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RESEARCH ARTICLE

Correlation between the systemic clearance of drugs and their food effects in humans

Venugopal P. Marasanapalle[1], Ramesh R. Boinpally[2], Haijian (Jim) Zhu[1], Andreas Grill[1], and Fuxing Tang[1]

[1]Exploratory Pharmaceutics, Forest Research Institute, Farmingdale, NY, USA and [2]Clinical Pharmacology & Drug Dynamics, Forest Research Institute, Jersey City, NJ, USA

Abstract

Context: Food effects were defined as *positive*, when coadministration of food causes an increase in the extent of absorption ($AUC_{0-\infty}$) of a drug when compared with fasted state drug administration and *no effect* when coadministration of food causes no change in $AUC_{0-\infty}$. In general, low solubility drugs exhibit positive food effects due to improved solubility in fed state administration. But, certain high-solubility and high-permeability drugs that undergo extensive presystemic metabolism exhibit positive food effects because of the increased splanchnic hepatic blood flow in the fed state presumably causing a fraction of drug to bypass first-pass metabolism during absorption.

Objective: In this study, systemic clearance (Cl) of structurally diverse high-permeability and high-solubility drugs was correlated to their food effects to explore whether drugs undergoing low clearance exhibited no food effects and drugs undergoing high clearance exhibited positive food effects.

Methods: Six drugs exhibiting positive food effects and nine drugs exhibiting no food effects (for comparison) were selected for linear regression analysis.

Results: Regression analysis of the selected drugs indicated that percent food effects correlated linearly to Cl and fitted the equation: percent food effects = $0.9163 \times Cl - 6.4789$. The R^2, *p*-value and power of the regression model were >0.88, 0.9999, respectively indicating the direct correlation between Cl and food effects of the selected model drugs; other statistical tests validated the model.

Conclusion: The model indicated that high-solubility and high-permeability drugs undergoing Cl of more than 27 L/h may exhibit statistically significant positive food effects.

Keywords: Food effect, clearance, blood flow, metabolism, modeling, permeability and solubility

Introduction

The oral route is a convenient, less expensive, and preferred route of drug delivery[1,2]. Coadministration of drugs with food can result in changes of their pharmacokinetics[3]. Depending upon a drug's onset, its duration of action, and its therapeutic window, a change in its pharmacokinetics could affect its treatment outcome[4]. Food effects were defined as any difference in the pharmacokinetics of a drug due to coadministration with food, when compared with the drug's administration on a fasted stomach[5,6]. Food effects can be reflected in changes of one or many of a drug's pharmacokinetic parameters i.e. area under the curve, $AUC_{0-\infty}$, peak plasma concentration, C_{max} and time at maximum plasma concentration, T_{max}[3]. A classification of drugs administered in immediate release dosage forms, as exhibiting *positive*, *negative* or *no food effects*, based on the change of one pharmacokinetic parameter, the $AUC_{0-\infty}$ was adopted, because $AUC_{0-\infty}$ reflects the extent of absorption of a drug, and this parameter is generally used to understand the effectiveness of the therapy[5,7], whereas, C_{max} is dependent on both rate and extent of drug absorption, and is used to understand the toxicity of the drug[8]. Food effects were classified

Address for Correspondence: Fuxing Tang, PhD, Exploratory Pharmaceutics, Forest Research Institute, 220 Sea Lane, Farmingdale, NY 11735, USA. Tel.: 631-501-5330. Fax: 631-501-5400. E-mail: fuxing.tang@frx.com

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as *positive*, when coadministration of food caused a 25% or more increase in $AUC_{0-\infty}$; *negative*, when food caused 20% or more decrease in $AUC_{0-\infty}$; and lastly, *no effect* when coadministration of food caused no statistically significant change (80–125%) in the $AUC_{0-\infty}$ of a drug, when compared with the fasted state drug administration[5,7].

