Computational Prediction of Oral Drug Absorption Based on Absorption Rate Constants in Humans

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Models for predicting oral drug absorption kinetics were developed by correlating absorption rate constants in humans (K_a) with computational molecular descriptors. The K_a values of a set of 22 passively absorbed drugs were derived from human plasma time−concentration profiles using a deconvolution approach. The K_a values correlated well with experimental values of fraction of dose absorbed in humans (FA), better than the values of human jejunal permeability (P_{eff}) which have previously been used to assess the *in vivo* absorption kinetics of drugs. The relationships between the K_a values of the 22 structurally diverse drugs and computational molecular descriptors were established with PLS analysis. The analysis showed that the most important parameters describing log K_a were polar surface area (PSA), number of hydrogen bond donors (HBD), and log *D* at a physiologically relevant pH. Combining log *D* at pH 6.0 with PSA or HBD resulted in models with Q^2 and R^2 values ranging from 0.74 to 0.76. An external data set of 169 compounds demonstrated that the models were able to predict K_a values that correlated well with experimental FA values. Thus, it was shown that, using a combination of only two computational molecular descriptors, it is possible to predict with good accuracy the K_a value for a new drug candidate.

Introduction

Early prediction of human intestinal absorption kinetics is important in the selection of potential orally active drugs. The rate and extent of intestinal absorption are mainly dependent on the dissolution rate of the drug in the gastrointestinal fluids and the rate of transport across the intestinal membrane. It has been hypothesized that the predominant process of absorption for most conventional drugs is passive diffusion,[1] which is often described by the permeability coefficient (10^{-6} cm/s). It is noteworthy that although influx and efflux transporters also have a role in the absorption of some drugs,[2,3] an active transport process is not always quantitatively significant in the *in vivo* absorption of a drug.

In vivo animal studies and epithelial cell culture models are both used routinely for the assessment of intestinal drug permeability. However, these techniques are costly and laborious. Several recent studies have shown that physicochemical descriptors of molecules such as lipophilicity, polar surface area (PSA), and hydrogen bonding descriptors correlate with cell culture permeabilities and intestinal absorption.[4−7] This relationship between molecular descriptors and permeability facilitates the prediction of absorption because the descriptors of a molecule can be rapidly calculated with computational methods.

The fraction of dose absorbed in humans (FA), which describes the extent of the dose that crosses the intestinal wall, has been modeled in several studies. Using a set of 20 passively absorbed drugs, Palm and co-workers[8] showed that the calculated dynamic PSA has a sigmoidal relationship with FA. In many studies, multiparameter equations for predicting FA have been developed by correlating various molecular descriptors to FA values.[4−6] In the work of Zhao and co-workers,[5,6] five Abraham molecular descriptors were successfully used to model the FA values of 169 diffusion rate-limited drugs.

Human jejunal permeability (P_{eff}) is another parameter that has been correlated with physicochemical descriptors of molecules.[9−11] Winiwarter and co-workers,[9] using multivariate data analysis, correlated the P_{eff} values of a set of 13 passively absorbed compounds to several physicochemical descriptors. This analysis, although performed using a limited number of compounds, yielded three models with good statistics. The most important molecular descriptors in determining the P_{eff} values of the 13 drugs were found to be the number of hydrogen bond donors (HBD), PSA, and the lipophilicity descriptors. The study of Winiwarter and co-workers[9] demonstrates that the method of determining human jejunal P_{eff}, although too complicated for routine assessment of a compound's intestinal absorption, is a tool that can be used to increase our understanding of the absorption process. However, considering the limited number of compounds for which P_{eff} has been determined, the considerable error associated with the P_{eff} value measurements,[3] and the fact that P_{eff} values do not correlate very well with FA (an analysis performed in this study), it is obvious that the study of the relationships between absorption kinetics and molecular descriptors should be based on a more practical and reliable method than the human jejunal perfusion system.

The present study is the first investigation that correlates the physicochemistry of passively absorbed drugs with human intestinal absorption rate constants (K_a) derived using deconvolution analysis, an approach that is commonly used in the assessment of drug release and drug absorption from orally administered drug formulations. In the deconvolution approach, the plasma time−concentration profile following intravenous (iv) administration is subtracted from the plasma time−concentration obtained following oral (po) administration. This

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Table 1. Molecular Descriptors for Drugs in Data Set 1

