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Research Paper

Predicting Effect of Food on Extent of Drug Absorption Based on Physicochemical Properties

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Purpose. To develop a statistical model for predicting effect of food on the extent of absorption (area under the curve of time–plasma concentration profile, AUC) of drugs based on physicochemical properties.
Materials and Methods. Logistic regression was applied to establish the relationship between the effect of food (positive, negative or no effect) on AUC of 92 entries and physicochemical parameters, including clinical doses used in the food effect study, solubility (pH 7), dose number (dose/solubility at pH 7), calculated Log D (pH 7), polar surface area, total surface area, percent polar surface area, number of hydrogen bond donor, number of hydrogen bond acceptors, and maximum absorbable dose (MAD).
Results. For compounds with MAD ≥ clinical dose, the food effect can be predicted from the dose number category and Log D category, while for compounds with MAD < clinical dose, the food effect can be predicted from the dose number category alone. With cross validation, 74 out of 92 entries (80%) were predicted into the correct category. The correct predictions were 97, 79 and 68% for compounds with positive, negative and no food effect, respectively.
Conclusions. A logistic regression model based on dose, solubility, and permeability of compounds is developed to predict the food effect on AUC. Statistically, solubilization effect of food primarily accounted for the positive food effect on absorption while interference of food with absorption caused negative effect on absorption of compounds that are highly hydrophilic and probably with narrow window of absorption.

KEY WORDS: food effect prediction; logistic regression; physicochemical properties.

INTRODUCTION

Food exerts complicated effect on pharmacokinetic and/or pharmacodynamic profiles of a drug. In this study, the key physicochemical parameters that contribute to the food effect were identified by statistical analysis of the effect of food on the extent of drug absorption. A prediction model was also established using logistic regression.

The effect of food on oral absorption may be attributed to specific mechanism for an individual compound. For example, food may interfere with specific transporters that are involved in absorption of a specific compound (1). Food may increase the splanchnic blood flow rate and increase the bioavailability of compounds that undergo extensive first pass effect (2). Certain compounds, e.g., tetracycline and digoxin, can also chelate to specific components of food leading to reduced bioavailability (3,4). These specific food effects may be difficult to predict based on physicochemical descriptors of compounds.

However, food also exerts general physiological changes and its effect on drug absorption may be statistically predicted for compounds with similar physicochemical properties. With food intake, the gastric pH increases initially to about pH 6, followed by decrease in pH value to 2 in approximately 1 h because of increased acid secretion (5,6). The bile secretion also increases with food intake, which may enhance the solubility of lipophilic compounds (6). It was suggested that the permeability may be reduced in general for poorly permeable compound because food impedes the diffusion of the compound to the mucosal surface (7). Larger volume after food intake, which leads to lower concentration of dissolved compound, also reduces the amount absorbed in a definite period of time. Additionally, general binding between drug and food components and incorporation of drug in the micelles of food may also impede the access of the drug to the epithelium surface and hence absorption. It was also well known that food causes delayed gastric emptying leading to delayed tmax and lower Cmax (8,9), although these parameters were not analyzed in this study.

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Fleisher *et al.* summarized the general trend of food effect on drug absorption based on BCS classification (7). BCS class I compounds are likely to have no food effect; BCS class II compounds are likely to have positive effect (increased absorption); BCS class III compounds are likely to have negative effect (decreased absorption) and there is no clear trend for BCS class IV compounds (7). For the 92 entries used in this study, the relationship between BCS classification and the effect of food on the extent of absorption (area under the curve of the time–plasma concentration curve, AUC) was summarized (Table I). If using the criteria that BCS class 1 shows no food effect, BCS classes 2 and 4 show positive food effect and BCS class 3 shows negative food effect as suggested by Fleisher *et. al,* 67% of entries were predicted into the right category. This result suggests that it is possible to build a statistical model to predict the effect of food on extent of drug absorption based on physicochemical properties. In the current study, more descriptors are used to statistically predict the food effect to improve accuracy for prediction.

MATERIALS AND METHODS

Clinical data of food effect of 90 marketed compounds (92 total entries including hydrochlrothiazide at two different doses with different food effect and free base and mesylate salt of saquinavir) were collected from the literature and Physician Desk Reference (10) (Tables II and III). Hydrochlrothiazide at lower dose is listed in Table II as the dose is less than the maximum absorbable dose (MAD) while the higher dose entry is listed in Table III with the dose > MAD. The food effect on the extent of absorption was separated into three categories: positive food effect (statistically significant increase in AUC with food, 31 entries), negative food effect (statistically significant decrease in AUC with food, 24 entries) and no food effect (no statistically significant difference in AUC, 37 entries).

The following physicochemical parameters were collected for these compounds: clinical dose used in the published food effect study, solubility at pH 7, calculated log D at pH 7 using ACD software (11), total surface area (calculated using ACD software), polar surface area (calculated using ACD software), number of hydrogen bond donor (calculated using ACD software), number of hydrogen bond acceptor (calculated using ACD software). The solubility values were collected from the literature (10,12–15). For compounds with solubility reported based on USP definition but without specific value, the lower value of the range defined in the USP was chosen (12). From these parameters, additional parameters were derived. The dose number was calculated as ratio of dose to the solubility at pH 7 (16), which was further assigned into three categories (dose number category): denoted as 1 if dose number <50, 2 if 50 ≤ dose number ≤ 250, and 3 if dose number >250. The Log D was also categorized into three categories (LogD category): denoted as 1 if Log D < −1, 2 if −1 ≤ Log D ≤ 1 and 3 if log D > 1. The maximum absorbable dose (MAD) was calculated using the following equation (17):

