitable formulation and size control strategies have been employed to ensure close to complete absorption in the fasted state. For some poorly water-soluble compounds, adequate control of particle size can therefore lead to the elimination of food effects (Butler and Dressman, 2010; O'Shea *et al.*, 2019)

b) For drugs, which supersaturate *in vivo* such as some low solubility weak bases, and for formulations which utilize supersaturation as a bio-enabling strategy, simple dissolution experiments directly in FaSSIF/FeSSIF will not capture the potentially critical gastric dissolution process, nor adequately reflect gastric emptying kinetics or any subsequent saturation/precipitation.

c) The micellar components in food (and in the *in vitro* set ups), whilst typically increasing bulk drug concentration in solution, may entrap dissolved drug in the small intestinal lumen, reducing the free drug concentrations, and therefore reducing the availability of drug for absorption at the gut wall (Miller *et al.*, 2011).

d) *In vivo* impact of food intake that is unrelated to drug dissolution and solubility, such as the impact of binding to specific food components like trypsin (Lee *et al.*, 2016), the

influence of food on pre-systemic drug metabolism (Melander et al., 1988), or the impact on efflux transporters (Sharma and Prasad, 2021) will clearly not be accounted for in a typical dissolution-based *in vitro* model.

To overcome some of these limitations, modifications to compendial paddle methods have been proposed in recent years to improve biorelevance. These include:

1) Adding an absorption stage to the dissolution test, to mimic permeation across the gut wall, which is thought to be primarily accessible to the free drug, rather than to strongly micellar bound drug. There are several different methods reported in the literature to modify compendial set ups to achieve this. One approach is to use an immiscible organic liquid layer such as octanol (Frank *et al.*, 2014; Mudie *et al.*, 2012; Xu *et al.*, 2017), in the compendial apparatus. However, these biphasic methods need to be used with caution with micelle-containing media (due to possible emulsification of octanol), so their application to food effect prediction may be limited. Even so, their use with biorelevant media in food effect prediction has been reported (Xu *et al.*, 2017). Alternatively, a semi-permeable membrane that only allows the permeation of free drug, rather than micelle bound drug can be used. A range of set ups have been proposed for potential use in combination with compendial dissolution apparatus (Berben *et al.*, 2018a; Berben *et al.*, 2018b; Borbás *et al.*, 2019; Borbas *et al.*, 2018; Hens *et al.*, 2015). In this case, the surface-to-volume ratio of the respective permeation method should be considered, as it often limits the transfer of the drug to the acceptor compartment (complete transfer to the acceptor is usually not achieved). A detailed review of the best practices in drug permeation assessment has recently been published (O'Shea *et al.*, 2022).

2) Use of two-stage biorelevant dissolution in which the gastric and intestinal environments are mimicked in sequence. This may be done with a simple transfer model (Kostewicz *et al.*, 2004; Wagner *et al.*, 2012) in which drug is pre-dissolved in a simulated gastric media and supersaturation/precipitation measured upon controlled transfer at a fixed rate to intestinal media, with mixing in the intestinal media provided by the stirring action in a standard paddle apparatus. The biorelevant media used, and the transfer rate can be altered to represent that likely to be seen *in vivo*, including that observed in the fasted and fed states (Litou *et al.*, 2020; Ruff *et al.*, 2017). Alternatively, a two-stage dissolution test set up in which a second media is added to mimic the change from a gastric environment to an intestinal environment may be used (Berben *et al.*, 2019; Mann *et al.*, 2017). Using a methodology which combines both two-stage biorelevant dissolution, and the use of a permeation bag to mimic the permeation barrier, Hens *et al.* determined the free drug concentrations available for absorption for two formulations of fenofibrate, in both the fasted and fed state (Hens *et al.*, 2015). This work demonstrated that it was the free drug concentrations that were key to predicting the actual food effects observed *in vivo* with the two formulations. One potential disadvantage with two-stage methods is that typically, an intestinal medium is added to the gastric media rapidly at an uncontrolled rate. This rapid addition of a second medium contrasts with comparatively slower gastric emptying *in vivo*, especially in the fed state.

3) Replacement of the paddle or basket for agitation with pressure application devices to simulate the forces associated with gastrointestinal motility and transit. This has been explored through the use of the Stress Test apparatus, developed at the University of Greifswald (Garbacz *et al.*, 2010). In terms of food effect prediction, this apparatus has

been shown to be especially advantageous in the assessment of extended-release matrix tablets (Garbacz *et al.*, 2009; Garbacz *et al.*, 2008; Koziolek *et al.*, 2013).

Ultimately, although compendial based set ups can provide useful insights - provided appropriate biorelevant media are used - the design of the currently available compendial apparatus restricts the opportunities for adequate simulation of the highly dynamic GI environments *in vivo*, meaning more complex *in vitro* tools and/or the incorporation of dissolution data into a PBPK model which can account for these other factors may be required for reliable food effect prediction.

