Polar Molecular Surface Properties Predict the Intestinal Absorption of Drugs in Humans

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Purpose. A theoretical method has been devised for prediction of drug absorption after oral administration to humans.

Methods. Twenty structurally diverse model drugs, ranging from 0.3 to 100% absorbed, were investigated. The compounds also displayed diversity in physicochemical properties such as lipophilicity, hydrogen bonding potential and molecular size. The dynamic molecular surface properties of the compounds were calculated, taking into account their three-dimensional shape and flexibility.

Results. An excellent sigmoidal relationship was established between the absorbed fraction after oral administration to humans (FA) and the dynamic polar molecular surface area (PSA_d) ($r^2 = 0.94$). The relationship was stronger than those obtained for more established predictors of drug absorption. Drugs that are completely absorbed (FA > 90%) had a $PSA_d \leq 60$ Å^2 while drugs that are < 10% absorbed had a $PSA_d \geq 140$ Å^2.

Conclusions. The results indicate that PSA_d can be used to differentiate poorly absorbed drugs at an early stage of the drug discovery process.

KEY WORDS: polar molecular surface area; hydrogen bonding potential; lipophilicity; drug absorption; intestinal drug transport; membrane permeability.

INTRODUCTION

The search for new pharmacologically active compounds in drug discovery programmes often neglects biopharmaceutical properties such as drug absorption. As a result, poor biopharmaceutical characteristics constitute a major reason for the low success rate for drug candidates in clinical development (1). Since the cost of drug development is many times larger than the cost of drug discovery, predictive methodologies aiding in the selection of orally bioavailable drug candidates are of profound significance.

The vast majority of well absorbed drugs are transported passively across the (lipophilic) cell membranes. Therefore, physicochemical descriptors of drug molecules that are believed to influence transcellular transport are routinely used in attempts to predict drug absorption. However, single physicochemical descriptors such as partition coefficients are not reliably predictive of drug absorption, as the correlations often break down when structural diversity is introduced (2,3).

Recently, we developed a theoretical method, based on the determination of dynamic surface properties of drug molecules (4). Dynamic molecular surface properties not only take into consideration the three-dimensional shape of the molecule, but also allow for their conformational flexibility. In our earlier study of a homologous series of drug molecules, excellent correlations between PSA_d and passive drug transport *in vitro* were established ($r^2 = 0.99$). This correlation was stronger than that between calculated lipophilicity and permeability ($r^2 = 0.80$) (4).

In this study, the relationship between the absorption of 20 structurally diverse model drugs in humans after oral administration and PSA_d was investigated. The results were compared with those from two theoretical models commonly used to predict drug absorption: the calculation of partition coefficients and of molecular hydrogen bonding capacity.

METHODS

Selection of Model Drugs

The model drugs (Table I) were chosen to cover a wide range of absorption after oral administration (FA = 0.3 – 100%) as well as a wide range of physicochemical properties such as lipophilicity, charge, and number of hydrogen bonds. The distribution of the physicochemical properties was comparable to that of registered drugs intended for oral administration (5). Stringent inclusion criteria were used in the selection of the model drugs. These included: i) the availability of reliable data on the absorbed fraction in humans, and ii) clear indications that the drugs were predominantly absorbed by a passive process. In addition, complicating factors such as low solubility and presystemic metabolism either were negligible or had already been accounted for in the determination of the absorbed drug fraction.

Molecular Surface Area Calculations

The three-dimensional structures of the drugs were determined by automated conformational analysis (MM2) using the BatchMin program included in the MacroModel v5.0 package (6). A 1,000 to 25,000 step Monte Carlo search was performed on each compound. Since the MM2 force field does not contain appropriate parameters for the drug phenazone, we used the Amber force field for calculations of this compound. The energy minimisations were performed in vacuum, with all compounds in their un-ionised state. The conformational properties of the six β-adrenoreceptor antagonists were taken from our previous study (4).