$$\mathrm{MAD} = \mathrm{Solubility(mg/mL\ at\ pH\ 7)} \times 250\mathrm{(mL)} \times 180\mathrm{(min)} \times \mathrm{absorption\ rate\ constant}\left(\mathrm{min}^{-1}\right) \quad (1)$$

where the absorption rate constants of 0.0006, 0.003 and 0.0134 were used for poorly permeable (Caco-2 permeability < 20 nm/sec), moderately permeable (Caco-2 permeability between 20 and 100 nm/sec) and highly permeable (Caco-2 permeability > 100 nm/sec) compounds, respectively (18). The absorption rate constants were estimated based on the correlation between Caco-2 and human permeability of 20 compounds (18). For compounds without reported Caco-2 permeability value, the MAD value was determined from the reported value of percent absorbed in human pharmacokinetics studies. For example, tamsulosin hydrochloride was reported to be 100% absorbed at the clinical dose, the MAD to dose ratio is therefore assigned as 1 (10). This estimation may not be accurate in terms of absolute value of MAD but it is accurate in terms of the relationship between MAD and dose. Since compounds are categorized in the model based on whether the MAD is ≥ or < the dose, the relationship between MAD and dose is important for the model rather than the absolute value of MAD. Since Caco-2 permeability data were not available for all compounds in the study, Caco-2 permeability was not used as an individual parameter for prediction. In the above equation, we used 180 min as the small intestine residence time in human instead of 270 min used in the original paper (5).

All compounds were first separated into two categories: MAD < clinical dose and MAD ≥ clinical dose. The clinical dose is the dose studied for food effect in the published references. For compounds with MAD ≥ clinical dose, complete absorption is achievable. Therefore, theoretically these compounds may not show positive food effect and were fitted into negative food effect and no food effect categories, using logistic regression. Compounds with MAD < clinical dose were fitted into positive food effect, negative food effect and no food effect categories by logistic regression with cross validation using SAS™ 8.2 (19).

Logistic regression is often used to investigate the relationship between binary response (negative and no food

Table I. Relationship Between Food Effect on the Extent of Absorption (AUC) and BCS Classification of Compounds

Food Effect/BCS	Class 1	Class 2	Class 3	Class 4	Total
Negative	9 (30%)	0 (0%)	14 (61%)	1 (9%)	24
No effect	20 (67%)	8 (29%)	7 (30%)	2 (18%)	37
Positive	1 (3%)	20 (71%)	2 (9%)	8 (73%)	31
Total	30	28	23	11	92

The number of compounds in each BCS class for a specific food effect category is listed and the percentage is provided in the parentheses.

Table II. List of Compounds with Maximum Absorbable Dose (MAD) Greater than Clinical Dose and Their Physicochemical Properties

Compound	BCS class	Dose (mg)	S[a]	Dose #[b]	LogD[c]	P[d] nm/s	PSA[e]	TSA[f]	HBD #[g]	HBA #[h]	MAD to Dose Ratio[i]	F Ratio[j]
5-Aminosalicylic acid	3	1 (10)	1 (10)	1	−3	3.2 (34)	79.3	158.1	4	4	27	0.52 (10)
Acyclovir	3	800 (10)	10	80	−1.76	18 (35)	117.6	238.9	4	8	1.69	1 (10)
Albuterol (Salbutamol)	1	4 (36)	33	0.12	0.97	100 (37)	78.7	291.8	4	4	4975	1 (36)
Aripiprazole	2	15 (10)	0.001	15,000	5.3	–	47.9	462.1	2	2	1	1 (10)
Bromazepam	1	10 (38)	0.1	100	2.6	–	47.6	262.9	1	4	1	0.7 (38)
Bromocriptine	3	7.5 (39)	0.8	9.4	5.21	21 (40)	110.4	622.2	3	10	14.4	1 (39)
Capecitabine	1	1,255 (41)	26	48	0.97	–	119	382.3	3	9	1	0.7 (41)
Captopril	3	100 (42)	160 (42)	0.63	−3.2	20	57.8	246.3	1	4	216	0.7 (42)
Cefdinir	3	300 (10)	20 (10)	15	−5.4	2 (43)	155.4	360.8	5	10	1.8	0.9 (10)
Ceftibuten dihydrate	1	400 (10)	33 (10)	12	−5.9	100 (44)	159.3	377.7	5	10	49.7	0.83 (10)
Cimetidine	3	400 (45)	10	40	−0.01	20 (46)	81.2	296.4	3	6	6.75	1 (45)
Ciprofloxacin	3	500 (47)	10	50	−1.3	28.8 (48)	74.1	331.2	2	6	2.7	1 (47)
Clodronate	3	800 (49)	397	2	−5.4	0.5 (50)	124.7	191.8	4	6	13.4	0.7 (49)
Didanosine (videx)	3	300 (33,42)	27	11	−1.2	20	90.5	246.5	2	7	12.15	0.45 (42)
Dolasetron mesylate	1	200 (51)	33	6.1	2.68	129 (52)	26.3	316.4	1	5	99.5	1 (51)
d-Sotalol	3	300 (53)	10	30	−2.23	–	87	314	3	5	4.5	0.8 (53)
Entecavir	3	0.1 (42)	2.5	0.04	0.11	–	126.5	288.9	4	5	675	0.79 (42)
Eptastigmine	1	30 (54)	700	0.04	3.55	–	46.8	440.8	1	5	1	0.63 (54)
Ethinyl estradiol	1	0.03 (10)	0.01	3	4.52	170 (40)	38.6	321.4	2	2	201	1 (10)
Fexofenadine	3	120 (55)	5	24	2.68	2 (21)	81.5	545	3	5	1.125	0.73 (55)
Fluoxetine hydrochloride	1	200 (10)	33	6.1	1.83	521 (56)	24.6	320.8	1	2	99.5	1 (10)
Frusemide (Furosemide)	3	40 (57)	2.25	18	−1.0	3 (35)	121	305.6	4	7	1.5	0.55 (57)
Hydralazine	1	100 (58)	30	3.3	1	160 (41)	66.6	170.5	3	4	180.9	0.52 (58)
Hydrochlorothiazide	3	12.5 (59)	0.7	17.9	−0.07	–	131.2	205.4	7	4	1.5	1 (59)
Isoniazid	1	50 (10)	100	0.2	−0.89	–	69.3	153	3	4	1	0.57 (10)
Isosorbide Mononitrite	1	60 (60)	0.5	120	−0.5	–	95.9	190	1	7	1	1 (60)
Lamivudine	1	150 (61)	70	2.1	−0.27	–	89.4	232.9	3	6	1	1 (61)
Lansoprazole	1	30 (10)	0.8	37.5	2.36	124 (40)	62.5	344.8	1	5	16.1	1 (10)