Complex in vitro tools to predict food effects for poorly water-soluble compounds

Complex *in vitro* tools that have shown benefit in the prediction of food effects for drug products include the TIM-1 / tiny-TIM systems (Verwei *et al.*, 2016), as well as the Dynamic Gastric Model (DGM) / Model Gut system (Thuenemann *et al.*, 2015). Typically, these systems were developed for understanding of the interplay between GI motility, food digestion and nutrient dissolution. In addition to the TIM and DGM systems discussed below, there are a wide range of other complex *in vitro* tools applied in food science that could theoretically be used to understand and predict food effects of oral drug products. Several comprehensive reviews of these systems are available (Dupont *et al.*, 2019; Li and Kong, 2022). It's also worth noting that based on the ability of TIM systems to predict relative pharmacokinetic performance of different formulations, their application to completely replace pre-clinical models for formulation performance evaluation has been proposed and adopted by some pharmaceutical companies (Dickinson *et al*., 2012; Barker *et al.*, 2014).

The TIM systems and the DGM model are designed to mimic the dynamic situation resulting from secretions, digestion, transfer of material and motility in the human GI tract. Originally developed with applications to the food industry in mind, these systems have the capability to test drug

products in the presence of the exact meal used in any clinical study, with the meal being added to the model after being homogenized, or by actual chewing by the operator during the experiment set up. A summary table of TIM model applications to predict food effects is shown in Table 1.

As can be seen from the table, Verwei *et al.* showed that TIM-1 and tiny-TIM models correctly predicted the positive food effect for a posaconazole suspension, and the lack of a food effect for an immediate release ciprofloxacin tablet formulation. However, both systems overpredicted the positive food effect of the Noxafil® suspension. This discrepancy between the *in vitro* and *in vivo* data might be explained by the high permeability of posaconazole, which partially compensates the poor solubility in fasted state human intestinal fluids. Ojala *et al.* demonstrated for immediate release formulations of a poorly water-soluble, weakly basic drug that the TIM-1 model was a more reliable predictor of fasted/fed pharmacokinetics than simpler compendial set-ups with biorelevant media (Ojala *et al.*, 2020). In addition, Lloyd *et al.* were able to show that the TIM-1 model could be predictive of a negative food effect observed for the low solubility, zwitterionic drug danirixin (Lloyd *et al.*, 2020).

Table 1. Prediction of food effects using TIM systems.

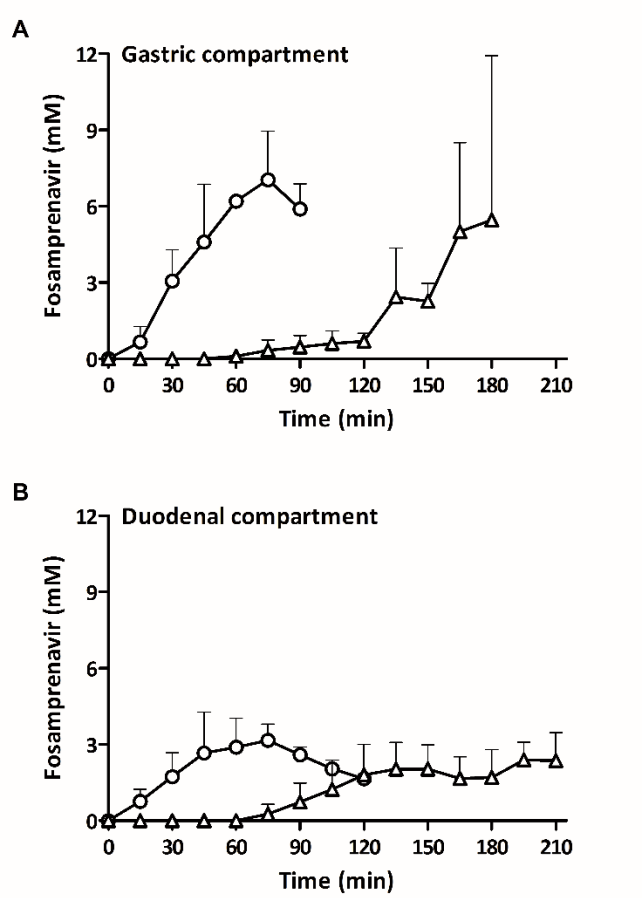
API	**Formulation**	**Meal type**	***In vivo* fed/fasted ratio**	**TIM *in vitro* fed/fasted ratio**	**Publication TIM data**
Danirixin	DNX HBr	High fat meal	0.6 (AUC0-inf)	0.6 (TIM-1)	(Lloyd *et al.*, 2020)
Diclofenac	Cataflam IR	Ensure Plus	1.0 ($AUC_{0\text{-}8h}$)	1.0 (TIM-1)	(Van Den Abeele *et al.*, 2017)
Ciprofloxacin	Ciproxin ER	High fat meal	1.0 (AUC)	1.2 (TIM-1) 1.0 (tiny-TIM)	(Verwei *et al.*, 2016)
Acetaminophen	Paracetamol IR	High caloric meal	0.9 ($AUC_{0\text{-}inf}$)	1 (TIM-1)	(Souliman *et al.*, 2006)
Acetaminophen	Sinaspril **crushed*	Infant formula	No food effect	No food effect (tiny-$TIM_{pediatrics}$)	(Havenaar *et al.*, 2013)