drug	MW	PSA	HBD	HBA	ClogP	ACDlogP	exp log $D_{7.4}$[x]	ACDlog$D_{7.4}$	ACDlog$D_{6.5}$	ACDlog$D_{6.0}$	ACDlog$D_{5.5}$
acetaminophen	151	56	2	3	0.49	0.34	0.51[a]	0.34	0.34	0.34	0.34
acetylsalicylic acid	180	60	1	4	1.02	1.19	−1.90[b]	−1.89	−1.59	−1.24	−0.80
antipyrine	188	24	0	3	0.41	0.27	0.41[c]	0.27	0.27	0.27	0.27
atenolol	266	93	4	5	−0.11	0.10	−1.68[d]	−1.66	−2.44	−2.74	−2.90
bumetanide	364	121	4	7	3.90	2.78	0.10[e]	−0.21	0.29	0.71	1.15
caffeine	194	47	0	6	−0.06	−0.13	−0.03[f]	−0.13	−0.13	−0.13	−0.13
cimetidine	252	84	3	6	0.35	0.26	0.21[g]	0.11	−0.37	−0.79	−1.23
eflornithine	182	94	3	4	−3.00	0.30	*h*	−2.30	−2.62	−2.87	−3.06
famotidine	337	182	8	9	−0.56	−0.40	−1.11[i]	−1.02	−1.74	−2.06	−2.26
felodipine	384	60	1	5	4.96	4.83	4.20[j]	4.83	4.83	4.82	4.80
furosemide	331	126	4	7	1.87	3.00	−0.92[k]	−0.12	0.02	0.26	0.62
hydrocortisone	362	96	3	5	1.70	1.43	1.54[l]	1.43	1.43	1.43	1.43
ibuprofen	206	40	1	2	3.68	3.72	0.88[m]	0.80	1.64	2.12	2.60
lamivudine	229	93	3	6	−1.54	−0.72	−0.92[n]	−0.71	−0.72	−0.72	−0.72
ondansetron	293	31	0	4	2.64	2.49	2.30[o]	2.14	1.46	1.02	0.61
oxprenolol	265	53	2	4	1.69	2.29	0.18[p]	0.57	−0.22	−0.53	−0.70
pindolol	248	63	3	4	1.67	1.97	0.09[q]	0.18	−0.59	−0.88	−1.03
scopolamine	303	61	1	5	0.26	1.34	0.21[r]	0.63	−0.18	−0.64	−1.07
sotalol	272	85	3	5	0.23	0.32	−1.38[s]	−1.46	−2.23	−2.52	−2.68
sumatriptan	295	75	2	5	0.58	0.67	−1.06[t]	−1.38	−2.07	−2.28	−2.38
terbutaline	225	80	4	4	0.48	0.48	−1.29[u]	−1.31	−2.07	−2.36	−2.52
theophylline	180	64	1	6	−0.06	−0.17	−0.03[v]	−0.20	−0.18	−0.18	−0.18
valproic acid	144	40	1	2	2.76	2.72	0.13[w]	0.16	1.03	1.51	1.95

[a] References 12−14. [b] References 14−16. [c] References 9, 12, 14, and 16. [d] References 9 and 13−18. [e] References 1, 14, and 19. [f] References 1, 12, 14, 15, and 18. [g] References 12, 14, 15, and 17. [h] Experimental log $D_{7.4}$ not available. [i] Experimental log *D* at pH 6.5, ref 20. [j] References 13, 17, and 21. [k] References 9, 13, 14, and 18. [l] References 12−16. [m] References 14 and 16. [n] Reference 22. [o] Reference 17. [p] References 13 and 16. [q] References 14−16. [r] Reference 15. [s] References 12 and 14. [t] References 12, 13, 23, and 24. [u] References 9, 12, 14, and 15. [v] References 13, 14, and 16. [w] Reference 13. [x] The experimental (exp) log $D_{7.4}$ values are averages of the values from several articles.

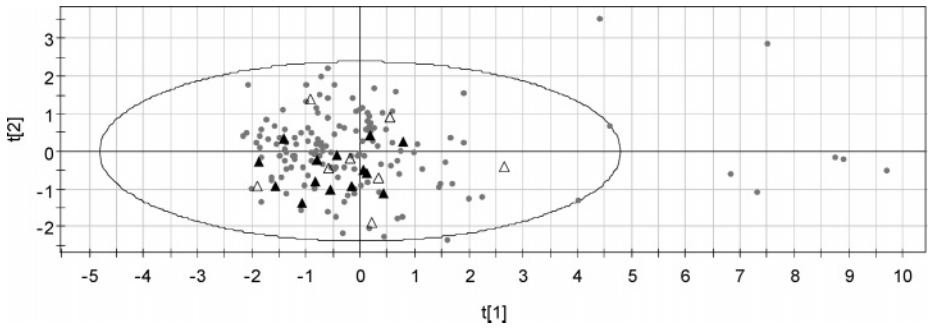

Figure 1. PCA score plot showing the second PC (t2) against the first PC (t1) for the 170 compounds in data set 2. Triangles indicate the compounds corresponding to the 23 compounds in data set 1. Drugs denoted by open triangles belong to the training set used in validating the predictivity of the models.

results in information about the overall rate of absorption as such. The deconvolution approach provides more information about the kinetics of absorption throughout the entire intestine than the jejunal perfusion system, which measures P_{eff} in only a 10-cm segment of the jejunum.

In this work the deconvolution method was used to determine the K_a values of 23 structurally diverse drugs from iv and po data of clinical studies. Our main aim was to derive a quantitative structure−property relationship (QSPR) equation which, on the basis of simple rapidly computed molecular descriptors, would allow the prediction of the K_a value of a predominantly passively absorbed drug in the human intestine.

Materials and Methods

Compound Data Sets. Two data sets of compounds were used in this study. Data set 1 consisted of 23 structurally diverse compounds (Table 1, Figure 1) for which the iv and po plasma time−concentration profiles required for the calculation of K_a values were available. The drugs selected for data set 1 (selection described in the following section) are absorbed predominantly by a passive process, and the rate of absorption is limited by diffusion, not dissolution. The data set covers a fairly broad range of absorption in humans (Table 2). Data set 2 consisted of the 23 compounds in data set 1 and an additional 147 compounds. All compounds from a data set used by Zhao and co-workers to model diffusion rate-limited drug absorption in the human intestine (FA) were included in data set 2. The only drug which was not taken from the data set used by Zhao and co-workers was eflornithine, which also belongs to data set 1.