Lomefloxacin	1	400 (62)	1.64	243.99	−0.18	159 (63)	73.2	351.7	2	6	2.47	1 (62)
Meloxicam	1	30 (64)	0.46	65.2	−0.07	195 (65)	99.6	320.1	2	7	9.25	1 (64)
Metformin	3	850 (10)	500	1.7	−5.4	–	82.6	165.9	5	5	79.4	0.86 (10)
Methylphenidate HCl	1	18 (66)	100	0.18	2.5	–	36.4	270.2	1	3	3,350	1 (66)
Morphine Sulphate	1	30 (67)	47.6	0.63	−0.77	100 (40)	58.2	280.9	2	4	957	1 (67)
Moxifloxacin	1	400 (68)	33	12.1	−0.53	–	77	401.6	2	7	49.7	1 (68)
Nitrofurantoin monohydrate	4	50 (10)	0.19	263	−0.47	–	118.9	232.3	1	9	1	1 (10)
Ofloxacin	1	300 (69)	4	75	−1.6	109 (40)	73	363.3	1	7	8.04	1 (69)
Pidotimod	3	800 (70)	37.8	21	−6	–	82.3	235.8	2	6	1.28	0.51 (70)
Pravastatin	3	20 (71)	300	0.067	0.87	23 (42)	121.6	483.4	4	7	2025	0.69 (71)
S(+)-Ibuprofen	2	600 (72)	2.3	260.9	1.15	590 (73)	38.3	258.5	1	2	2.3	1 (72)
Salsalate (salicylsalicylic acid)	1	1,500 (74)	10	150	−1	–	73.9	248.2	2	5	1	1 (74)
Tamsulosin hydrochloride	1	0.4 (10)	10	0.04	0.89	–	107.2	447.8	3	7	1	0.7 (10)
Temafloxacin HCl	2	200 (75)	0.11	1818	0.82	–	73.2	397.1	2	6	1	1 (75)
Tolectin (tolmetin)	3	400 (42)	10	40	−0.49	–	58.6	283.9	1	4	3.4	0.88 (42)
Tolterodine tartrate	1	2 (10)	12	0.17	1.83	–	21.3	382.3	1	2	1	1 (10)
Topiramate	1	100 (76)	12	8.3	2.25	284 (40)	126.5	334.2	2	9	72.4	1 (76)
Valdecoxib	2	10 (10)	0.01	1,000	1.44	1,000 (77)	90.2	314.5	2	5	2.7	1 (10)
Verapamil	1	80 (78)	83	0.96	1.9	100 (73)	63.5	527.5	0	6	626	1 (78)
Zalcitabine	1	1.5 (79)	76.4	0.02	−1.5	–	89.5	232.4	3	6	1	0.86 (79)
Zidovudine	3	300 (61)	20.1	14.9	−0.58	69 (22)	126.3	278.8	2	9	9	1 (61)
Zolmitriptan	3	5 (80)	33	0.15	−0.44	2.5 (81)	64	328.4	2	5	178	0.84 (80)
Zolpidem tartrate	1	10 (10)	23	0.43	2.49	694 (82)	31.5	347.8	0	4	1,387	0.85 (10)

[a] Aqueous solubility at pH 7 in the unit of mg/mL.
[b] Ratio of dose to solubility at pH 7 in the unit of mL
[c] The log D value is the log of octanol/water partition coefficient at pH 7 calculated by ACD software.
[d] Caco-2 permeability
[e] Polar surface area in the unit of $Å^2$
[f] Total surface area in the unit of $Å^2$
[g] Number of hydrogen bond donor
[h] Number of hydrogen bond acceptor
[i] Ratio of maximum absorbable dose, calculated using equation 1, to the clinical dose
[j] Ratio of bioavailability (area under the curve, AUC) at fasted state to that at fed state

effect in the case of MAD ≥ clinical dose) or ordinal responses (negative, no food effect and positive food effect in the case of MAD < clinical dose) and a set of explanatory variables (physicochemical variables in this study).