Because food and administered drugs are predominantly absorbed in the upper small intestine (duodenum and jejunum), the physicochemical and physiological changes associated with food intake in the upper intestinal lumen are important causes for food effects[7]. The increased gastrointestinal (GI) motility along with increased concentration of bile and lipid digestion products in the fed state improves dissolution and solubilization of poorly aqueous soluble drugs in the lumen[9]. Therefore, absorption of lipophilic drugs is more efficient in the fed state, resulting in their positive food effects[10]. Food constituents could also compete with prodrugs as substrates to enzymes and decrease their degradation in the intestinal lumen resulting in positive food effects e.g. the bioavailability of Cefpodoxime-proxetil an ester prodrug was enhanced by food due to the inhibition of luminal cholinesterase activity by nutrients[11].

The transient increase in splanchnic hepatic (SH) blood flow is also believed to cause food-induced reduction of metabolism of some drugs and higher systemic availability[12–14]. Coadministration of food may not cause any effects for high-permeability drugs that have low presystemic metabolism, because their metabolism is determined by the enterocytic and hepatic metabolic capacity rather than SH blood flow[12,15]. For certain high-solubility and high-permeability drugs such as propranolol that undergo extensive presystemic metabolism, the increased SH blood flow in the fed state was presumed to cause a fraction to bypass first-pass metabolism during absorption resulting in positive food effects[12,13,16,17]. Simulations by McLean et al. demonstrated the effect of increased SH blood flow on the bioavailability of drugs undergoing significant first-pass metabolism[12]. Another study showed that food causes a positive effect on propafenone, a highly soluble and well-absorbed molecule, in fast metabolizers but not in slow metabolizers[18]. In this investigation, systemic clearance (Cl) of structurally diverse high-permeability and high-solubility drugs was correlated to their food effects to explore whether low-clearance drugs exhibit no food effects, and high-clearance drugs exhibit positive food effects.

Theory and hypothesis

The oral bioavailability (F_{oral}) was repre sented as a product of fraction dose absorbed (F_{abs}), fraction escaping gut wall metabolism (F_g), and fraction escaping liver metabolism (F_h[19]).

$$F_{oral} = F_{abs} \bullet F_g \bullet F_h$$

Let F_{oral}-fed and $F_{oral\text{-}fasted}$ be the fed state and fasted state fraction dose absorbed (bioavailable); then the above equation was rewritten as:

$$F_{oral\text{-}fasted} = F_{abs\text{-}fasted} \bullet F_{g\text{-}fasted} \bullet F_{h\text{-}fasted}$$

$$F_{oral\text{-}fed} = F_{abs\text{-}fed} \bullet F_{g\text{-}fed} \bullet F_{h\text{-}fed}$$

High-permeability and high-solubility drugs according to the biopharmaceutical classification system (BCS, Class-I) are completely soluble in the GI tract in fasted and fed state administration[20]. Also, it was expected that their fraction absorption from the GI tract is unchanged in fasted and fed states[4,21]. Therefore, for such drugs, $F_{abs\text{-}fasted} = F_{abs\text{-}fed}$.

Let $Q_{g\text{-}fasted}$ and $Cl_{int\text{-}g\text{-}fasted}$ be the gut wall blood flow and intrinsic gut wall clearance in the fasted state, respectively; and let $Q_{g\text{-}fed}$ and $Cl_{int\text{-}g\text{-}fed}$ be the gut wall blood flow and intrinsic gut wall clearance in the fed state, respectively; then the ratio of $F_{oral\text{-}fed}$ and $F_{oral\text{-}fasted}$ was represented as follows:

$$\frac{F_{oral\text{-}fed}}{F_{oral\text{-}fasted}} = \frac{F_{g\text{-}fed} \bullet F_{h\text{-}fed}}{F_{g\text{-}fasted} \bullet F_{h\text{-}fasted}}$$

$$\frac{F_{oral\text{-}fed}}{F_{oral\text{-}fasted}} = \frac{Q_{g\text{-}fed} \Big/ \left(Q_{g\text{-}fed} + Cl_{int\text{-}g\text{-}fed}\right)}{Q_{g\text{-}fasted} \Big/ \left(Q_{g\text{-}fasted} + Cl_{int\text{-}g\text{-}fasted}\right)} \times \frac{Q_{h\text{-}fed}}{Q_{h\text{-}fasted}}$$