A computer program was constructed to calculate the surface area of each conformer of the compounds. This program calculates the free surface area of each atom as well as the molecular volume. The free surface areas, bounded by arcs of overlapping atoms, were determined analytically using the Gauss-Bonnet theorem (7). The molecular volume was determined numerically. Atomic van der Waals radii were used in the calculations (8). The polar surface area (PSA) is defined as the area occupied by nitrogen and oxygen atoms, and hydrogen atoms attached to these heteroatoms.

The PSA_d of each compound was calculated as a statistical average in which the surface area of each low energy conformation is weighted by its probability of existence (4). The dynamic

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Table 1. Summary of Absorption and Structural Properties of the Investigated Drugs[a]

Substance	FA[b] (%) mean		s.d.	PSA_d^c (Å²)	Ht[c]	Ha[c]	Hd[c]	CLogP[c]	Charge	SA_d^c (Å²)	Mw	V_d^c (Å³)
Metoprolol	102	±	5	53.1	9	7	2	1.20	+	395	267	364
Nordiazepam	99	±	19	45.1	5	4	1	3.06	0	287	271	279
Diazepam	97		[d]	33.0	4	4	0	3.08	0	310	285	301
Oxprenolol	97	±	13	46.8	9	7	2	1.69	+	373	265	355
Phenazone	97	±	7	27.1	4	4	0	0.41	0	252	188	233
Oxazepam	97	±	11	66.9	8	6	2	3.29	0	294	287	283
Alprenolol	96		[d]	37.1	7	5	2	2.65	+	366	249	343
Practolol	95	±	3	73.4	11	8	3	0.76	+	372	266	343
Pindolol	92	±	11	56.5	9	6	3	1.67	+	341	248	317
Ciprofloxacin	69	±	7	78.7	11	9	2	1.56	+−	372	331	365
Metolazone	64	±	23	94.5	12	9	3	1.92	0	379	366	377
Tranexamic acid	55	±	2	69.2	8	5	3	−1.84	+−	225	157	205
Atenolol	54	±	17	90.9	12	8	4	−0.11	+	371	266	343
Sulpiride	36	±	20	100.2	12	10	2	1.11	+	400	341	393
Mannitol	26		(1–89)	116.6	18	12	6	−4.67	0	216	182	197
Foscarnet	17	±	4	115.3	13	10	3	−1.78	--(−)	130	126	102
Sulfasalazine	12[e]	±	5[e]	141.9	17	14	3	3.83	−	418	398	409
Olsalazine	2.3	±	0.8	141.0	18	14	4	4.50	--	319	302	299
Lactulose	0.6	±	0.3	177.2	30	22	8	−5.69	0	357	342	347
Raffinose	0.3		(0.1–0.9)	242.1	43	32	11	−8.09	0	488	504	507

[a] The oral drug absorption in humans (FA), dynamic polar surface area (PSA_d), maximum number of hydrogen bonds (Ht), number of hydrogen bond acceptors (Ha), number of hydrogen bond donors (Hd), calculated lipophilicity (CLogP), charge at pH 7.4, dynamic total surface area (SA_d), molecular weight (Mw) and dynamic volume (V_d) are shown.
[b] The values represent the percentage of each drug absorbed after oral administration to humans (16). Values are the mean ± standard deviation (s.d.) where available and median (range) for mannitol and raffinose.
[c] PSA_d, Ht, Ha, Hd, CLogP, SA_d and V_d were calculated as described in the Methods section.
[d] Not reported.
[e] Personal communication, Märta Ryde, Pharmacia & Upjohn, Uppsala, Sweden.

total surface area (SA_d) and the dynamic volume (V_d) were defined and determined similarly.

Maximum Number of Hydrogen Bonds

The maximum number of hydrogen bonds (Ht) was calculated as the sum of hydrogen bond donors (Hd) and acceptors (Ha) (9).

Calculated Log P

Theoretical estimates of the octanol/water partition coefficients (CLogP) were determined using CLOGP v4.42 (Daylight C.I.S., Inc. Irvine, CA) for all compounds but foscarnet, since the appropriate fragments for this drug were missing. For foscarnet, log P was calculated using ProLogP v4.2 (CompuDrug NA, Inc. Rochester, NY). The predictive power of the two methods is equal (5,10).