Selecting the Compounds for Data Set 1. The drugs in data set 1 were selected on the basis of the following requirements: (1) diffusion, not dissolution, limits absorption; (2) a reliable FA value is available; (3) passive diffusion is the predominant process of absorption; (4) iv and po profiles required for the deconvolution analysis are available. Since all compounds in the large data set of Zhao and co-workers[6] fulfilled the first two requirements, an extensive literature search was carried out to find iv and po plasma time−concentration profiles for these 169 compounds. Studies in which both the iv and po pharmacokinetics of a drug had been investigated in the same healthy volunteers were primarily searched for.

This search yielded the plasma time−concentration profiles of 35 drugs. The meager result of the search was not solely due to the lack of studies in which the iv and po pharmacokinetics of a drug were investigated but also due to the fact that plasma time−concentration profiles were not always reported. The decision to exclude actively transported drugs and drugs administered as formulations that may limit the rate of absorption reduced the number of drugs accepted for data set 1 from 35 to 23. Indications

Table 2. Experimental FA Values, Values of Rate Constants Derived from Deconvolution Analysis, and Details of Clinical Data Used in Deconvolution Analysis

drug	FA	K_{app} (h^{-1})	K_a (h^{-1})	log K_a (h^{-1})	lag time (min)	no of volunteers in clinical study[a]
acetaminophen	0.87	3.354	2.918	0.465		18[b]
acetylsalicylic acid	1.0	6.228	6.228	0.794	3	6[c]
antipyrine	1.0	6.420	6.420	0.807	6	6[d]
atenolol	0.54	0.470	0.254	−0.596		12[e]
bumetanide	1.0	1.356	1.356	0.132	3	12[f]
caffeine	1.0	4.296	4.296	0.633		10[g]
cimetidine	0.76	0.870	0.661	−0.180	4	12[h]
eflornithine	0.55	0.265	0.146	−0.836	36	6[i]
famotidine	0.43	0.504	0.217	−0.664	9	16[j]
felodipine	1.0	4.512	4.512	0.654	11	10[k]
furosemide	0.61	0.756	0.461	−0.336	1	18[l]
hydrocortisone	0.96	3.792	3.640	0.561	1	8[m]/15[n]
ibuprofen	1.0	2.670	2.670	0.427	1	8[o]/15[p]
lamivudine	0.87	1.086	0.945	−0.025	6	12[q]
ondansetron	1.0	1.890	1.890	0.276	26	5[r]
oxprenolol	0.80	3.318	2.654	0.424	3	6[s]
pindolol	0.87	1.380	1.201	0.079	10	6[t]
scopolamine	0.95	1.644	1.562	0.194		6[u]
sotalol	1.0	0.535	0.535	−0.271	19	7[v]
sumatriptan	0.57	0.408	0.233	−0.633	10	18[w]
terbutaline	0.73	0.450	0.329	−0.483	4	6[x]
theophylline	0.99	2.364	2.340	0.369		20[y]/10[y]
valproic acid	1.0	4.128	4.128	0.616	4	6[z]/14[aa]

[a] If two values are given, the iv and po data were not obtained from the same volunteers. The first value shows the number of volunteers in the iv study, and the second, the number of volunteers in the po study. [b] Reference 25. Iv and po data given for a representative subject. [c] Reference 26. [d] Reference 27. Iv and po data given for one subject. [e] Reference 28. [f] Reference 29. [g] Reference 30. [h] Reference 31. [i] Reference 32. [j] Reference 33. [k] Reference 34. [l] Reference 35. [m] Reference 36. [n] Reference 37. [o] Reference 38. [p] Reference 39. [q] Reference 40. Volunteers were infected with HIV. The volunteers were only accepted if their HIV status was asymptomatic, or they had no symptoms more severe than persistent generalized lymphadenopathy. [r] Reference 41. [s] Reference 42. [t] Reference 43. [u] Reference 44. [v] Reference 45. [w] Reference 46. [x] Reference 47. [y] Reference 48. 20 asthmatic volunteers in the iv study and 10 of them in the po study. [z] Reference 49. [aa] Reference 50.

of the drugs being substrates of active or efflux transporters were searched for from the literature. The transporter database complied by Ozawa and co-workers[51] was used as an aid in this process. Evidence of active and efflux transport was found for several of the drugs. Passive diffusion was, however, considered to be the predominant process of absorption for all of the drugs chosen for data set 1.

Zhao and co-workers[6] inferred, on the basis of computational solubility, dose, and FA, that the rate of absorption of the drugs in their data set was limited by diffusion. However, since we wanted to be sure that the rate of absorption of the drugs in the present study was limited by diffusion and not dissolution, we performed a further analysis to determine the rate-limiting step of absorption. For those drugs that had been administered orally as a formulation other than a solution, suspension or a rapidly disintegrating tablet, we searched the literature for a study in which the drug had been administered as a solution. If the study in which the drug had been administered as a solution showed that the time to reach peak concentration (t_{max}) was the same (difference in t_{max} not more than 25%) for the solution as for the other formulation, e.g., tablet, the po data of the tablet formulation were accepted for the deconvolution analysis. However, if the t_{max} of the tablet was reached later (difference in t_{max} over 25%) than the t_{max} of the solution, the po data were taken from the study in which the drug had been administered as a solution. In the latter case, the iv and po profiles were not obtained from the same healthy volunteers. Details of the studies from which the iv and po plasma time−concentration profiles were obtained are given in Table 2.