The role of blood flow is minimal for gut wall metabolism[22]. Therefore, the above equation was rewritten as follows:

$$\frac{F_{oral\text{-}fed}}{F_{oral\text{-}fasted}} = \frac{\left(1 + Cl_{int\text{-}g\text{-}fasted}\right)}{\left(1 + Cl_{int\text{-}g\text{-}fed}\right)} \times \frac{F_{h\text{-}fed}}{F_{h\text{-}fasted}}$$

Let $Q_{h\text{-}fasted}$ and $Cl_{h\text{-}fasted}$ be the hepatic blood flow and hepatic clearance in fasted state, respectively; and let $Q_{h\text{-}fed}$ and $Cl_{h\text{-}fed}$ be the hepatic blood flow and hepatic clearance in fed state, respectively. Let $Cl_{int\text{-}h\text{-}fed}$ and $Cl_{int\text{-}h\text{-}fasted}$ be fed and fasted state intrinsic clearances, respectively and, assuming that the fraction of drug unbound to plasma (f_{up}) is unchanged in fasted and fed states, then, the ratio of $F_{oral\text{-}fed}$ and $F_{oral\text{-}fasted}$ was represented as follows:

$$\frac{F_{oral\text{-}fed}}{F_{oral\text{-}fasted}} = \frac{\left(1 + Cl_{int\text{-}g\text{-}fasted}\right)}{\left(1 + Cl_{int\text{-}g\text{-}fed}\right)} \times \frac{Q_{h\text{-}fed} \Big/ \left(Q_{h\text{-}fed} + f_{up} \cdot Cl_{int\text{-}h\text{-}fed}\right)}{Q_{h\text{-}fasted} \Big/ \left(Q_{h\text{-}fasted} + f_{up} \cdot Cl_{int\text{-}h\text{-}fasted}\right)}$$

$$\frac{F_{oral\text{-}fed}}{F_{oral\text{-}fasted}} \times \frac{\left(1 + Cl_{int\text{-}g\text{-}fasted}\right)}{\left(1 + Cl_{int\text{-}g\text{-}fed}\right)} \times \frac{Q_{h\text{-}fed} \bullet \left(Q_{h\text{-}fasted} + Cl_{int\text{-}h\text{-}fasted}\right)}{Q_{h\text{-}fasted} \bullet \left(Q_{h\text{-}fed} + Cl_{int\text{-}h\text{-}fed}\right)} \quad (1)$$

The mean portal blood flow in the fasted state was reported as 13.5 mL/Kg/min[23] or about 1.05 L/min[24]. Blood flow to the GI tract is directly related to its activity. After food

intake, blood flow to the intestinal tract increases and returns to the resting level over the next 2–4 h[25]. Madsen et al. reported that splanchnic blood flow increases to 1.6 L/min after meal intake, and Svensson et al. reported that it increases to about 1.55 L/min[24,26]. So, $Q_{\text{h-fasted}} < Q_{\text{h-fed}}$ and $\frac{Q_{\text{fed}}}{Q_{\text{fasted}}} > 1$.

Assuming that SH blood flow rate (Q_{fasted} and Q_{fed}) changes in a consistent proportion in fed and fasted states among subjects in clinical studies, and food constituents interacts with the metabolic clearance in a consistent proportion, then, for drugs with low metabolic clearance, $Q >>$ Cl and $F_{\text{oral-fed}}/F_{\text{oral-fasted}} \approx 1$. For drugs that undergo significant metabolic clearance, the $F_{\text{oral-fed}}/F_{\text{oral-fasted}}$ ratio increases because of the increase in SH blood flow ($Q_{\text{fed}} > Q_{\text{fasted}}$) and also due to the possibility of competitive inhibition of metabolic enzymes of drugs by food constituents ($\text{Cl}_{\text{int-g-fed}} < \text{Cl}_{\text{int-g-fasted}}$ and $\text{Cl}_{\text{int-h-fed}} < \text{Cl}_{\text{int-h-fasted}}$). This could be reflected as a net positive food effect, $F_{\text{oral-fed}} > F_{\text{oral-fasted}}$.