For the binary response model, the linear logistic model has the following form for the probability (p) of a response given the observed x:

$$\log it(p) \equiv \log\left(\frac{p}{1-p}\right) = \alpha + \beta' x \tag{2}$$

Where α is the intercept parameter and β is the vector of slope parameters, which gives the probability of negative food effect as:

$$p = \frac{1}{1+\exp\left(-(\alpha+\beta x)\right)} \tag{3}$$

and the probability of no food effect is $1-p$.

For the ordinal response model, the three possible responses of Y were denoted by 1, 2, and 3 ($Y=1$ if negative food effect, $Y=2$ if no food effect, and $Y=3$ if positive food effect) and x was the vector of explanatory variable. The linear logistic regression model with common slopes was fitted using LOGISTIC procedures in SAS™ 8.2 as the following:

$$\log it(p) \equiv \log\left(\frac{p}{1-p}\right) = \alpha_i + \beta' x, i = 1,2 \tag{4}$$

where $p = \Pr(Y \le i|x)$ is the cumulative probability, which means when $i=2$, $p = \Pr(Y \le 2|x) = \Pr(Y=1|x) + \Pr(Y=2|x)$; α_1, α_2 are two intercept parameters and β is the vector of slope parameters.

This model gives the probabilities of Y being 1 (p_1), 2 (p_2), and 3 (p_3) of given x as:

$$p_1 = \frac{1}{1+\exp\left(-(\alpha_1+\beta x)\right)}, \tag{5}$$

$$p_2 = \frac{1}{1+\exp\left(-(\alpha_2+\beta x)\right)} - p_1, \tag{6}$$

and

$$p_3 = 1 - p_1 - p_2 \tag{7}$$

The score chi-square statistics was used to ensure the adequacy of common slope assumption in the ordinal response model.

During model-building, four variable selection methods: forward selection, backward elimination, stepwise selection, and best subset selection were used to select the explanatory variables based on the 0.05 significance level.

RESULTS

From logistic regression, compounds with MAD < clinical dose, the probabilities of positive, negative and no food effect were determined using the following equations:

Probability of negative food effect (p_1):

$$p_1 = \frac{1}{1+\exp\left\{-[-1.28 - 1.04 * (\text{dose number category})]\right\}} \tag{8}$$

Probability of positive food effect (p_2):

$$p_2 = \frac{1}{1+\exp\left\{-[1.53 - 1.04 * (\text{dose number category})]\right\}} - p_1 \tag{9}$$

Probability of no food effect (p_3):

$$p_3 = 1 - p_1 - p_2 \tag{10}$$

In the above model, the score chi-square test has a p-value of 0.20, indicating adequacy of common slope assumption for the cumulative probability in the logistic model.

For compounds with MAD ≥ clinical dose, the probabilities of negative and no food effect were determined by following equations:

Probability of negative food effect (p_1):

$$p_1 = \frac{1}{1+\exp\left\{-[6.66 - 2.97 * (\text{dose number category}) - 1.56 * (\text{Log D category})]\right\}} \tag{11}$$

Probability of no food effect (p_2):

$$p_2 = 1 - p_1 \tag{12}$$

The predicted food effect of each compound was assigned based on the highest probability of food effect category. The prediction results are provided in Tables IV and V and are summarized in Table VI. Overall, 74 out of 92 entries (80%) were predicted into the correct category. Compounds with positive food effect can be distinguished more easily as 97% of compounds with positive effect (30 out of 31 entries) were predicted into correct category while 79% (19 out of 24 entries) and 68% (25 out of 37 entries) compounds with negative and no food effect were predicted into correct category, respectively (Table VI). For a given prediction, the probability of correct prediction is 83, 73 and 83% for positive, negative and no food effect, respectively (Table VII). This statistical method provides more accurate prediction than the estimation based on BCS classification with 67% of the entries being predicted correctly (Table I). It should be mentioned that the accuracy of the current model is based on cross-validation, which may not hold true for an external dataset. The parameters used in present prediction are similar to those used to categorize BCS classes. The success of prediction using the current model further validates the importance of parameters used in BCS classification for oral absorption. It's interesting to note that parameters, such as polar surface area, total surface area, percent polar surface area, number of hydrogen bond donors

Table III. List of Compounds with Maximum Absorbable Dose (MAD) Less than Clinical Dose and Their Physicochemical Properties