Fosamprenavir	Telzir IR	Scandi-shake Mix	No food effect AUC Effect on disintegration	No food effect bioacc. Effect on disintegration (TIM-1)	(Brouwers *et al.*, 2011)
Celecoxib	Celebrex	High fat meal	1.6 ($AUC_{0\text{-}inf}$)	2.0 (TIM-1)	(Lyng *et al.*, 2016)
Nifedipine	Adalat XL MR	High fat meal	1.7 ($AUC_{0\text{-}9h}$)	3.5 (TIM-1) 3.6 (tiny-TIM)	(Verwei *et al.*, 2016)
Posaconazole	Noxafil Suspension	High fat meal	4 ($AUC_{0\text{-}72h}$)	13.8 (TIM-1) 12.9 (tiny-TIM)	(Verwei *et al.*, 2016)
Undisclosed investigational drug	Tablets: doses 10-80mg	High fat meal	2.2 ($AUC_{0\text{-}t}$) at 10mg* 3.2 ($AUC_{0\text{-}t}$) at 80mg*	2.9 (tiny-TIM) at 10mg 2.7 (tiny-TIM) at 80mg	(Luo *et al.*, 2022)
Ibuprofen	Advil FR and Advil LG	High fat meal	0.9 (AUC Advil FR)* 0.9 (AUC Advil LG)*	No food effect (tinyTIM Advil FR) No food effect (tinyTIM Advil LG)	(Chiang *et al.*, 2022)

**TIM data incorporated into a PBPK model to optimally predict AUC*

The data in the table demonstrates that human food effects can be adequately predicted by the TIM models. Even so, some caution is needed – the magnitude of the food effect for pozaconazole was overpredicted, whilst not all the mechanisms leading to negative food effects are likely to be captured by the model.

A specific advantage of using these predictive complex *in vitro* tools is that the mechanisms behind specific food effects can be investigated and then confirmed by simpler *in vitro* methods. Lyng *et al.* used the TIM-1 model to show that bile salt driven micellar solubilization was the primary reason for the positive food effect for a celecoxib immediate release capsule (Lyng *et al.*, 2016). Brouwers *et al.* used a combination of the TIM-1 model and separate imaging of disintegration by MRI to show that differences in onset in the fasted and fed state for fosamprenavir tablets could be linked to delays in tablet disintegration in the fed state, see **Figure 5** (Brouwers *et al.*, 2011). Further scientific efforts will be needed to integrate information from complex *in vitro* systems into PBPK models.



294

295 **Figure 5**. Fosamprenavir concentration–time profiles in the stomach (A) and duodenum
296 (B) compartment of TIM-1, simulating the fasted (open circles) and fed (open triangles) state.
297 Results are expressed as mean ± sd (n = 3). Reprinted from European Journal of Pharmaceutics
298 and Biopharmaceutics, 77, Brouwers, J., Anneveld, B., Goudappel, G.-J., Duchateau, G.,
299 Annaert, P., Augustijns, P., Zeijdner, E. "Food-dependent disintegration of immediate release
300 fosamprenavir tablets: In vitro evaluation using magnetic resonance imaging and a dynamic
301 gastrointestinal system", 313-319, Copyright (2011), with permission from Elsevier.

302

303 Often, the simulation of GI physiology in the *in vitro* system and the *in silico* model are different,
304 which makes direct integration of data very challenging. For instance, data from Tiny-TIM and

TIM-1 are used to verify predictions from PBPK modelling, but the information are typically not used as direct inputs. To derive parameters such as dissolution rate or precipitation rate from the complex in vitro experiments, in silico models must be developed, in which the in vitro experiment is simulated.

Using the Dynamic Gastric Model (DGM), Vardakou *et al.* demonstrated that antral grinding forces could be mimicked with much greater accuracy than using compendial dissolution apparatus (Vardakou *et al.,* 2011a). Investigational work also showed that the model could predict the differing drug release properties of various immediate release capsules in the fed and fasted state (Vardakou *et al.,* 2011b). In addition, *in vitro* work on the DGM model has been used to show that this system is likely to have specific advantages for investigating the dissolution properties of extended-release matrices in the fed state, compared to fasted (Chessa *et al.*, 2014; Mason *et al.*, 2016).

One specific concern regarding the impact of food on the performance of oral dosage forms is that of the impact on extended release matrices, where the influence of GI motility can play a critical role in formulation robustness and drug release, sometimes leading to so called “dose dumping” events, where a large proportion of the dose is released rapidly, circumventing the extended release design of the product. In addition to the Stress Test apparatus mentioned in the previous section on modified compendial apparatus, more complex tools such as TIM-1, TinyTIM and DGM which are more commonly used to predict immediate release formulation performance in the presence of food, may also be applied to understanding the *in vivo* behavior of extended release products (Chessa *et al.,* 2014; Mason *et al.,* 2016). Note that *in vitro* tools to study the impact of food on extended release formulations, have previously been reviewed in detail (Koziolek *et al.*, 2018),

whilst *in vitro* tools to study the impact of food on immediate release formulations have also been the topic of a recent review article (Lex *et al.*, 2022).