Methods

Percent food effects

The extent of food effect was mathematically represented as follows:

$$\text{Food effect}\,(\%) = \frac{\left[\text{AUC}_{(0-\infty)\text{fed}} - \text{AUC}_{(0-\infty)\text{fast}}\right]}{\text{AUC}_{(0-\infty)\text{fast}}} \times 100$$

Criteria for selection of drugs

The criteria for selection of drugs for model development are as follows:

1. The available literature was screened for high solubility and high-permeability drugs exhibiting positive food effects and no food effects in human clinical food effect studies[5,7]. Low solubility drugs were excluded.
2. Drugs that were classified according to BCS as Class-I drugs by Lindenberg et al. were initially screened for selection[27]; other literature sources were used for additional drugs.
3. Six drugs exhibiting positive food effects were obtained. Chloroquine, primaquine, propranolol, metoprolol, propafenone and diprafenone were selected[18,28–31].
4. Nine drugs exhibiting no food effects were included for comparison. Diazepam, fluconazole, pindolol, prednisolone, pyrazinamide, quinidine, stavudine, theophylline and timolol were selected.
5. Drugs within the molecular size range of 200–500 Da were selected to minimize the unknown variability of size among drugs.

Cl and percent food effects

The food effect data, $\text{AUC}_{0-\infty}$ in fed and fasted state administrations and Cl of model drugs were collected from literature as shown in Table 1. In the clinical studies the *fasted state* (preprandial) drug administration typically involved the administration of a drug with water or liquids on an overnight fasted stomach, and a *fed state* (postprandial) drug administration involved the administration of a drug after a standard breakfast or a high-fat meal on an overnight fasted stomach[5].

Table 1. The food effects and systemic clearance of selected drug molecules.

Drug	Systemic clearance (L/h)#	Excretion/elimination	Substrate of	Inhibitor of	Food effects (%)
Chloroquine	43.32[48]	55% urinary[48]			+41.81*[49]
Diprafenone	44.46 ± 7.44[50]	Hepatic extraction ratio of 0.82[50]			+36.16*[31]
Metoprolol	63 ± 12.6[51]	Primarily hepatic[52]	CYP2D6[47]		+38.88*[16]
Primaquine	28.7[53]	Gut and/or hepatic[53]			+14.24*[53]
Propafenone	60 ± 6[30]	Primarily hepatic[52]	CYP1A2 and CYP2D6[47]	CYP2D6[47]	+55.78*[18]
Propranolol	67.2 ± 21[51]	Hepatic extraction ratio of 0.74–0.79	CYP1A2, CYP2D6, and CYP2C19[47]		+62.56*[17,41]
Diazepam	1.5[54]	Hepatic[55,56]	CYP1A2, CYP2C9, CYP2C19, and CYP3A4[47]		−5.77[57]
Fluconazole	1.17 ± 0.28[58]	Hepatic[55,56]		CYP2C9[47], CYP2C19[47]	−6.19[59]
Pindolol	26.40[60]	35–40% is excreted unchanged in the urine and 60–65% is metabolized[55,56]	CYP2D6[47]		+15.31[61]
Prednisolone	4.25[62]	Hepatic[47]	CYP3A4[47]		+5.55[63]
Pyrazinamide	3.59 ± 0.86[64,65]	70% urinary			+0.95[64,65]
Quinidine	16.8[52]	Mostly hepatic and up to 20% in urine	CYP3A4[47]	CYP2D6[47]	−3.09[66]
Stavudine	12.21[67]	40% urinary[68]			−6.65[67]
Theophylline	3.11[69]	Hepatic[55,56]			+8.24[70]
Timolol	32.41 ± 5.18[71]	20% urinary[72]	CYP2D6[47,73]		+18.98[44]

*Significant positive food effect ($p < 0.05$).
#Some calculations were made assuming an average body weight of 70 Kg.