Statistical Analysis

The sigmoidal equation: $FA = 100/(1 + (x/x_{50})^{\gamma})$ was fitted to the data, where x is a structural property in Table I, the dynamic polar fraction of the total surface area ($\%PSA_d$) or the non-polar surface area ($NPSA_d$). x_{50} is the value of x when the FA is predicted to be 50% and γ is a slope factor. The equation was fitted to the data minimising the unweighted sum of squared residuals. The root mean square error (RMSE), i.e. the standard error of regression, and the coefficient of determination (r^2) were used to measure the fit of the equation.

RESULTS AND DISCUSSION

In this paper, a new theoretical method is validated for the prediction of passive drug absorption in humans. A strong correlation was obtained between the absorbed fraction after oral administration and the dynamic polar surface area for a set of structurally diverse model drugs. These results indicate that PSA_d can be used to identify drugs which may be poorly absorbed at an early stage of the drug discovery process. The method should also be applicable in the prediction of passive drug transport across other epithelial barriers, such as the blood-brain barrier.

A strong sigmoidal relationship was observed between PSA_d and FA (RMSE = 9.2%, $r^2 = 0.94$; Fig. 1). The sigmoidal relationship indicates that drugs with a $PSA_d < 63$ Å² will be completely absorbed (FA > 90%) while drugs with a $PSA_d > 139$ Å² will be <10% absorbed. A weaker sigmoidal relationship was obtained when $\%PSA_d$ was correlated with FA (RMSE = 12.7%, $r^2 = 0.89$). No correlation was observed between FA and $NPSA_d$. Sigmoidal relationships were also observed between FA and the hydrogen bond descriptors Ht and Ha (RMSE = 13.9%, $r^2 = 0.87$ and RMSE = 14.1%, $r^2 = 0.87$, respectively) (Fig. 2). Hd displayed a weaker relationship with FA (RMSE = 24.4%, $r^2 = 0.60$). The relationship between the absorbed fraction and PSA_d was much stronger than that observed between FA and CLogP (Fig. 3). For instance, a sigmoidal equation poorly described the data points in Fig. 3 (RMSE = 31.6%, $r^2 = 0.34$).

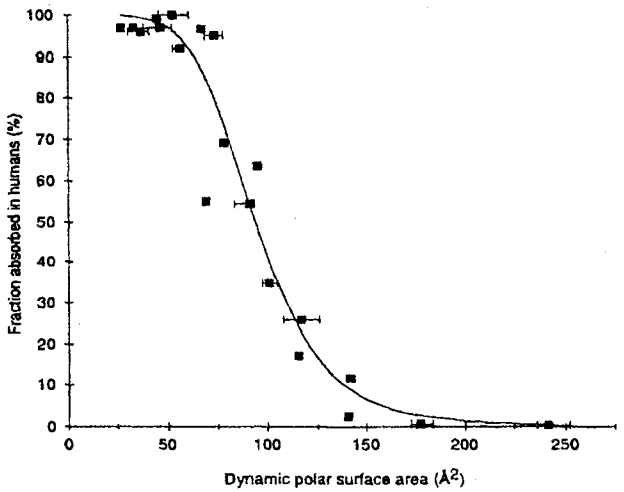

Fig. 1. Sigmoidal relationship between PSA_d of the 20 structurally diverse model drugs and absorption in humans after oral administration. PSA_d is presented as the dynamic mean value and the range of all low energy conformations.