In vivo models for food effect predictions

As highlighted in the previous sections, food effects on drug bioavailability are the result of the complex interplay of different physiological factors that change after the intake of food (Koziolek *et al.*, 2019a). Before complex and powerful *in vitro* tools (*e.g.* TIM-1, DGM) and *in silico* models (*e.g.* SimCYP, GastroPlus) were made commercially available, food effect prediction was primarily performed in animal models. Theoretically, different animal models such as mice, rats, dogs, pigs or monkeys may be used for this purpose as they are available in pharmaceutical R&D units. However, for the selection of the most suitable animal model, pharmaceutical scientists need to take a deeper look at the following requirements:

1. The animal model should be able to simulate the conditions of the human GI tract in both fasted and fed state. One of the major challenges is not only to simulate fed state conditions in a way that is comparable to the human situation, but also to enable a realistic assessment of drug product performance in fasted state. Only if both, fasted and fed state, are simulated correctly, a food effect on oral bioavailability can be predicted.
2. The formulation plays an important role in the occurrence of food effects. It is therefore not enough to simply administer neat API or simple suspensions/solutions to the animal. Ideally, the finished drug product can be administered to the animal to make a realistic food effect assessment. Moreover, a suitable protocol must be taken into place to adequately simulate food effect studies in humans (FDA, 2002, 2022).

3. The animal GI tract can differ in various aspects from the human GI tract. Based on the pharmacokinetic, pharmacological and physicochemical properties of the drug product, certain mechanisms leading to food effects can be expected (Hatton *et al.*, 2015; Koziolek *et al.*, 2019a; Sjogren *et al.*, 2014). Based on this expectation, some models may be more relevant than others.

For mice and rats, which are used broadly during drug discovery and also at preclinical stages, their GI anatomy and physiology (including the digestive enzymes) is highly different from the human GI tract (Hatton *et al.*, 2015; Koziolek *et al.*, 2019a). Moreover, larger formulations cannot be administered to these animals. Therefore, they may be used to elucidate certain mechanisms potentially leading to food effects (Holmstock *et al.*, 2013), but they do not represent ideal models for an accurate prediction of food effects on oral bioavailability. On the other hand, for monkeys, which are considered to be the best model for oral bioavailability prediction in humans (Musther *et al.*, 2014), there is very limited experience with food effect prediction. Although the physiological conditions in fed cynomolgus monkeys have been characterized and compared to the human situation in two studies by Kondo and colleagues (Kondo *et al.*, 2003a; Kondo *et al.*, 2003b), a standard protocol on how to simulate fed conditions in monkeys has not been established yet. Moreover, due to the small size of the cynomolgus monkeys (< 10 kg), it is probably difficult to administer larger formulations. Therefore, monkeys are typically not used for food effect predictions. Instead, the Beagle dog represents the most widely used animal model for human food effect prediction. In the last years, some groups also reported on the use of pigs for food effect prediction. In the following text, we will therefore focus on these two animal models and discuss their potential application based on selected case examples.

In many pharmaceutical companies, the Beagle dog is the primary animal model to predict food effects on oral bioavailability. First studies on the application of this model for simulation of drug product performance in fed state have been published more almost 40 years ago (Cox *et al.*, 1985; Shiu *et al.*, 1989). Therefore, there is large experience within the pharmaceutical industry on the application of this animal model. However, whereas various guidance documents were issued by regulatory authorities on food effect studies in humans (EMA, 2012; FDA, 2002), there is still no standard protocol in terms of pre-treatment, type and timing of food intake, fluid intake during administration as well as subsequent food or liquid intake for food effect studies in dogs. Studies in which the dog model was successfully applied to predict drug product performance in presence of food, often have anecdotal character and can hardly be compared to other food effect studies in dogs. Nonetheless, the dog model can provide useful insights into drug product performance in fed state. For instance, Wu and colleagues nicely illustrated how a dog model was used to support the development of a nanocrystalline formulation of MK-0869 (aprepitant). Canine data could demonstrate that this formulation has a reduced food effect as compared to a conventional suspension, see **Figure 6** (Wu *et al.*, 2004). However, only few systematic studies on the use of dogs for food effect prediction have so far been performed (Lentz *et al.*, 2007; Mathias *et al.*, 2015; Zane *et al.*, 2014). In this context, one of the most relevant articles was published in 2007 by Lentz and colleagues, who studied the impact of the study protocol and investigated the correlation between food effect in dogs and humans (Lentz *et al.*, 2007). Based on two model compounds (atazanavir and pravastatin), it was first shown that, to achieve the best correlation to human data, a 50 g aliquot of the FDA meal should be used and that dogs should be pretreated with pentagastrin to stimulate gastric acid secretion in fasted state.