Regression analysis

Statistical analysis and plotting were performed using Sigmaplot® version 10.0 (Systat Software, Inc. Chicago, IL), NCSS/PASS® software (Kaysville, UT) and MS Excel® (Redmond, WA).

Results

As shown in Figure 1 below, a linear relationship was observed for the model drugs between their food effects and systemic plasma clearance. The correlation between food effects and Cl fitted a linear equation as shown below:

$$\text{Percent food effects} = 0.9163 \times \text{Cl} - 6.4789 \quad (2)$$

The results of various statistical tests on the linear statistical model are summarized in Table 2. Q^2, the leave-one-out cross-validated correlation coefficient was used to validate the model without selecting another sample, or splitting the data[32,33]; the Q^2 for the linear model was 0.8355, indicating high correlation between food effects and Cl. As shown in Figure 2, the normality tests indicated that the residuals were normally distributed. The normal probability plot of the residuals from the linear model showed that all the points lie close to a straight line, a characteristic of normal distribution of residuals. Residual analysis of the data revealed a random, symmetric scattering of points about zero.

Test for serial-correlation gave a Durbin–Watson (D–W) statistic of 1.9224 for the model. The *dL* and *dU* levels for 5% significant points using $n = 15$ and one regressor are 0.811 and 1.070, respectively[34]. Since the D–W statistic was more than *dU*, we cannot reject the null hypothesis of zero autocorrelation. Furthermore, since the linear model has an intercept, a test for negative autocorrelation was performed, whereby 1.9224 was subtracted from 4, which gives 2.0776. Since 2.0776 is greater than *dU*, the residuals may not be negatively autocorrelated as well (reject alternate hypothesis for negative autocorrelation[34]). Thus, all statistical tests validated the model.

Discussion

The major phase-I metabolizing enzyme systems, cytochrome P-450 enzymes, are expressed in the liver and the gut wall[35–40]. The fraction of drug that escapes the enterocytic metabolism passes through the portal vein in the SH blood flow to the liver. Some BCS-I drugs such as propranolol exhibited positive food effects[17,41]. This was attributed to two mechanisms as follows: (i) The transient increase in SH blood flow is believed to cause food-induced reduction of metabolism of some drugs and increased systemic availability[12,42], and (ii) diet

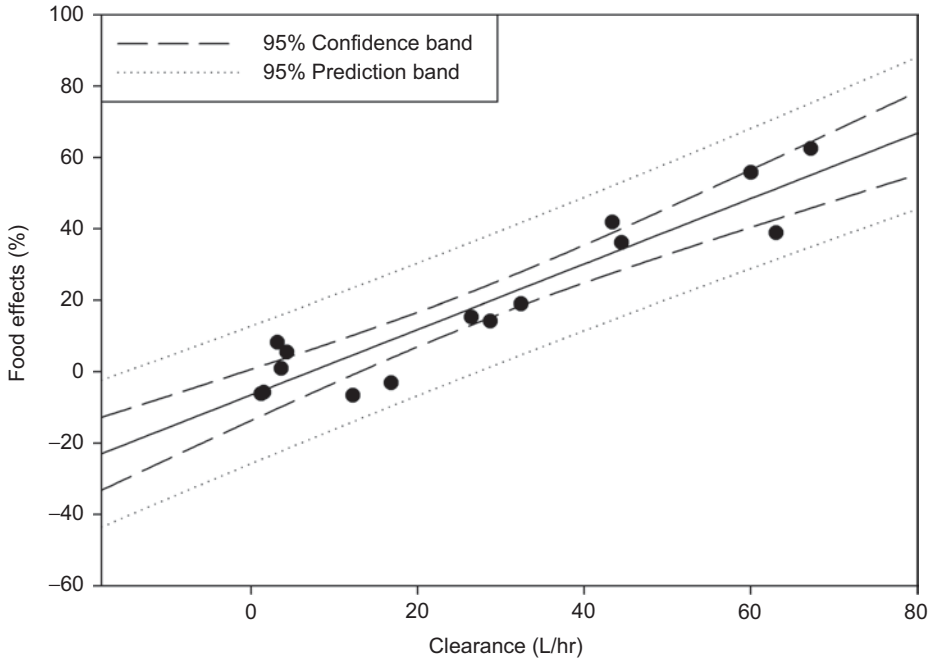

Figure 1. Linear correlation between food effects and systemic clearance.