Compound	BCS class	Dose (mg)	S[a]	Dose #[b]	LogD[c]	P[d] nm/s	PSA[e]	TSA[f]	HBD #[g]	HBA #[h]	MAD to dose ratio[i]	F ratio[j]
Abacavir sulfate	1	300 (83)	77	3.9	0.22	–	95.1	321.3	4	7	0.85	1 (83)
Acitretin	1	25 (10)	0.1	250	3.1	–	45.54	398.9	1	3	0.59	1.9 (10)
Albendazole	2	5200 (10)	0.01	20,000	3	100 (84)	64.2	265.3	2	5	0.03	3 (10)
Amiodarone hydrochloride	2	200 (85)	0.07	2,857	5.7	–	40	516.9	0	4	0.95	1.5 (85)
Atazanavir sulfate	2	400 (10)	0.04	10,000	3.8	–	158.7	772.4	5	13	0.4	1.57 (10)
Atovaquone	2	1,000 (86)	0.01	100,000	1.6	–	49.4	359.1	1	3	0.027	1.32 (86)
Bicalutamide	2	50 (31)	0.005	10,000	4.89	–	96.9	385.2	2	6	0.06	1 (31)
Bropirimine	2	500 (87)	0.04	12,500	1.3	HP (88)	69.5	218.3	3	4	0.048	1.9 (87)
Cefditoren pivoxil	4	200 (10)	0.1	2,000	−4	75 (89)	151.5	470.2	4	11	0.068	1.7 (10)
Cefuroxime axetil	4	250 (10)	0.01	25,000	−4.6	9.7 (40)	168	402.7	4	12	0.001	1.4 (10)
Celecoxib	2	50 (10)	0.01	5,000	3	HP (90)	81.1	352.1	2	5	0.12	2.4 (10)
Clopidogrel bisulfate	3	75 (91)	100	0.75	4.3	–	30.3	317	0	3	0.5	1 (91)
Danazol	2	100 (32)	0.01	10,000	4.7	220 (92)	45.2	364.2	1	3	0.06	3 (32)
Efavirenz	2	600 (10)	0.01	60,000	4.9	56 (42)	40.2	280.8	1	3	0.002	1.2 (10)
Fenoldopam	4	100 (93, 94)	0.06	1,667	−0.23	–	78.1	295.5	4	4	0.81	0.6 (93, 94)[k]
Ganciclovir	4	1,000 (95)	4.3	232.6	−2.1	27 (40)	138.3	267.2	5	9	0.58	1.2 (95)
Griseofulvin	2	125 (10)	0.012	1.00E+06	3.5	363 (40)	72.3	345.4	0	6	0.058	1.7 (10)
Halofantrine hydrochloride	2	250 (96)	0.0003	8.30E+05	4.4	–	25.2	506.1	1	2	0.1	2.9 (96)
Hydrochlorothiazide	3	50 (97)	0.7	71.4	−0.07	–	131.2	205.4	7	4	0.38	1.2 (97)
Imiquimod	2	100 (98)	0.01	10,000	1.8	−28	49.5	264.9	2	4	0.06	1 (98)
Indinavir	4	200 (99)	0.015	13,333	2.66	8.7 (40)	115	677.4	4	9	0.002	0.65 (99)
Irbesartan	2	300 (100)	0.37	810.8	3.1	–	87.8	470.1	1	7	0.74	1 (100)
Isotretinoin	2	80 (10)	0.01	8,000	4.2	–	36.7	385.6	1	2	0.075	1.9 (10)
Itraconazole	2	100 (33)	0.001	1.00E+06	8.5	571 (101)	93.7	705.8	0	12	0.006	2 (33)
Manidipine hydrochloride	2	20 (102)	0.0001	2.00E+05	5.6	–	115.5	633.4	1	10	0.003	1.4 (102)
Mefloquine hydrochloride	2	750 (103)	1	750	4.12	–	41.4	334.5	2	3	0.8	1.4 (103)
Misoprostol	1	0.2 (104)	33	0.006	2.91	–	83.9	494.9	2	5	0.9	1 (104)
Nefazodone hydrochloride	2	250 (105)	0.06	417	3.35	111 (40)	53.9	517.6	0	7	0.14	1.18 (105)
Nelfinavir mesylate	4	1,250 (10)	4.5	278	4.6	35 (40)	97.6	623.4	4	7	0.49	5 (10)
Nitrofurantoin monohydrate	4	100 (10)	0.19	526	−0.47	–	118.9	232.3	1	9	0.45	1.4 (10)
Pleconaril	2	200 (106)	0.002	1.00E+06	4.9	HP (107)	70	390.6	0	6	0.006	2.23 (106)
Ribavirin	3	200 (10)	100	2	−2.6	–	148.2	254.2	5	9	0.6	1.7 (10)
Ritonavir	4	600 (10)	0.01	60,000	5.98	15.8 (108)	132.5	769.7	4	11	0.002	1.14 (10)
Rofecoxib	2	50 (10)	0.01	5,000	1.63	241	63.7	308.5	0	4	0.12	1 (10)
Saquinavir free base	4	800 (10)	0.01	80,000	4.76	1.5 (109)	142.4	712	6	11	0.0003	6.7 (10)
Saquinavir mesylate	4	600 (10)	2.22	270	4.76	1.5 (109)	142.4	712	6	11	0.1	6.7 (10)
Sertraline	1	100 (110)	3.8	26.3	2.74	–	14.5	305.6	1	1	0.9	1 (110)
Ticlopidine hydrochloride	2	250 (111)	0.1	2,500	3.7	100 (40)	3.98	263.8	0	1	0.24	1.2 (111)
Triclabendazole	2	600 (112)	0.01	60,000	6.34	–	34.3	313.6	1	3	0.01	3.7 (112)
Troglitazone	2	400 (10)	0.01	40,000	4.94	–	85.2	456.3	2	6	0.015	1.6 (10)
Ziprasidone hydrochloride	2	20 (113)	3.00E−04	66,667	3.1	123	53.8	395.4	1	5	0.009	2 (113)

[a] Aqueous solubility at pH 7 in the unit of mg/mL.
[b] Ratio of dose to solubility at pH 7 in the unit of mL.
[c] The log D value is the log of octanol/water partition coefficient at pH 7 calculated by ACD software.
[d] Caco-2 permeability
[e] Polar surface area in the unit of $Å^2$
[f] Total surface area in the unit of $Å^2$
[g] Number of hydrogen bond donor
[h] Number of hydrogen bond acceptor
[i] Ratio of maximum absorbable dose, calculated using Eq. 1, to the clinical dose
[j] Ratio of bioavailability (area under the curve, AUC) at fasted state to that at fed state
[k] Food significantly reduced plasma AUC of fenodopam but has less significant effect on the AUC of active metabolite of fenoldopam. Relative bioavailability calculated from unine excretion data also show no significant change with food.