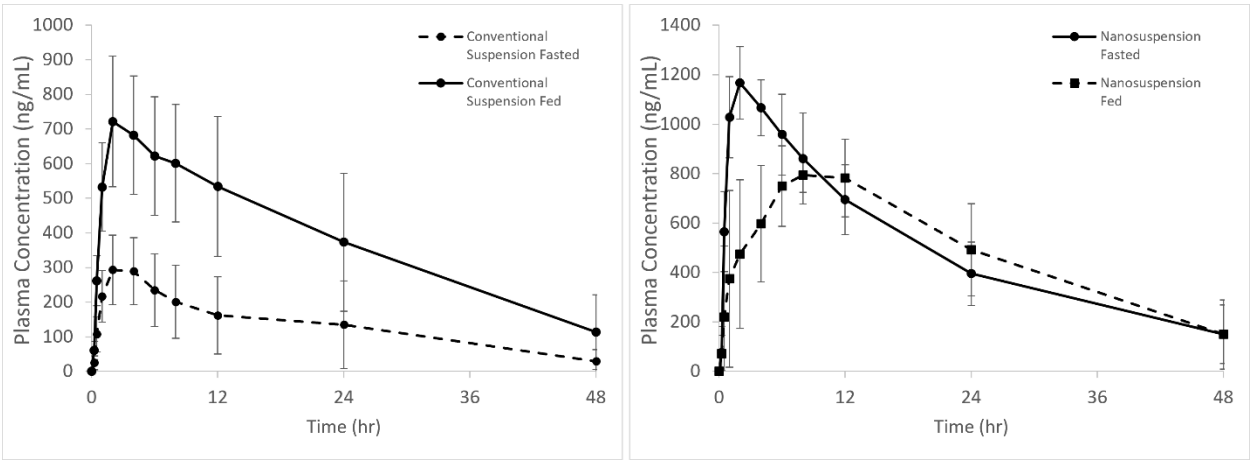


Figure 6. Assessment of food effect for conventional (left) and nanosized (right) suspensions in dogs. Based on data from Wu et al, Int J Pharm, 285 (2004), 135-146.

The optimized protocol was then applied in three Beagle dogs, who received nine different drug products with different types of food effect (*i.e.* negative, positive or no food effect) in a cross-over design. This dog model was able to capture positive food effects for drugs which also showed positive food effects in humans. Also, for drugs with negative food effects, it indicated the correct direction of the food effect. However, there was a slight tendency to overestimate drug product performance in fed state and therefore, for two out of three drugs, which showed no food effects in humans, a positive food effect was seen in dogs. This study was one of the first to provide a scientific basis for the application of a preclinical dog model, but the small sample size is a major limitation, especially if the huge variability is considered that is often seen in dog studies.

In a follow-up study by Mathias, 15 different compounds were studied in dogs and PK data were again compared to human data (Mathias *et al.*, 2015). Here, the food effect ratio in dogs correlated linearly with the food effect ratio in humans ($R^2 = 0.74$). Again, the dog model was able to predict the direction of food effects in most cases, whereas the extent was not always predicted correctly. Another interesting study was published by Zane and colleagues in 2014, who used the dog model to study the performance of different formulations of four drugs (Zane *et al.*, 2014). This study

412 was performed in a cross-over design with eight Beagle dogs that were pretreated with
413 pentagastrin. Despite the fact that very different formulation concepts were compared to each other
414 (*e.g.*, capsules vs. tablets, salt vs. lipid based formulations), the authors found a clear relationship
415 between canine and human data. In each case, the dog model was able to predict the direction of
416 food effects. However, it was not able to adequately predict the extent of the food effect seen in
417 humans for the different formulations tested.
418 A correct prediction of the food effect on oral bioavailability is often impeded by certain
419 differences in terms of canine GI anatomy and physiology as compared to humans. Recently,
420 Koziolek and colleagues used the SmartPill to further study the physiological conditions in dogs
421 under different prandial conditions as well as after different pretreatments (pentagastrin and
422 famotidine) (Koziolek *et al.*, 2019b). The data could be directly compared to similar data obtained
423 in humans that were generated earlier by the same authors. Interestingly, canine and human GI
424 physiology were comparable in various aspects such as gastric or intestinal pH. However, some
425 important differences were noted in terms of gastric transit time in fed state, small intestinal transit
426 time as well as in gastrointestinal pressures. All these parameters can play an important role for
427 oral drug delivery and thus, they may affect the prediction of food effects. It should be noted that
428 parameters such as gastric pH or gastric residence time highly depend on the type of meal used in
429 these studies. Therefore, the protocol can be of major importance for the outcome of food effect
430 predictions. Unlike in humans, where the FDA has issued a guidance on how to perform food
431 effect studies, the protocols used in the pharmaceutical industry differ among the different
432 companies. For instance, different meals such as dog food or shredded FDA meal are used
433 depending on the individual protocol. In addition, there are further differences between human and
434 dogs in terms of paracellular absorption as well as in terms of enzyme and transporter expressions

(Martinez *et al.*, 2019). Thus, data from dog studies should always be interpreted with care and further data from *in vitro* and *in silico* models should confirm the findings.

Another animal model that may be useful for food effect prediction is the pig. This animal model is widely used by food scientists to simulate digestive processes but also to model certain diseases. However, its application in pharmaceutical R&D is rather limited. In recent years, Brendan Griffin and team were studying the suitability of the pig model for food effect predictions. Despite the fact that the simulation of fasted state conditions is complex in pigs due to slow gastric emptying of digesta and in particular large objects (Henze *et al.*, 2021; Henze *et al.*, 2019), which limits the application of this model for slowly or non-disintegrating monolithic dosage forms, the model may be valuable for the prediction of food effects for immediate release formulations of poorly water-soluble drugs as was shown recently for fenofibrate (Henze *et al.*, 2019). It will be interesting to see if further studies will confirm this hypothesis and if this model will receive broader attention for food effect prediction in case of drugs with poor aqueous solubility.

In conclusion, animal models such as the Beagle dog have been and still are valuable tools for prediction of the direction of food effects on oral bioavailability and the assessment of formulation performance in fasted/fed state. However, various physiological parameters differ significantly between humans and laboratory animals commonly used for food effect prediction, which may impair their predictive power. Generally, like in humans, the study protocol has huge impact on the outcome of food effect studies in animals. In light of the 3R approach to reduce, replace and refine the use of animal in pharmaceutical R&D, some companies have stopped using animal models to support formulation development and food effect assessment. Apart from ethical reasons, the relatively high costs associated with animal studies, the high variability often seen in PK studies as well as the limited predictability with respect to human PK have been important

reasons for this decision. With further improvement of the various *in vitro* and *in silico* tools and their predictive power, the number of animal studies will most probably further decline in the coming years.