Human Intestinal Absorption Data. The experimental FA values for the 23 drugs in data set 1 (Table 2) were taken from the reports providing the iv and po profiles of the drug. However, if the FA value was not given in the report, the FA value was taken from the work of Zhao and co-workers.[6] Cimetidine's FA value was obtained from the work of Bodemar and co-workers,[52] and felodipine's FA value, from the work of Wessel and co-workers.[4] The FA values of the compounds in data set 2 that did not belong to data set 1 were obtained from the work of Zhao and co-workers.[6]

Determination of Absorption Rate Constants. For the 23 drugs in data set 1, the deconvolution module in the software WinNonlin[53] was used to determine the K_a values from the iv and po plasma time−concentration profiles. To determine the absorption process following oral administration of a drug, WinNonlin uses the principle of deconvolution through convolution. The extent of drug input is given in terms of fraction input ($A(t)$), which is defined, in a nonextrapolated way, as the fraction of drug input at time t relative to the amount of input at the last sample time t_{end}:

$$A(t) = \int_0^t f(t)\,dt / \int_0^{t_{end}} f(t)\,dt \quad (1)$$

At the last observation time t_{end}, $A(t)$ will by definition have a value of 1. This value should not be confused with the fraction input relative to the dose.

The absorption of all drugs in data set 1 was found to follow first-order absorption, after a possible short lag time (t_{lag}), until the time point at which $A(t)$ reached the value of 0.75 ($t_{0.75absorbed}$) (Figure 2). Thus, the fraction input profiles obtained by deconvolution analysis could be fitted to eq 2 to yield the rate constant describing the loss of drug from the site of absorption (K_{app})

$$A(t) = 1 - e^{-K_{app}(t - t_{lag})} \quad (2)$$

where $A(t)$ is the fraction of drug input at time t ($t_{0.75absorbed} \geq t \geq t_{lag}$) relative to the amount of input at the last sample time.

To obtain the K_a value of each drug in data set 1, the K_{app} values acquired from the fraction input profiles were multiplied by experimental FA values.

$$K_a = K_{app}(FA) \quad (3)$$

The FA values used in the calculation of the K_a values are given in Table 2.

The exact data points of the iv and po drug plasma time−concentrations profiles were required for the deconvolution analysis. If these points were not given in the reports on the pharmacokinetics of the drug, they were obtained from the graphs provided by the reports.

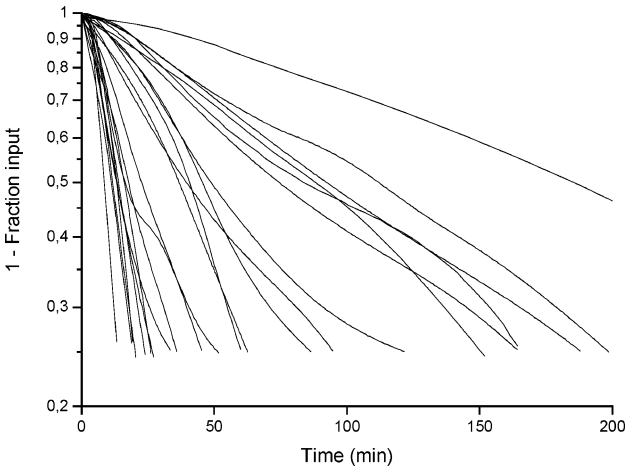

Figure 2. Semilog plots of fraction unabsorbed (1 − fraction input) versus time profiles obtained from deconvolution analyses of drugs in data set 1. K_{app} is the slope of the plots. The possible short lag times before absorption are not shown in this figure.

The mean unit impulse response parameters (macro-rate constants associated with the distribution and elimination phases) required for the deconvolution analysis were estimated from the plasma concentration−time data following iv bolus or infusion input using one of the compartmental models in the WinNonlin PK library. The appropriate model was chosen on the basis of best fit.

Molecular Descriptors. The values for the logarithms of the octanol−water partition coefficients of the neutral form (ACDlogP) and at pH 7.4, 6.5, 6.0, and 5.5 ($ACDlogD_{7.4}$, $ACDlogD_{6.5}$, $ACDlogD_{6.0}$, and $ACDlogD_{5.5}$) were calculated with the ACD/Labs LogP and LogD software packages.[54] The prediction of log *P*/log *D* by the ACD/Labs program is based on a structure fragment approach. The molecular structures were imported from the ACD/ dictionary or drawn in ACD/ChemSketch.[55] The experimental log *D* values at pH 7.4 (log $D_{7.4}$) were taken from the literature. The values for the molecular weights (MWs) were taken from ACD/ ChemSketch.

The values for the PSA, HBD, number of hydrogen bond acceptors (HBA), and ClogP were taken from the work of Zhao and co-workers,[5] who obtained these values with the following calculations. PSA was calculated using the SAVOL program.[56] HBD and HBA values were counted from the molecular structure of the drug so that hydrogen-bonding donors were any of the O−H or N−H groups and hydrogen-bonding acceptors were any of the O or N atoms, including those in the donor groups. ClogP was calculated using *ClogP for Windows* software.[57] All the molecular descriptor values of the drugs in data set 1 are given in Table 1.