Table IV. Prediction Results of Compounds with Maximum Absorbable Dose (MAD) Greater than Clinical Dose

Compound	Probability of Negative Effect	Probability of No Effect	Predicted[a]	Observed[b]
5-Aminosalicylic acid	0.894	0.106	Negative	Negative
Acyclovir	0.303	0.697	No effect	No effect
Albuterol	0.638	0.362	Negative	No effect
Aripiprazole	0.001	0.999	No effect	No effect
Bromazepam	0.019	0.981	No effect	Negative
Bromocriptine	0.269	0.731	No effect	No effect
Capecitabine	0.638	0.362	Negative	Negative
Captopril	0.894	0.106	Negative	Negative
Cefdinir	0.894	0.106	Negative	Negative
Ceftibuten	0.894	0.106	Negative	Negative
Cimetidine	0.638	0.362	Negative	No effect
Ciprofloxacin	0.303	0.697	No effect	No effect
Clodronate	0.894	0.106	Negative	Negative
Didanosine	0.894	0.106	Negative	Negative
Dolasetron mesylate (Anzemet)	0.269	0.731	No effect	No effect
d-Sotalol	0.894	0.106	Negative	Negative
Entecavir	0.638	0.362	Negative	Negative
Eptastigmine	0.269	0.731	No effect	Negative
Ethinyl estradiol	0.269	0.731	No effect	No effect
Fexofenadine	0.269	0.731	No effect	Negative
Fluoxetine HCl	0.269	0.731	No effect	No effect
Frusemide	0.638	0.362	Negative	Negative
Hydralazine	0.638	0.362	Negative	Negative
Hydrochlorothiazide (12.5 mg)	0.638	0.362	Negative	No effect
Isoniazid	0.638	0.362	Negative	Negative
Isosorbide mononitrite	0.083	0.917	No effect	No effect
Lamivudine	0.638	0.362	Negative	No effect
Lansoprazole	0.269	0.731	No effect	No effect
Lomefloxacin	0.083	0.917	No effect	No effect
Meloxicam	0.083	0.917	No effect	No effect
Metformin HCl	0.894	0.106	Negative	Negative
Methylphenidate HCl	0.269	0.731	No effect	No effect
Morphine Sulphate	0.638	0.362	Negative	No effect
Moxifloxacin	0.638	0.362	Negative	No effect
Nitrofurantoin	0.005	0.995	No effect	No effect
Ofloxacin	0.303	0.697	No effect	No effect
Pidotimod	0.894	0.106	Negative	Negative
Pravastatin	0.638	0.362	Negative	Negative
S(+)-Ibuprofen	0.001	0.999	No effect	No effect
Salsalate	0.083	0.917	No effect	No effect
Tamsulosin HCl	0.638	0.362	Negative	Negative
Temafloxacin HCl	0.005	0.995	No effect	No effect
Tolectin (tolmetin)	0.638	0.362	Negative	Negative
Tolterodine tartrate	0.269	0.731	No effect	No effect
Topiramate	0.269	0.731	No effect	No effect
Valdecoxib	0.001	0.999	No effect	No effect
Verapamil	0.269	0.731	No effect	No effect
Zalcitabine	0.894	0.106	Negative	Negative
Zidovudine	0.638	0.362	Negative	No effect
Zolmitriptan	0.638	0.362	Negative	Negative
Zolpidem tartrate	0.269	0.731	No effect	Negative

[a] The food effect on oral absorption predicted from the calculated probability by the present statistical model.
[b] The food effect on oral absorption observed clinically.

and acceptors, do not contribute significantly to the food effect based on the statistical analysis. The model also indicates that food effect is sensitive to the category of the properties rather than the individual value, suggesting that compounds in the same category possess similar properties for food effect.

The current model was able to predict all compounds with true positive food effect in the database of this study into the correct category except ribavarin. The model also predicted some compounds with no food effect into positive food effect category. It was more difficult to discriminate compounds with no food effect from compounds with

Table V. Prediction Results of Compounds with Maximum Absorbable Dose (MAD) Less than Clinical Dose