Physiologically Based Pharmacokinetic modeling

PBPK models have been historically utilized in the pharmaceutical industry primarily for first-in-human (FIH) dose predictions and for predicting drug-drug interactions (DDIs). With the expansion of PBPK models to modeling of oral absorption processes and guiding formulation development, there has been increased interest to the application of these models for food effect predictions, see Table 2. Since 2009, approximately 20 manuscripts have been published specifically discussing case studies of PBPK models applied to food effect prediction/characterization, covering more than 30, primarily BCS/BDDCS class 2 and 4 drugs. The principles and limitations of published PBPK models have been reviewed elsewhere (Kesisoglou, 2020; Li *et al.*, 2018).

Table 2. Summary of publications with PBPK models for food effect, listed chronologically (modified from Kesisoglou (Kesisoglou, 2020))

Publication	Compound	BCS	Food effect (AUC as primary endpoint)
(Parrott *et al.*, 2009)	Theophylline (CR)	I	None
	aprepitant	II	positive (micronized tablet), no (nanosuspension)
(Shono *et al.*, 2009)	Celecoxib	II	Positive
(Shono *et al.*, 2010)	Aprepitant	II	Positive/None (micron/nano - sized)
(Heimbach *et al.*, 2013)	Proprietary Compound (NVS732)	I	None
	Proprietary Compound (NVS406)	II	Positive
	Proprietary Compound (NVS701)	II	Positive
	Proprietary Compound (NVS113)	II	Negative

(Xia *et al.*, 2013)	Proprietary Compound (NVS123)	II	Positive
	Proprietary Compound (NVS169)	IV	None
	Proprietary Compound (NVS562)	II or IV	Positive
(Zhang *et al.*, 2014)	Proprietary Compound	II or IV	Positive
(Cristofoletti *et al.*, 2016)	Ketoconazole	II	Positive
	Posaconazole	II	Positive
(Parrott *et al.*, 2016)	Alectinib	II	Positive
(Sutton *et al.*, 2017)	Ziprasidone	II	Positive
(Rose *et al.*, 2017)	Propranolol	II	Positive
	Ibrutinib	II	Positive
(Andreas *et al.*, 2017)	Zolpidem MR	I	Negative
(Emami Riedmaier *et al.*, 2018)	Venetoclax	IV	Positive
(Tistaert *et al.*, 2019)	Proprietary Compound	I	None
	Mebendazole	II	Positive
	Bitopertin	II	Positive
	Proprietary Compound	II	None
(Radwan *et al.*, 2019)	Clarithromycin	II	None
(Gajewska *et al.*, 2020)	alpelisib	II	positive
(Lloyd *et al.*, 2020)	Danirixin HBr	IV	negative
(Arora *et al.*, 2020)	Ritonavir	IV	negative
	Ribociclib	II or IV	None
(Pepin *et al.*, 2021)	nefazodone-HCl	I	negative
	furosemide	IV	negative
	Aprepitant	II	Positive/None (micron/nano - sized)
(Wagner *et al.*, 2021)	pazopanib-HCl	II	positive
	ziprasidone-HCl	II	positive
	trospium-Cl	III	negative
(Kushwah *et al.*, 2021)	rivaroxaban	II	positive
(Jeong *et al.*, 2022)	tegoprazan	II	none
(Pepin *et al.*, 2022)	selumetinib	IV	negative

Evolution of the models over the years reflects the increased utilization of more complex *in vitro* methodologies discussed earlier in this manuscript; while initial models largely focused on the solubility differential in biorelevant media such as FeSSIF and FaSSIF, data from multi-

compartment systems to characterize dissolution and precipitation are now more commonly utilized.

Models are typically applied first in the preclinical, pre-FIH stage, to assess the possibility of food effect and inform formulation optimization or dosing instructions in the FIH study (Xia *et al.*, 2013). At this stage in the absence of clinical model validation, the primary focus is on prediction of relatively large food effect differences (>2-fold) and especially for positive food effect, to inform whether a different formulation approach should be implemented. The PBPK models are typically used as orthogonal to studies in preclinical/dissolution models to drive a decision based on totality of evidence. Once clinical food effect data are available, the model is refined for application to provide further mechanistic insights to the observed food effect and inform subsequent formulation efforts (Emami Riedmaier *et al.*, 2018; Tistaert *et al.*, 2019; Zhang *et al.*, 2014). Available clinical data allows for validation of the model and a decision whether the food effect mechanism can be captured. Based on experience across several pharmaceutical companies, Tistaert *et al.* recently proposed a workflow for implementation of food effect PBPK models during preclinical development (Tistaert *et al.*, 2019). Given that not all food effect mechanisms can be readily predicted, the authors recommended that model application focuses on BCS/BDDCS class 2 drug formulated in IR drug products, with linear pharmacokinetics without significant gut transporter involvement, where the major mechanisms for food effect is related to luminal solubilization (*e.g.*, increase in bile salts and presence of fatty acids with meal) and/or delay in gastric emptying. These recommendations are largely in agreement with a more recent analysis published by Riedmaier *et al.* where authors, as part of an IQ Consortium effort, assessed predictability of PBPK models in relation to the food effect mechanism and also concluded that