Table 2. Statistical test results of the linear model correlating systemic clearance and percent food effects.

R^2	*p*-value	Power	Adj. R^2 [32]	Standard error of estimate	*F*-ratio	Normality test (*p*-value)	Constant variance test (*p*-value)	Durbin–Watson statistic
0.8811	<0.0001	>0.9999	0.872	8.285	96.38	0.846 (passed)	0.763 (passed)	1.9224 (passed)

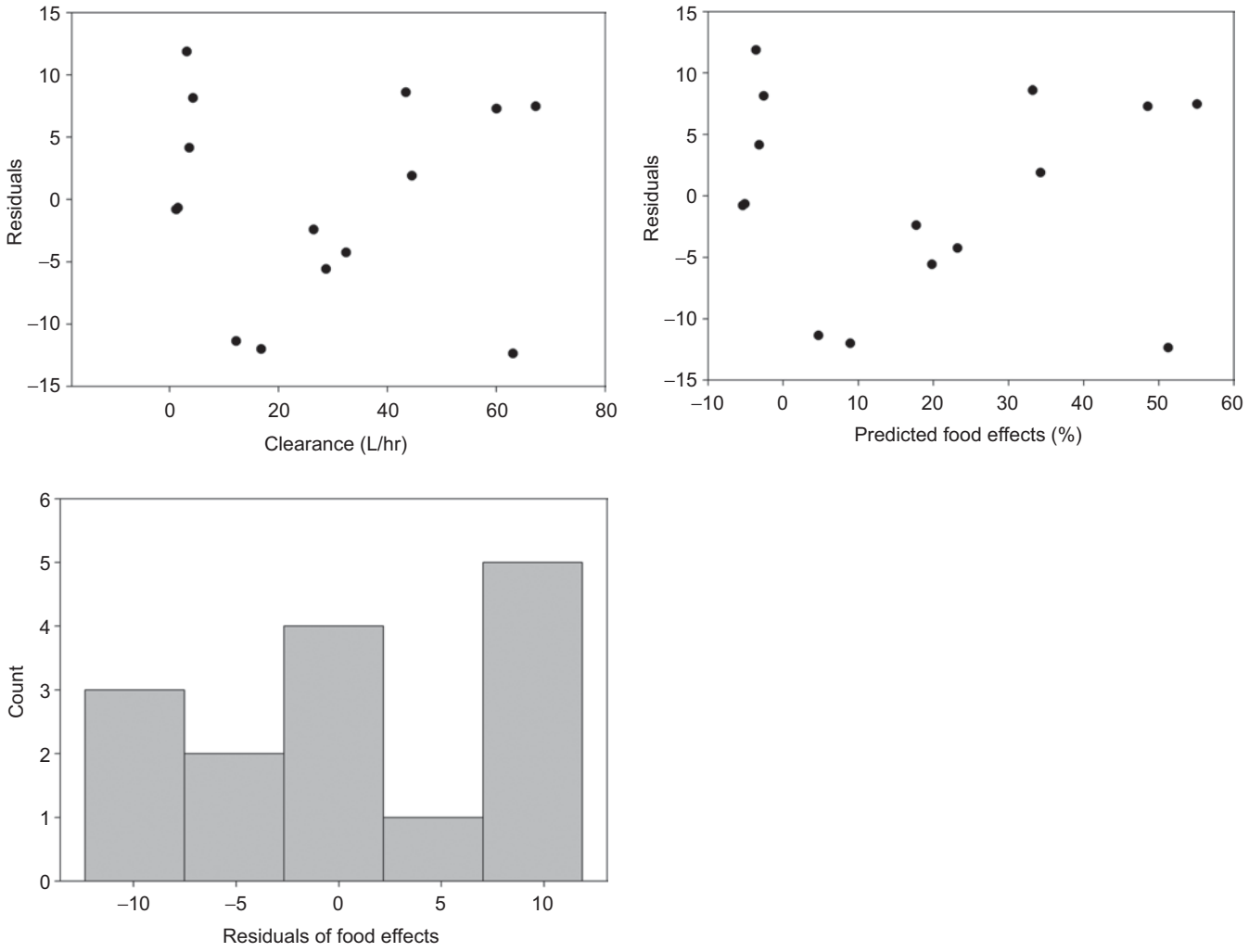

Figure 2. Residual plots of the linear correlation between systemic clearance and percent food effects.

contents such as proteins could competitively inhibit the metabolism of drugs and increase their bioavailability[12,43]. This was mathematically represented in Equation 1. Delineating the exact mechanisms of positive food effects of such drugs has been difficult[18].

High-permeability drugs are rapidly absorbed in the upper GI tract in fasted and fed states. In the fasted state, high-clearance drugs encounter a huge pool of enzymes for their metabolism and undergo significant first-pass metabolism. When coadministered with food, the rapid absorption of such drugs and nutrients could cause either saturation of the enzyme pool by the nutrients and/or the increased SH blood flow rate could cause lower residence time of the drugs resulting in a fraction of the absorbed drug to escape first-pass metabolism. One or both of these mechanisms may contribute to positive food effects of such high solubility, rapidly absorbed and highly metabolized drugs. This mechanism of food effect may not be evident for low permeability and highly metabolized drugs because of their slow and incomplete absorption from the GI tract.

A linear relationship was observed for high-permeability and high-solubility drugs between their food effects and systemic plasma clearance. Poorly aqueous soluble BCS-II drugs exhibiting positive food effects and high clearance were not selected for modeling because attributing the observed positive food effect to either the physiological avoidance of first-pass metabolism or to the physicochemical increase in solubility was difficult[7]. Certain BCS-II drugs such as indomethacin, ketoprofen, ibuprofen and diclofenac, which are completely soluble in the fasted and fed state intestinal pH and