Compound	Probability of Negative Effect	Probability of No Effect	Probability of Positive Effect	Predicted[a]	Observed[b]
Abacavir sulfate	0.089	0.531	0.38	No effect	No effect
Acitretin (soft gel)	0.033	0.331	0.635	Positive	Positive
Albendazole	0.012	0.156	0.832	Positive	Positive
Amiodarone HCl	0.012	0.156	0.832	Positive	Positive
Atazanavir sulfate	0.012	0.156	0.832	Positive	Positive
Atovaquone	0.012	0.156	0.832	Positive	Positive
Bicalutamide	0.012	0.156	0.832	Positive	No effect
Bropirimine	0.012	0.156	0.832	Positive	Positive
Cefditoren pivoxil	0.012	0.156	0.832	Positive	Positive
Cefuroxime axetil	0.012	0.156	0.832	Positive	Positive
Celecoxib	0.012	0.156	0.832	Positive	Positive
Clopidogrel bisulfate	0.089	0.531	0.38	No effect	No effect
Danazol	0.012	0.156	0.832	Positive	Positive
Efavirenz	0.012	0.156	0.832	Positive	Positive
Fenoldopam	0.012	0.156	0.832	Positive	No effect
Ganciclovir	0.033	0.331	0.635	Positive	Positive
Griseofulvin	0.012	0.156	0.832	Positive	Positive
Halofantrine HCl	0.012	0.156	0.832	Positive	Positive
Hydrochlorothiazide (50 mg)	0.033	0.331	0.635	Positive	Positive
Imiquimod	0.012	0.156	0.832	Positive	No effect
Indinavir	0.012	0.156	0.832	Positive	Negative
Irbesartan	0.012	0.156	0.832	Positive	No effect
Isotretinoin	0.012	0.156	0.832	Positive	Positive
Itraconazole	0.012	0.156	0.832	Positive	Positive
Manidipine 2HCl	0.012	0.156	0.832	Positive	Positive
Mefloquine HCl	0.012	0.156	0.832	Positive	Positive
Misoprostol	0.089	0.531	0.38	No effect	No Effect
Nefazodone HCl	0.012	0.156	0.832	Positive	Positive
Nelfinavir mesylate	0.012	0.156	0.832	Positive	Positive
Nitrofurantoin	0.012	0.156	0.832	Positive	Positive
Pleconaril	0.012	0.156	0.832	Positive	Positive
Ribavirin	0.089	0.531	0.38	No effect	Positive
Ritonavir	0.012	0.156	0.832	Positive	Positive
Rofecoxib	0.012	0.156	0.832	Positive	No effect
Saquinavir free base	0.012	0.156	0.832	Positive	Positive
Saquinavir mesylate	0.012	0.156	0.832	Positive	Positive
Sertraline	0.089	0.531	0.38	No effect	No effect
Ticlopidine HCl	0.012	0.156	0.832	Positive	Positive
Triclabendazole	0.012	0.156	0.832	Positive	Positive
Troglitazone	0.012	0.156	0.832	Positive	Positive
Ziprasidone HCl	0.012	0.156	0.832	Positive	Positive

[a] The food effect on oral absorption predicted from the calculated probability by the present statistical model.
[b] The food effect on oral absorption observed clinically.

negative food effect. The limitation of the model is described in the Discussion section.

DISCUSSION

In the statistical model, when MAD was greater than clinical dose (complete absorption, Table III), compounds with dose number category 1 (dose number <50) and log D category 1 or 2 (log D <1) were predicted to have negative food effect. Compounds with dose number category 1 and log D category 3 (log D > 1) were predicted to show no food effect. Compounds with dose number category 2 or 3 (dose number >50) and any log D category were also predicted to show no food effect. These results suggest that among compounds that can be completely absorbed, only compounds that are highly soluble (dose number <50) and hydrophilic (Log D <1) are statistically prone to show negative food effect. It has been suggested that food may serve as a physical barrier for drug absorption, which may reduce absorption of compounds with narrow window of absorption (7). Those compounds that are highly soluble and hydrophilic may belong to the class of compounds with narrow window of absorption and therefore show negative food effect.

However, the model failed to predict correctly the compounds with narrow window of absorption that are not highly soluble and hydrophilic. Based on the model, indinavir (log D = 2.66) was predicted to show positive food effect because of its low solubility and high log D value. However,

Table VI. Summary of Prediction of Food Effect Results Using Present Model

	Predicted food effect by current model			
	Negative	No Effect	Positive	Percent Correct Prediction
Negative food effect, 24 entries	19	4	1	79% (19/24)
No food effect, 37 entries	7	25	5	68% (25/37)
Positive food effect, 31 entries	0	1	30	97% (30/31)
Total 92 entries	75 entries predicted correctly			80% (74/92)

The number of compounds that were predicted into each food effect category is listed.

it showed negative food effect in the clinical study and was attributed to its narrow window of absorption (20), which was not statistically predicted based on descriptors used in the current model. On the other hand, some highly soluble and hydrophilic compounds may not exhibit narrow window of absorption, e.g., lamivudine. This compound was predicted to have negative food effect but showed no food effect clinically (71). The root cause of these incorrect predictions is the inaccurate correlation between log D and intestinal permeability. Fexofenadine (negative food effect) was predicted to have no food effect because of high log D value. However, it has poor intestinal permeability (21). In contrast, zidovudine showed no food effect because of moderate permeability despite low log D value (22). It was reported that the correct classification of human permeability based on Log D is 87% for 16 drugs (23). A better prediction in the present model may be achieved if human intestinal permeability data are available.

For compounds with MAD less than clinical dose (incomplete absorption, Table III) with dose number category 2 or 3 (dose number >50), the model predicted to have positive food effect. Therefore, for compounds that cannot be completely absorbed because of limited solubility or dissolution rate, food enhanced their oral absorption statistically. This solubilization effect of food can be explained physiologically. Food, especially high fat meal which is often used in the food effect study, introduces higher concentration of lipids and bile salts, leading to higher solubility and dissolution rate of lipophilic compounds, e.g., halofantrine (24). It should also be noted that, the dose number, in addition being an indicator of solubility dose relationship, may also reflect other properties of a compound that are susceptable to food effect. It was reported that food may in general inhibit both influx and efflux transporters (25). For compounds with high dose number, they are more likely to be substrates of efflux transporters and therefore more likely to show positive food effect. These compounds are also more likely to be absorbed through lymphatic uptake and the postprandial increase in lymphatic flow will cause the positive food effect (26). On the other hand, compounds with low dose numbers are more likely to be the substrate of influx transporters causing negative food effect.

