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TOWARD A QUANTITATIVE APPROACH FOR THE PREDICTION OF THE FRACTION OF DOSE ABSORBED USING THE ABSORPTION POTENTIAL CONCEPT

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ABSTRACT

An equation based on the absorption potential concept was developed. This enabled us to establish an approach for the quantitative prediction of the fraction of dose absorbed. Classification of drugs into three broad categories, according to their absorption potential values in relation to the fraction of dose absorbed, was attempted. The new approach was tested using literature data with very good results.

KEY WORDS Absorption potential Fraction absorbed Quantitative prediction Bioavailability

In the early stages of drug development, it is important to have defined the limit of absorbability of the drug, i.e. the extent of its absorption. Several *in vitro* biopharmaceutical studies[1] have been proposed for the estimation of the extent of absorption. Each of these studies is concerned with only one of:

1. the physicochemical factors, e.g. solubility, dissolution rate, ionization, etc.;
2. the physiological variables, e.g. membrane permeability of drug, pH, etc. which contribute to the availability characteristics.

Therefore, *in vitro* biopharmaceutical studies are designed to define, individually, all the independent processes or factors influencing absorption. Hence, the predicting ability of these procedures is limited since a great number of diverse factors are interposed between administration of the drug and its appearance in the body.

The inability of the existing methods to predict the fraction of dose absorbed (F_{abs}) prompted Dressman *et al.*[1] to develop the absorption potential (AP) concept. This is the only approach for the estimation of F_{abs} which takes into account many variables, namely, the 1-octanol-water partition coefficient of

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drug (P), the intrinsic solubility of drug (aqueous solubility of the non-ionized species at 37°) (S_o), the dose administered (X_o), the fraction of the non-ionized form of drug at pH 6·5 (F_{non}), and the volume of the lumenal contents (V_L). According to the authors the fraction of dose absorbed F_{abs} is a function of the above parameters. Relying on the fact that the absorption of drugs for the majority of cases follows the principles of pH-partition hypothesis, Dressman *et al.*[1] defined the absorption potential* AP by equation (1):

$$\mathrm{AP} = P.\ F_{non.}\ \frac{S_o.V_L}{X_o} \tag{1}$$

and showed that AP can be used for predicting F_{abs}. Indeed, the authors found strong correlation between the values of the dimensionless parameters AP and F_{abs} for seven drug examples considered.

Although the correlation of AP with F_{abs} is of great value, an explicit relationship between the two parameters is lacking. The purpose of the present paper is to reveal more features of the relation between AP and F_{abs}. An explicit relationship is derived and its utility in considering bioavailability problems is discussed in the light of the principles and constraints postulated by Dressman *et al.*[1]

Applying identical syllogisms to those used for the conceptual development of AP, one would argue that each chemical compound can be also characterized by its non-absorption potential (NAP) value. This parameter should be considered as an indicator of the inability of drug to be absorbed. In an analogous manner to that used to define AP, the non-absorption potential can be defined by equation (2):

$$NAP = \frac{1}{P} \cdot (1-F_{non}) \cdot \frac{X_o}{S_o.V_L} \tag{2}$$

The definition is based on the fact that the dimensionless parameters AP and NAP should be inversely related to the parameters P, X_o, S_o, and V_L. Obviously, the NAP is considered proportional to the ionized fraction of drug, $(1-F_{non})$ in the GI fluids. Needless to say, the NAP is not related to the non-absorbed portion of drug due to lumenal degradation and first-pass metabolism.

The discussion so far has been restricted to the biopharmaceutical viewpoints. Nevertheless, the variable of interest F_{abs} has been expressed[2,3] in terms of pharmacokinetic parameters by equation (3):

$$F_{abs} = \frac{k_a}{k_a + k_n} \tag{3}$$

*The logarithmic function for AP is not used in this paper.

where k_a, the absorption rate constant, and k_n, a composite first-order rate constant referring to processes leading to non-absorption. The rate constant k_n has been used previously to express kinetically either all paths leading to non-absorption[2] or the first-pass metabolism phenomenon.[3] For our purposes, however, k_n in equation (3) refers to the limited ability of drug to be absorbed because of its physicochemical properties such as hydrophilicity and ionization which impose a localization of drug on hydrophilic regions. Moreover, dose/solubility limitations and the associated dissolution rate constant may also be factors which limit absorption. The kinetics of these non-absorption phenomena are probably best described by first-order kinetics. Dose-dependent kinetics should be ruled out if one considers the conventional doses used in practice and in particular the amount of non-absorbed portion of drug. Hence, a generalized first-order rate constant, k_n, was introduced to describe kinetically the competing process of non-absorption. Apparently when such phenomena are not encountered, in other words when k_n=0, equation (3) implies that the drug is absorbed completely, i.e. F_{abs}=1. Again, the meaning of k_n in the present paper has nothing to do with lumenal degradation and first-pass metabolism.