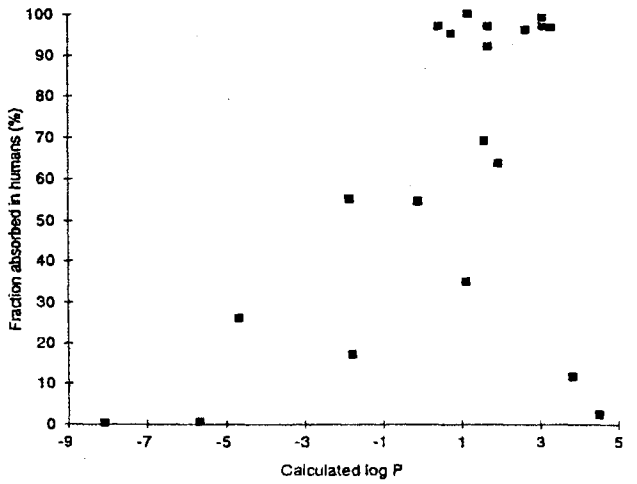

Fig. 3. Relationship between calculated octanol/water partition coefficients (CLogP) and absorption in humans after oral administration for the 20 model drugs.

To investigate which physicochemical parameters that are described by PSA_d a correlation matrix was established of all structural parameters in Table 1. Strong correlations with PSA_d were only observed with Ht, Ha and Hd, respectively (r^2 = 0.92, 0.92 and 0.81). This is in agreement with previous studies, where strong correlations were established between polar surface area and Ha and Hd, respectively (11). One limitation of PSA_d, Ht, Ha, and Hd, is that no consideration has been made of differences in the strengths of the hydrogen bonds (13). In addition, parameters such as molecular charge and size might be expected to influence absorption. In this study, molecules of different sizes and with both positive and negative charges were investigated. Despite this, a strong relationship between FA and PSA_d was observed.

From these results, it may be assumed that the simple descriptors Ht or Ha may substitute for PSA_d as predictors of drug absorption. However, intramolecular hydrogen bond formation, which can dramatically change the absorption properties of a drug molecule (12), is not accounted for in the calculations. This problem will be more pronounced for more structurally flexible molecules, such as those often generated in combinatorial chemistry programmes (5). In contrast, intramolecular hydrogen bonding is accounted for when using PSA. The weakness of Ht and Ha as predictors is also clear from a closer examination of the steep parts of the curves in Fig. 2. Failure to account for the formation of two or three intramolecular hydrogen bonds in a drug with an intermediate FA may result in erroneous conclusions being drawn from the sigmoidal relationship regarding FA. In addition, the scatter observed in the intermediate range further supports the conclusion that Ht and Ha are less reliable for prediction of drug absorption than PSA_d.

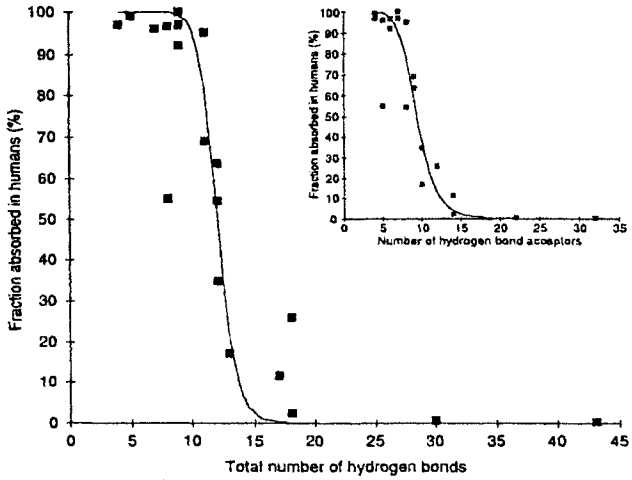

Fig. 2. Sigmoidal relationship between Ht of the 20 model drugs and absorption in humans after oral administration. The insert shows the corresponding relationship between Ha and FA.

During the course of this work, two other theoretical methods for the prediction of passive drug permeability have been presented (11, 14). In these studies, the flexibility of the molecules was not accounted for. Thus, the "chameleonic" behaviour of flexible molecules (15) was not considered. Since calculated descriptors can vary considerably between conformations this can result in less reliable predictions. This is in contrast to the approach in the present study, where the dynamic properties were calculated from all low energy conformations. Thus, we conclude that our method also compares favourably with more recently developed theoretical methods for prediction of drug permeability.

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