For compounds with incomplete absorption, if the dose number was less than 50, it was predicted to have no food effect. This result suggests that if incomplete absorption is caused by factors other than solubility, food generally exerts no effect on absorption. It is interesting to note that the food effect category is separated by dose number 50 rather than the value 250 used in BCS classification (27). The dose number 50 (the dose that can be solubilized with 50 mL of water at pH 7) was chosen arbitrary in this study to separate compounds that are highly soluble with respect to dose (dose number <50) from those that are moderately soluble ($50 \leq$ dose number ≤ 250). Indinavir is the only compound with MAD less than clinical dose in the entry showed negative food effect.

It is noted that all poorly soluble weak bases except indinavir in this database showed positive food effect, which suggests that initial higher gastric pH under fed condition does not impede the overall amount of weak bases dissolved as secretion of HCl with food reduces the gastric pH to around 2 within 60 min (5,6). Furthermore, the residence time of the drug in the stomach is longer with food, which may enhance the total amount dissolved. Slower entry to the intestine (delayed gastric emptying), lower duodenal pH and higher concentration of lipid and bile salts under fed conditions may also reduce the precipitation of weak bases in intestine leading to higher bioavailability.

The present model heavily relies on the accuracy of estimated MAD, which is determined by the accuracy of solubility and permeability. However, discrepancy may exist between *in vitro* estimated solubility and permeability and *in vivo* absorption. For some lipophilic compounds, the solubility in the intestinal fluid may be significantly higher than the aqueous solubility used in the current calculation, leading to underestimation of MAD values (28). The absorption rate

Table VII. Probability of Correct Prediction of Food Effect Using Present Model

	Observed Food Effect			
	Negative	No Effect	Positive	Probability of Correct Prediction
Predicted negative food effect, 25 entries	19	7	0	73% (19/26)
Predicted no food effect, 31 entries	4	25	1	83% (25/30)
Predicted positive food effect, 36 entries	1	5	30	83% (30/36)

used to calculate MAD is the average value. Some compounds may show higher absorption rate than the average value, which also leads to underestimation of MAD values. The absorption window of 3 h was used to calculate MAD, which may underestimate the MAD value of highly permeable compound with colonic absorption. Imiquimod and rofecoxib were predicted to have positive food effect but showed no food effect clinically. The estimated MADs of these two compounds based on the highest absorption rate suggested in the literature are much lower than the clinical dose because of very high dose number (18). However, it is reported that rofecoxib (29) and imiquimod (30) showed complete oral absorption in clinical study. The Cmax of these two compounds was also unaltered in the presence of food, suggesting lack of food effect on dissolution. The underestimation of MAD values of these 2 compounds lead to incorrect prediction of the food effect. The incorrect prediction for bicalutamide (predicted to have positive food effect but showed no effect clinically) is also caused by underestimated MAD value. Postpandial dosing of bicalutamide resulted in significant increase in Cmax although without effect on AUC (31). The higher Cmax may be caused by increased solubility with food. However due to high permeability, complete absorption was achieved leading to no food effect on AUC (31). It is also worth mentioning that the solubility and permeability values are collected from various sources and therefore may be associated with inaccuracy. We also only used solubility value at pH 7 and the pH effect on solubility was not considered in this study. However, since the model used categorized parameters instead of absolute values, the variability in the source data may be somewhat mitigated.

The prediction accuracy of current model is limited by the physicochemical parameters used in the model, and may not represent all factors contributing to the effect of food on AUC, such as effect on metabolism and specific chelation between food and drug. The current model also cannot predict food effect on the activity of a specific transporter responsible for the absorption of a particular compound as the current understanding of food effect on transporter is limited. Ribavirin is the only entry that showed positive food effect clinically but was not predicted correctly. It is reported that intestinal absorption of ribavirin is mediated by the concentrative Na^+ nucleoside purine (CN1) transporter and can be saturated with increasing dose (1). Although the mechanism of food effect on ribavirin is unknown, the current model will not be able to predict its food effect if the activity of nucleoside purine (N1) transporter is altered by food.

The current model considers only the intrinsic properties of a compound and their relationship to the food effect. Formulations may significantly change the intrinsic property of a compound and therefore its food effect. Danazol, when dosed as conventional capsule showed significant positive food effect as predicted (32). However, no food effect was observed when danazol was dosed as an emulsion (32). Itraconazole is another example that the conventional capsule formulation showed positive food effect as predicted from the molecular properties (33) but the hydroxypropyl-β-cyclodextrin solution formulation showed negative food effect as the formulation changed the intrinsic property (solubility) of the compound (33).

Despite the limitation of the model, it successfully predicts the food effect of a compound with reasonable accuracy based on physicochemical properties. The model may be improved if additional parameters could be included when better understanding of effect of food on permeability and metabolism is achieved.

CONCLUSIONS

A statistical model is established to predict the food effect on extent of absorption based on solubility, permeability and dose of a compound. It was found that critical parameters for food effect prediction include maximum absorbable dose (MAD) category (a parameter that combines information of dose, solubility and permeability), category of dose number (a parameter that combines dose and solubility) and category of Log D (an indicator of permeability). For overall 92 entries, 80% were predicted into the correct category. 97, 79 and 68% of entries with positive, negative and no food effect, were predicted into respective correct categories. Given a compound, the probability of correct prediction is 83, 73 and 83% if it is predicted to show positive, negative or no food effect, respectively. Since all parameters used in the model can be estimated during the discovery stage, the model may be used to predict the possible food effect in early discovery.

The statistical analysis revealed that positive food effect on absorption is primarily caused by solubilization effect of food. Statistically, food causes negative effect on absorption because it interferes with absorption of compounds that are highly hydrophilic and probably with narrow window of absorption.

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