It is now reasonable to argue that the kinetic parameters k_a and k_n are related proportionally to the AP and NAP, respectively:

$$k_a = \lambda\ (\mathrm{AP}) \tag{4}$$

$$k_n = \mu\ (\mathrm{NAP}) \tag{5}$$

where λ and μ are proportionality coefficients with dimensions identical to those assigned to k_a and k_n, i.e. $(\mathrm{time})^{-1}$ and their magnitudes are associated with the relationship of the variables of equations (4) and (5) in the specific physical system of the GI tract of humans.

Therefore, equation (3) can be written

$$F_{abs} = \frac{\lambda\ (AP)}{\lambda\ (AP) + \mu\ (NAP)} \tag{6}$$

From equation (1) and (2) it can be obtained

$$NAP = \frac{F_{non}\ (1-F_{non})}{(AP)} \tag{7}$$

Substituting equation (7) in equation (6) gives after re-arrangement

$$F_{abs} = \frac{\lambda\ (AP)^2}{\lambda\ (AP)^2 + \mu\ F_{non}\ (1-F_{non})} \tag{8}$$

which can be written more conveniently as

$$F_{abs} = \frac{(AP)^2}{(AP)^2 + (\mu/\lambda)\, F_{non}\,(1-F_{non})} \tag{9}$$

In the simplest case $\mu=\lambda$ and therefore equation (9) can be written as

$$F_{abs} \square \frac{(AP)^2}{(AP)^2 + F_{non}\,(1-F_{non})} \tag{10}$$

Equation (10) reveals that F_{abs} asymptotically approaches one (complete absorption) as AP increases. Also, the relative importance of AP and F_{non} $(1-F_{non})$ in determining the fraction of dose absorbed can be revealed by inspecting equation (10).

In fact, for relatively high values of AP ($AP \geq 0{\cdot}5$) drugs can be classified in two broad categories shown in Table 1. This distinction was made assuming that the maximum value of $F_{non}\,(1-F_{non})$ is 0·25 (50 per cent ionization). Nevertheless, when $AP < 0{\cdot}5$ the parameters AP and F_{non} $(1-F_{non})$ have comparable magnitudes, and therefore the individual contribution of each parameter to the F_{abs} value cannot be clearly distinguished. In addition, since the variable AP includes the factor F_{non}, the consideration of the effect of these two factors on the F_{abs} is not simple. Under these circumstances ($AP < 0{\cdot}5$), the F_{abs} is dependent upon both factors, i.e. AP and F_{non} $(1-F_{non})$ as quoted in Table 1. More specifically, equation (10) may be written in the form:

$$F_{abs} = \frac{(P.S_o.V_L/X_o)^2\, F_{non}}{[\,(P.S_o.V_L/X_o)^2 - 1\,]\, F_{non} + 1} \tag{11}$$

which shows that the higher the values of $P.S_o.V_L/X_o$ and F_{non} the higher the absorption of drug. This is compatible with the pH-partition hypothesis as well as the absorption potential concept.

Each one of the three categories of drugs classified in Table 1, shows a different degree of sensitivity for the fraction of dose absorbed against ionization changes in the GI tract which affect F_{non}. According to this classification, the more lipophilic group ($AP>5$) is expected to be absorbed completely regardless of the degree of ionization of the drug. An identical observation for drugs with $AP>10$ has been also explicitly pointed out by Dressman *et al.*[1] It is interesting to note, however, the theoretically anticipated behaviour of drugs belonging to the more hydrophilic group ($AP<0{\cdot}5$). Although the theoretical prediction allows for $0<F_{abs}<1$ (Table 1) it is most unlikely that a hydrophilic drug ($AP<0{\cdot}5$) would possess sufficiently high values for both parameters $P.S_o.V_L/X_o$ and F_{non}. Therefore, the drugs in this category should exhibit poor absorption. In addition, the absorption of these drugs should be extremely prone

Table 1. Classification of drugs according to AP values in relation to the fraction absorbed as predicted from equation (10)