exhibit no food effects, fit the hypothesis and the model without affecting the R^2 value. Timolol lies on the border of drugs exhibiting no food effects and positive food effects; it failed the statistical test for positive food effects narrowly[44]. The high-permeability and high-solubility drug labetalol has a Cl of 115.38 ± 25.02 L/h and exhibited statistically significant positive food effects, +11.25%, which was in accordance with the hypothesis[13]. But, labetalol was not included in the model because it had extremely high clearance and the extent of positive food effects was not proportional according to the model. There was one exception to the hypothesis; the high-permeability and high-solubility drug diltiazem (not plotted) undergoes high Cl, 48.3 L/h[45] but does not exhibit significant positive food effects +12.43%[46].

Diltiazem is primarily metabolized by CYP3A4 enzyme, and it was an inhibitor of the same enzyme, which may partially explain its no food effect[47].

Previous investigations by McLean et al. using computer simulations indicated that the temporal increase in SH blood flow may significantly increase the bioavailability of drugs undergoing first-pass metabolism[12]. Similar observations have been made by Axelson et al. on propafenone correlating its food effect and intrinsic hepatic clearance[18]. In this study, the interplay of permeability (absorption) and metabolism in contributing to positive food effects was explored for structurally diverse BCS-I drugs, and a linear correlation between their food effects and Cl (Equation 2) was determined. This is a first reported study to find such a correlation for structurally diverse drugs and may aid in the prediction of food effects based on BCS and metabolism.

Conclusion

A linear correlation model between food effects and Cl of structurally diverse high-permeability and high-solubility drugs was described. High-solubility and high-permeability drugs undergoing Cl of more than 27 L/h may exhibit statistically significant positive food effects.

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Declaration of interest

The authors report no conflicts of interest.

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