Multivariate Data Analysis. Multivariate data analyses were performed with Simca-P[58] using the default settings. The molecular diversity of the compounds in data set 1 was analyzed with principal component analysis (PCA). This analysis was based on the 170 compounds in data set 2 and the five molecular descriptors MW, ClogP, HBD, HBA, and PSA that have been shown to be relevant to oral absorption in earlier studies.[8,9,59]

The relationships between the log K_a values and the molecular descriptors (Table 1) of the drugs in data set 1 were determined by Partial Least Squares (PLS) analysis. The final models were built using 22 of the 23 compounds in that data set. Cross-validation was performed to quantify the predictive capability of the derived PLS models. The predictivity of the models was further validated by dividing data set 1 into a training set and a test set. The training set was selected by identifying eight representative compounds from the score plot (Figure 1).

Correlating ACDlogD Values with Experimental log *D* Values. The $ACDlogD_{7.4}$ values of the compounds used in our analyses were correlated to their experimental log $D_{7.4}$ values. An extensive literature search yielded the experimental log $D_{7.4}$ values for 22 of the 23 compounds in data set 1 (values given in Table 1) and for 85 of the 170 compounds in data set 2 (values given in the Supporting Information).

Table 3. R^2 (Ordinary Correlation Coefficient) and Q^2 (Cross-validated Correlation Coefficient) Values Obtained from Correlations between log K_a and Each Individual Molecular Descriptor

parameter	Q^2	R^2
exp log $D_{7.4}$	0.35	0.48
$ACDlogD_{7.4}$	0.34	0.49
$ACDlogD_{6.5}$	0.49	0.60
$ACDlogD_{6.0}$	0.54	0.61
$ACDlogD_{5.5}$	0.55	0.59
ACDlogP	0.12	0.15
ClogP	0.25	0.28
PSA	0.40	0.43
HBD	0.46	0.49
HBA	0.06	0.17
MW	−0.10	0.03

Correlating Predicted log K_a Values with Experimental FA Values. The PLS models developed here were further tested by using them to predict the log K_a values of the drugs in data set 2. The predicted log K_a values were then plotted against the experimental FA values of the drugs. An ideal relationship between log K_a and FA was calculated with a compartmental absorption and transit (CAT) model equation based on the CAT model developed by Amidon's group.[60]

$$FA = 1 - (1 + 0.32K_a)^{-7} \quad (4)$$

Amidon and co-workers have evaluated the original CAT model equation using P_{eff} values. Equation 4 was obtained from the original equation on the basis of the relationships prevailing between K_a and P_{eff}. Equation 4 assumes that the radius of the intestine is 1.2 cm instead of 1.75 cm which was used by Amidon's group. A radius of 1.2 cm is also used by the commercial GastroPlus program[61] developed on the basis of the CAT model.

Results

Structural Diversity of the Drugs. PCA was performed to ensure that the 23 compounds in data set 1 were structurally representative of the 170 compounds in data set 2. The PCA resulted in two principal components explaining 94% of the variance in the data set. The first principal component explained 75.4%, and the second 18.6% of the variance. Figure 1 shows the score plot of the 170 compounds in data set 2. All 23 compounds in data set 1 (denoted by triangles) lie within the elliptic 95% tolerance volume, indicating that there are no outliers in the score space. The compounds in data set 1 are reasonably well separated, implying that they are representative of the drugs in data set 2.

Determined K_{app} and K_a Values. The K_{app} values obtained by fitting eq 2 to the fraction input profiles (Figure 2) are given in Table 2. The loss of drug from the site of absorption followed first-order kinetics fairly nicely for all the drugs in data set 1 (R^2 values ranged from 0.94 to 1.00) until the time point at which $A(t)$ reached the value of 0.75. The K_a values, determined by multiplying the K_{app} values by experimental FA values, are also listed in Table 2. The K_a values ranged from 0.15 h^{-1} (eflornithine) to 6.42 h^{-1} (antipyrine).

QSPR Model Development and Validation. The relationships between the log K_a values of the drugs in data set 1 and the calculated molecular descriptors were determined with PLS analysis. Before performing the multivariate analyses, the linear correlation between log K_a and each molecular descriptor was calculated (Table 3). The best correlations were obtained with the log *D* descriptors, HBD, and PSA.

The first PLS model ($R^2 = 0.68$ and $Q^2 = 0.62$) was built using all the molecular descriptors found in Table 1. The variable

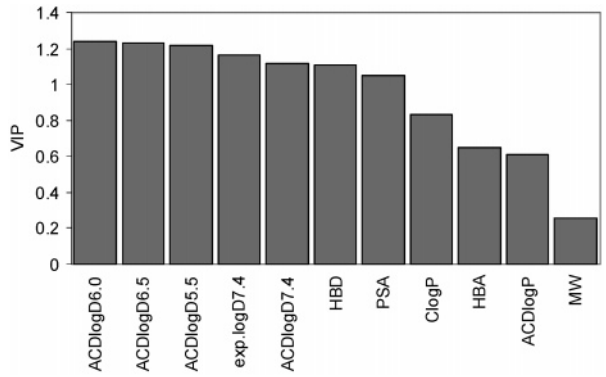

Figure 3. Variable importance plot from PLS analysis with 11 molecular descriptors.