499 successful predictions were associated with changes in the gastrointestinal luminal fluids or
500 physiology (Riedmaier *et al.*, 2020).
501 At later stages of development, the desire is to use PBPK models for regulatory interactions, such
502 as replacing clinical studies. However, despite the numerous successful examples in the literature,
503 best practice and regulatory acceptance of PBPK models for food effect predictions are still
504 evolving. As a result, confidence in the models by regulators is still low (Li *et al.*, 2018).
505 Development of standardized input and model development workflows have been recently
506 proposed (Riedmaier *et al.*, 2020) as a step towards that direction. In practice, validation of the
507 prediction against early-stage clinical food effect data before use of the model for *a priori*
508 predictions, as recommended by Tistaert *et al.* and Kesisoglou (Kesisoglou, 2020; Tistaert *et al.*,
509 2019), is likely going to be a prerequisite for model application at later development stages and in
510 a regulatory setting.

511 **Clinical Development and Regulatory Considerations**

512 Evaluation of the effect of food on drug bioavailability is a core component of the Clinical
513 Pharmacology/Biopharmaceutics program during development of a new chemical entity. Barring
514 any specific dosing restrictions informed by specific drug, formulation and target patient
515 population characteristics (*e.g.*, if very low bioavailability is expected in the fasted state, one may
516 decide to conduct early studies with dosing with a meal), food effect is often evaluated early in
517 clinical development, comparing fasted and fed administration, as part of the first-in-human single-
518 ascending or multiple-ascending dose studies. These studies, typically conducted with healthy
519 volunteers using standardized dosing conditions, such as a high-fat/high-caloric breakfast
520 described in the US FDA guidance (FDA, 2022), serve as the basis to inform dosing in subsequent
521 clinical trials when studies expand to larger number of patients. Even for indications such as

oncology where first-in-human dosing may be in patients, it is generally recommended that the effect of food is explored early on. In many cases, food effect studies may be repeated later in development to test food effect for new formulations, to assess different meal types or when the program expands to a new population (*e.g.*, pediatrics). For post-approval of significant formulation changes and for generic drug products, fed bioequivalence studies may be required depending on the drug product label and the type of formulation used (FDA, 2021).

Assessment of food-drug interactions is covered by guidelines by all major health authorities for both new chemical entities (EMA, 2012; FDA, 2022; HealthCanada, 2018) and generic drug products (EMA, 2010; FDA, 2021; NIHS-Japan, 2012). The available guidelines provide recommendations on study design, meals to be evaluated and interpretation of the results. Based on current regulatory guidelines the presence of a food effect is established based on pharmacokinetic bioequivalence bounds (*i.e.*, if the 90% confidence interval for the geometric mean ratio for AUC and C_{max} between fed and fasted dosing meets the limits of 80%-125%). Nevertheless, during clinical development, decisions on dosing instructions for clinical studies and eventually for drug labeling are typically more flexible and take into account safety and efficacy margins to define the clinical relevance of the food effect. In early clinical studies with smaller populations before food effect has been thoroughly evaluated, or when a fit-for-purpose formulation is used, it is often feasible to adopt more prescriptive dosing instructions such as fasted administration. However, as dosing expands to larger populations in Phase 2 trials and beyond, especially in pivotal studies, it is generally desirable to be able to dose medications without regard to food, as compliance to more strict dosing regimens can be an issue and is difficult to track. The dosing regimen implemented in late-stage pivotal trials is usually very similar to that on the drug prescribing information.

If the physicochemical and metabolic properties of the compound are not inherently supportive of comparable bioavailability in fasted and fed state, formulation interventions may be considered as discussed later in the following section. In cases where a formulation solution is not implemented, dosing instructions for administration with or without food may be also considered as long as they are supported by the established clinically relevant bounds. For example, for products with a positive food effect, that require administration with food to achieve adequate bioavailability, it is highly desirable that, at minimum, dosing instructions are not prescriptive of the type of meal required. Thus, whether administration with lighter meals is feasible is commonly evaluated to provide more flexibility to patients. This is the case for example for vericiguat or venetoclax where for the former the tablets are recommended to be taken with food, but high-fat, high-calorie or low-fat, low-calorie meals are both acceptable as they result in similar pharmacokinetics (VERQUVO® prescribing information (Merck & Co., Inc., Rahway, NJ, USA, 2021)), whilst the latter can be taken with either a low fat and a high-fat meal, even though the magnitude of the food effect is affected by fat content, as both result in sufficient, and much improved over fasted state bioavailability (VENCLEXTA® prescribing information (Abbvie, 2021)). However sometimes the exposure differences between meals are significant, as was the case with telaprevir (INCIVEK^{TM}), where systemic exposure increase was approximately 117% and 330% with low-fat and high-fat meal respectively. For INCIVEK, administration with food (not low fat) is prescribed in the label. A positive food effect may also result in different dose recommendation in the fed and fasted state. This is the case for ceritinib, where the recommended administration is a 450 mg dose with food, but 750 mg fasted may be used for patients unable to take drug with food (ZYKADIA EPAR-Product Information (Novartis, 2021)). If the increase in bioavailability with food, or specific types of food, raises safety concerns, specific wording may be included in the

prescribing information, such as is the case with ibrutinib where patients are advised not to take the drug with grapefruit or Seville oranges (IMBRUVICA EPAR-Product Information (Janssen, 2021)). For compounds with significantly negative food effect, one could consider staggering food intake with compound administration as is the case for semaglutide. According to the Rybelsus® label, it is recommended that the drug is taken "at least 30 minutes prior to the first food, beverage or other oral medications of the day with no more than 4 oz of plain water only" (RYBELSUS® prescribing information (NovoNordisk, 2021)).

Mitigation of food effects by formulations

Depending on the root cause of the food effect, drug formulation can have a huge impact on the direction and the extent of food effects. For instance, itraconazole, a poorly water soluble but highly permeable drug (BCS class II), shows a positive food effect if formulated as pellets based on an amorphous solid dispersion (Barone *et al.*, 1993). Due to longer residence times in the stomach and higher bile salts levels in the small intestine, the intake together with food provides improved conditions for dissolution in luminal fluids, which ultimately leads to higher oral bioavailability in fed state. However, the oral solution formulation based on cyclodextrins shows a negative food effect (Barone *et al.*, 1998). Here, the higher bile salt levels potentially lead to the displacement of the drug from the apolar cavity of the cyclodextrins, which results in precipitation (Stappaerts and Augustijns, 2016). Another prominent example was published by Wu and colleagues, who could show in a Beagle dog model that food effect for MK-0869 (aprepitant) could be reduced if the formulation was changed from a conventional oral suspension to a nanocrystalline formulation (Wu *et al.*, 2004). Therefore, the commercial formulation (EMEND) can be taken irrespective of food intake (Shadle *et al.*, 2012).

These examples nicely illustrate that by optimization of the formulation, food effects on oral bioavailability can be reduced. This topic was specifically highlighted for oral anticancer drugs in a recent article by Herbrink and colleagues, who stated that for 16 out of 28 drug products low bioavailability and high variability is observed (Herbrink *et al.*, 2017). Since they regard those "creaky formulations" as inadequate, they call for an improvement of the formulations. Although this call is comprehensible, one should first take a deeper look at the current possibilities for pharmaceutical industry in terms of this question. In this regard, O´Shea and colleagues summarized existing literature on this topic in an excellent review (O'Shea *et al.*, 2019). They showed that if the oral bioavailability is mainly limited by solubility of the drug in luminal fluids, the use of bio-enabling formulation techniques such as amorphous solid dispersions, lipid-based formulations or cyclodextrins presents a valid strategy for food effect reduction. Thereby, any strategy for reduction of the food effect should aim to enhance the oral bioavailability in fasted state, rather than reducing the oral bioavailability in fed state. In addition, it must be considered that bioavailability is only one of the key design requirements in drug product development. Stability and manufacturability must also be considered and sometimes represent major roadblocks to the development of certain formulations even if bioavailability is improved. Moreover, the demand for a short time to market for highly potent drugs often represents another obstacle to formulation optimization in later clinical stages. Best practice is to address food effects already at preclinical or early clinical stages in order to study the potential of a novel drug in terms of oral bioavailability and to enable the early development of a formulation with reduced food effect.

In a recent work by Pandey *et al.*, it was nicely shown how a large positive food effect identified in early clinical studies was addressed by formulation optimization and accompanied by the application of proper *in vivo*, *in vitro* and *in silico* methods (Pandey *et al.*, 2014). In general, a food

effect can only be reduced by formulation optimization if adequately reliable *in vivo* (*e.g.,* dog model), *in vitro* (*e.g.,* Dynamic Gastric Model, TIM-1 system) and/or *in silico* tools (*e.g.,* SimCYP, GastroPlus) are available. If applied in a meaningful manner as presented in Figure 1, these can provide mechanistic insights into the potential root causes of the food effect and by this, can guide the formulation activities during drug product development.

However, the optimization of an oral formulation in terms of drug release does not necessarily result in a reduction of food effects. If the food-induced changes of oral bioavailability are associated with food effects on drug absorption or subsequent events such as splanchnic blood flow, metabolism or elimination, it will be difficult, often impossible, to reduce the food effect simply by formulation changes. In particular, negative food effects which are often associated with how food affects drug absorption or metabolism, are difficult to formulate away (O'Shea *et al.*, 2019).

Summary and outlook

The assessment of food effects remains a complex issue, best addressed early on in the drug development cycle by a variety of techniques spanning from simple solubility studies and complex dissolution/permeation assays to animal models and software-based modelling tools. The combination of these *in vitro*, *in vivo* and *in silico* methods is a necessary requirement to understand the food effect mechanisms and, on this basis, to develop a strategy for their control or mitigation, usually via changes in the formulation. It is important to emphasize that due to the lack of standardization of the various tools, this current approach for food effect assessment can only be successfully implemented by the careful collaboration of scientists with sufficient knowledge in the methods that are being employed, including experts in biopharmaceutics and in clinical

pharmacokinetics. Hence, continued efforts to develop a unified, standard approach in dealing with food effects are required, to decrease food-effect driven risks in oral drug development.

Credit author statement

All authors contributed equally to this review. In addition, Zahari Vinarov and Patrick Augustijns were responsible for putting the individual parts together and revising the manuscript.

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