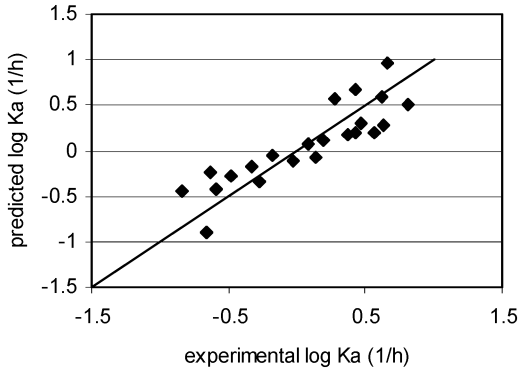

Figure 4. Correlations between predicted and experimental log K_a values. The log K_a values were predicted using model 1a. The straight line shows the ideal relationship between predicted and experimental values.

influence on projection (VIP) function available in Simca-P was then used to determine the descriptors that best explained log K_a in the PLS model. The descriptors with VIP values over 1 have an above average influence on log K_a. Inspection of the VIP plot (Figure 3) showed that the log *D* descriptors, HBD, and PSA had VIP values above 1. MW had the lowest VIP value. Of the log *D* descriptors, $ACDlogD_{6.0}$ had the highest and $ACDlogD_{7.4}$ the lowest VIP value.

Since the descriptors with VIP values over 1 were the same ones that gave good correlations with log K_a on their own, we decided to exclude the descriptors with VIP values smaller than 1 (ClogP, ACDlogP, HBA, MW) from future analyses. The log *D* descriptors with the lowest correlations and VIP values ($ACDlogD_{7.4}$ and experimental log $D_{7.4}$) were also omitted from future analyses.

Several combinations of the remaining variables were analyzed. The best models were obtained by combining any of the remaining lipophilicity descriptors ($ACDlogD_{6.5}$, $ACDlogD_{6.0}$, $ACDlogD_{5.5}$) with HBD and/or PSA. The number of components in these models was one, and the Q^2 and R^2 values of the models were between 0.68 and 0.76. The equations and the Q^2 and R^2 values of the models combining $ACDlogD_{6.0}$ with PSA and/or HBD are given in Table 4. The log K_a values predicted with model 1a are plotted against the experimental log K_a values in Figure 4.

All the above analyses were carried out using 22 of the 23 drugs in data set 1. Acetylsalisylic acid was excluded from the analyses as it was found that the large K_a value determined for it did not correlate with its physicochemical parameters (Tables 1 and 2): The inclusion of this drug would have lowered the Q^2 and R^2 values of the PLS models 1a, 2a, and 3a by about 0.06 units. The lack of correlation might be explained by the po plasma time−concentration data used in determining the K_a value. The oral absorption from a soluble acetylsalisylic acid formulation was reported to be slower in another investigation[62] than in the investigation used in the present study (t_{max} = 20 min vs t_{max} = 10 min).

The developed PLS models were further validated by dividing the drugs in data set 1 into a test set and a training set. Eight of the 22 compounds were selected for the training set (Figure 1). The training set compounds were then used to develop PLS models that combine $ACDlogD_{6.0}$ with HBD and/or PSA. The remaining 14 test set compounds were used to validate the developed PLS models (models 1b, 2b, and 3b). The results of these PLS analyses are given in Table 4.

Correlating ACDlogD Values with Experimental log *D* Values. Since the computationally predicted values of log *D* are sometimes inaccurate, we decided to compare the ACDlogD values of the compounds used in our analyses to their experimental log *D* values. Because experimental log *D* values at pH 5.5, 6.0, or 6.5 were found only for a few compounds, the available log $D_{7.4}$ parameter was used in the analysis. An extensive literature search yielded experimental log $D_{7.4}$ values for 22 of the 23 compounds in data set 1 and for 85 of the 170 compounds in data set 2. The correlation between the experimental and computational log $D_{7.4}$ values of the drugs in data set 1 was found to be excellent (R^2 = 0.96, RMSE = 0.31, range of the experimental values = −1.9−4.2). The correlation between the experimental and computational log *D* values of the drugs in data set 2 was also very good (R^2 = 0.86, RMSE = 0.59, range of the experimental values = −1.9−4.8).

Correlation between Predicted log K_a and Experimental FA. The PLS models 1a, 2a, and 3a were further tested by using them to predict the log K_a values of 169 of the 170 drugs in data set 2. Digoxin was left out of the analyses because in the work of Zhao and co-workers[5] the PSA value was considered to be unreliable by the authors. For five of the poorly absorbed drugs (FA under 0.05), it was not possible to calculate a log *D* value with ACD/logD. For these drugs, the log *P* value calculated with ACD/logP was used.

When the predicted log K_a values of the 169 drugs were plotted against experimental FA values, it could be seen that the log K_a values followed fairly nicely the sigmoidal curve modeling an ideal relationship between log K_a and FA over the entire range of values. The curve modeling the ideal relationship was calculated with the CAT model equation (eq 4). The log

Table 4. Equations and Statistics of Derived PLS Models

model	equation	Q^2	R^2	RMSE[a]	RMSEP[a]
1a	$\log K_a = 0.623 + 0.154 \log D_{6.0} - 0.007(\text{PSA})$	0.75	0.76	0.25	
1b		0.82	0.84	0.26	0.29
2a	$\log K_a = 0.424 + 0.143 \log D_{6.0} - 0.129(\text{HBD})$	0.74	0.75	0.26	
2b		0.75	0.80	0.29	0.29
3a	$\log K_a = 0.636 + 0.098 \log D_{6.0} - 0.004(\text{PSA}) - 0.088(\text{HBD})$	0.69	0.71	0.28	
3b		0.80	0.87	0.26	0.36

[a] RMSE = root-mean-squared error for the training set; RMSEP = root-mean-squared error for the test set.

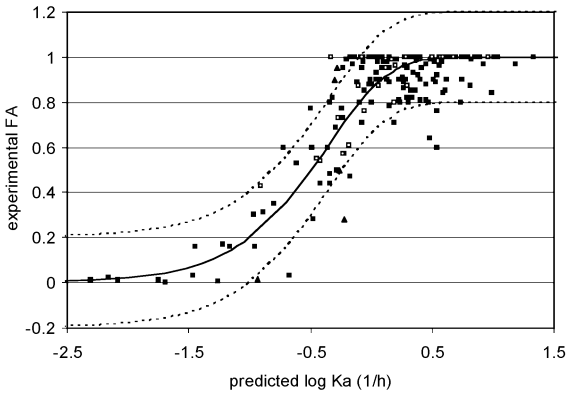

Figure 5. Correlation between predicted log K_a values and experimental FA values. The log K_a values of 169 of the 170 compounds in data set 2 were predicted using model 1a. Digoxin was left out of the analyses because in the work of Zhao and co-workers[5] the PSA value was considered to be unreliable by the authors. Compounds depicted with open symbols belong to data set 1. The deviating log K_a values of the five compounds depicted with triangles could be explained by errors in the computational ACDlogD values. The dashed lines show ±20% deviation from the ideal FA.

K_a values predicted with model 1a are plotted against the experimental FA values in Figure 5. The dashed lines show ±20% deviation from the ideal FA.

Discussion

This is the first study that predicts oral absorption on the basis of human absorption rate constants derived using a deconvolution approach. Models for predicting passive intestinal absorption kinetics were derived by correlating the K_a values of a set of 22 structurally diverse drugs with computational molecular descriptors. Multivariate PLS analysis showed that the most important parameters describing log K_a were PSA, HBD, and the lipophilicity descriptors ACDlog$D_{6.5}$, ACDlog$D_{6.0}$, and ACDlog$D_{5.5}$. Combining PSA and/or HBD with any of the log D descriptors resulted in statistically similar models with Q^2 and R^2 values ranging from 0.68 to 0.76.

Linear correlations between log K_a and the molecular descriptors also showed that the log D descriptors, HBD, and PSA are important parameters in explaining log K_a (Table 3). Of the log D descriptors, the highest correlation was found with ACDlog$D_{6.0}$ ($Q^2 = 0.54$, $R^2 = 0.61$) and the lowest correlations were found with ACDlog$D_{7.4}$ and experimental log $D_{7.4}$ ($Q^2 = 0.35$, $R^2 = 0.49$ and $Q^2 = 0.34$, $R^2 = 0.48$). This finding might reflect the fact that the pH in the intestine is nearer to 6 than 7.4. No correlation was found between log K_a and MW, which is generally considered an important predictor of absorption. The lack of correlation might be due to the narrow molecular weight range (144−384) of the molecules investigated. Most of the conventional drugs lie in this weight range, however.

In an earlier study, the human jejunal P_{eff} values of a set of 13 passively absorbed compounds were correlated with a number of physicochemical descriptors[9] using multivariate data analysis. The analysis, although performed using a limited number of compounds, yielded three models with good statistics. Of the three models, the one combining computational PSA and HBD with experimental log $D_{5.5}$ was the best predictor of P_{eff}. Thus, the same combination of descriptors is a good predictor of both P_{eff} and K_a. In a later study, Winiwarter and co-workers[10] used different hydrogen-bonding descriptors in an attempt to improve the models developed earlier. However, as they themselves stated, the developed models were not better than the models previously reported.

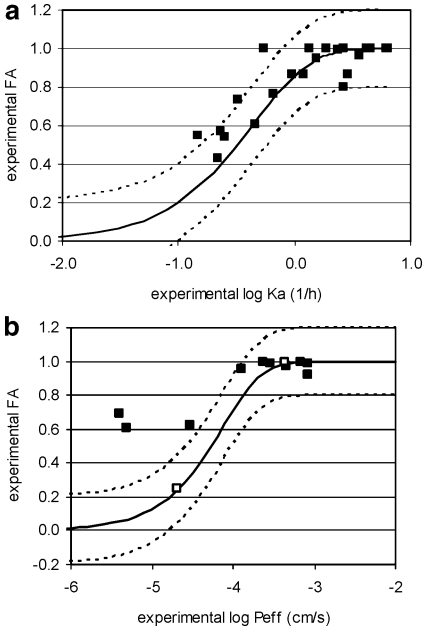

Figure 6. (a) Experimental log K_a values plotted against experimental FA values. The log K_a values of the 23 compounds in data set 1 follow fairly nicely the sigmoidal curve modeling an ideal relationship between log K_a and FA. (b) Experimental log P_{eff} values plotted against experimental FA values. The experimental log P_{eff} values of the 13 compounds in the data set of Winiwarter and co-workers[9] do not follow the sigmoidal curve modeling the ideal relationship between log P_{eff} and FA. The compounds in the data set of Winiwarter and co-workers[9] with possible dissolution rate-limited absorption are depicted with open squares. The original CAT model equation was used to model the ideal relationship between log P_{eff} and FA, and eq 4 was used to model the ideal relationship between log K_a and FA. The dashed lines show ±20% deviation from the ideal FA.

The studies of Winiwarter and co-workers[9,10] demonstrate that the method of determining human jejunal P_{eff},[63] although too complicated for routine assessment of a compound's intestinal absorption kinetics, provides information that can be used in the search for the molecular descriptors determining human intestinal absorption kinetics. However, there are some problems in the use of P_{eff}: there is a considerable error associated with the P_{eff} value measurements,[3] P_{eff} has been determined only for a limited number of compounds, and P_{eff} values[9] do not correlate very well with FA (Figure 6). In light of this, it could be argued that the study of the relationships between absorption kinetics and molecular descriptors should rely on K_a values that correlate well with FA (Figure 6). The finding that K_a correlates better than P_{eff} with FA indicates the ability of K_a to describe the overall absorption kinetics better than P_{eff} that is related to the absorption restricted to a 10-cm segment of the jejunum.

It should be taken into consideration that, in the data set of Winiwarter and co-workers,[9] dissolution, not permeability, may limit the *in vivo* absorption of some of the compounds. However, according to the work of Zhao and co-workers,[5] the absorption of all of the compounds except enalaprilat is limited by permeability and not dissolution. The *in vivo* absorption of carbamazepine, which does not belong to the data set of Zhao and co-workers,[5] is probably limited by dissolution. Experimental error in the FA values obtained from the literature may also contribute to the poor correlation between P_{eff} and FA; however, any possible error is not likely to affect the correlation significantly. The FA values were taken from the work of Zhao et al.[6] for all the compounds except carbamazepine, which does not belong to their data set. The FA value of carbamazemine was taken from the work of Zhu and co-workers.[14]

The PLS models developed in this work were further tested by using them to predict the log K_a values of a set of 169 drugs. The predicted log K_a values were then plotted against the experimental FA values of the 169 drugs (Figure 5). A good correlation between the predicted K_a values and experimental FA values was found over the entire range of values. The correlation might have been even better if the actively transported compounds had been removed from the data set.

Although our analysis showed that the predicted ACDlog$D_{7.4}$ values of the compounds used to evaluate our models correlated well with experimental log $D_{7.4}$ values, the poor correlation of some of the predicted K_a values with FA (Figure 5) could be explained by errors in ACDlogD values; it was found that the three compounds with the largest differences between the ACD/Labs and experimental log $D_{7.4}$ values were compounds whose predicted K_a values did not follow the sigmoidal curve modeling the ideal relationship between log K_a and FA. These compounds and their predicted and experimental log $D_{7.4}$ values were as follows: (1) amiloride, 0.94 and −0.86; (2) timolol, −1.4 and 0.03; (3) terazosine, −1.01 and 1.14. Furthermore, the unexpectedly high predicted K_a values of netivudine and oubain might be due to errors in their computational ACDlogP values which were significantly higher than their computational ClogP values (netivudine, 0.2 and −2.03; oubain, −1.64 and −4.58). Experimental log D values were not available for these compounds.

It is noteworthy that the average error in the prediction of log D with ACD/Labs is likely to be higher for newly synthesized compounds with structures that differ from the compounds used in our analyses. This results partly from the established or commercial drugs being included in the training set of the ACD/Labs software. It would naturally be better to use an experimentally determined log D value in predicting the K_a value of a compound that has poorly characterized substituents. Experimental determination of log D can, however, be performed on selected compounds later in the drug discovery process. The excellent correlation between the experimental log $D_{7.4}$ and ACDlog$D_{7.4}$ values of the compounds used to build the models ($R^2 = 0.96$, RMSE = 0.31) indicates that our models are based on log D values that are close to experimental values.

It should also be noted that although the models predicted log K_a values that correlated well with experimental FA values for even the poorly absorbed compounds that did not fit into the elliptic 95% tolerance volume of the score plot (Figure 1), they are not applicable for predicting the K_a values of peptides, polysaccharides, or other compounds that do not fit into the defined property space.

Easy computational prediction of the K_a value of a drug is a valuable addition to the tools used by pharmaceutical industry to facilitate the process of selection of new drug candidates. Compared with predicted FA, predicted K_a is more informative in the drug discovery process because the rate of absorption among completely absorbed drugs can vary. In this work, the K_a values of the drugs with FA values of 1 varied over an order of magnitude (0.15−6.4 h^{-1}, Table 2). K_a is also useful in the early design of release profiles of drug formulations. Unlike FA values, K_a values can be easily combined with absorption models such as the CAT model.[60] Together with a systemic pharmacokinetic model, the CAT model could be used to predict the plasma concentration−time profile of a drug. This naturally would require also the prediction of the systemic clearance of the drug, which is not yet possible. Thus, the prediction of K_a is the first step toward the aim to predict the plasma concentration−time profile of a drug.

Conclusions

It was found that the log K_a values of a set of 22 structurally diverse drugs, derived from human plasma time−concentration profiles with a deconvolution approach, followed nicely the ideal sigmoidal relationship prevailing between a parameter describing the kinetics of oral absorption and FA. When multivariate PLS analysis was applied to establish the relationships between the log K_a values of the 22 drugs and simple computed molecular descriptors, three models with good statistics and predictivity were derived. The results showed that, by using a combination of two or three (ACDlog$D_{6.0}$ combined with PSA and/or HBD) simple, rapidly computed molecular descriptors, it is possible to predict passive intestinal absorption kinetics in humans. The present method, which enables easy computational prediction of passive absorption, is a promising addition to the tools used by the pharmaceutical industry to facilitate the process of discovery and development of drugs.

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Supporting Information Available: Table of molecular descriptors and FA values for the compounds in data set 2. This material is available free of charge via the Internet at: http://pubs.acs.org.

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