$AP<0{\cdot}5$	$0{\cdot}5\leq AP\leq 5$	$5<AP$
The fraction absorbed depends on two parameters, i.e. $P.S_o.V_L/X_o$ and F_{non}. According to equation (11) the higher the values of $P.S_o.V_L/X_o$ and F_{non} the better the absorption. Theoretically: $0<F_{abs}<1$	The fraction absorbed depends primarily on the AP and secondly on the ionization of drug. Theoretically: $0{\cdot}50\leq F_{abs}\leq 0{\cdot}99$	The fraction absorbed depends solely on the AP, and complete absorption is anticipated, $F_{abs}=1$
	Drug examples*	
Acyclovir (0·03) Chlorothiazide (0·13)	Griseofulvin (2·29) Captopril (4·57) Hydrochlorothiazide (5·00)†	Cimetidine (6·16) Phenytoin (10·00) Mefenamic acid (18·62) Prednisoline (79·43) Digoxin (1348·96)

*Classiciation of the drugs reported[1,5] according to their AP values quoted in parentheses.
†Note that hydrochlorothiazide is borderline with respect to the second and third categories.

to changes of F_{non} and therefore erratic absorption would also be expected. Drugs of this category and in particular those with pK_as 5–7, which is the typical pH range of the GI fluids at the absorption sites, should be dramatically affected even by slight changes in pH at the absorption sites. The influence of the virtual mucosal surface pH should be equally important.[4]

The drugs considered by Dressman *et al.*[1,5] were classified in Table 1 according to their AP values. Furthermore, the predicted values of F_{abs} have been calculated on the basis of equation (10) and the results are shown in Figure 1 along with the experimental data. As can be seen there is a very good prediction of F_{abs} for phenytoin, prednisolone, and digoxin classified in the lipophilic category of Table 1. The complete absorption anticipated for hydrochlorothiazide, griseofulvin, captopril, cimetidine, and mefenamic acid is not confirmed by the experimental data (Figure 1). The dramatic deviation of griseofulvin is certainly due to the low value of the solubility–dose term $S_o.V_L/X_o$, i.e. 0·015 which makes the dissolution rate, rate limiting overall. Finally, the predictive ability of equation (10) for the hydrophilic drugs acyclovir and chlorothiazide is poor as can be seen in Figure 1.

The above observations indicate that this approach for the estimation of F_{abs} is not adequately quantitatively predictive. This fact, in conjunction with the enormous range of AP values (0·03 – 1348·96, Table 1), which make qualitative

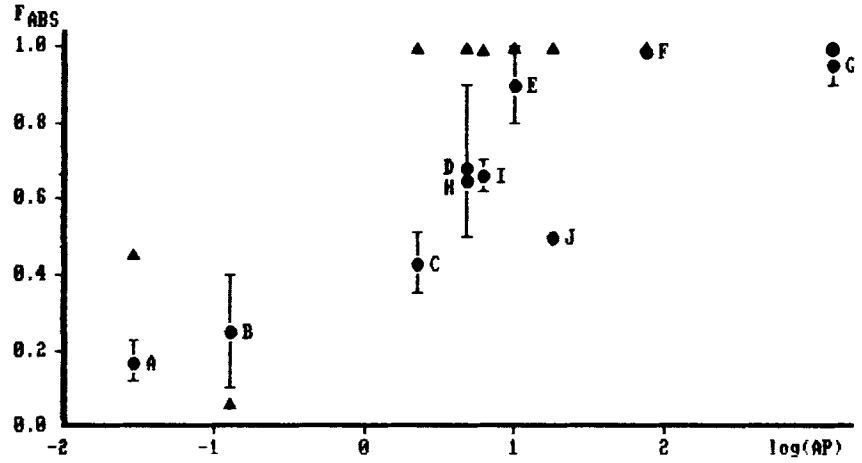

Figure 1. Plot of theoretical (Δ) and experimental (●) data[1,5] for the fraction absorbed (F_{abs}) versus log AP. To make the calculation possible the value of F_{non} for acyclovir, griseofulvin prednisolone, and digoxin was assigned to 0·999. Key: A acyclovir; B chlorothiazide solution; C microionized griseofulvin; D hydrochlorothiazide; E phenytoin; F prednisolone; G digoxin (Lanoxicaps); H captopril; I cimetidine; J mefenamic acid

correlations feasible but quantitative predictions inappropriate, prompted us to re-examine the relative quantitative contribution of the parameters P, F_{non}, and $S_o.V_L/X_o$ to the AP values used in the calculations for quantitative predictions.

The conceptual development of the absorption potential was based on the pH-partition hypothesis which is still the basic principle of drug absorption. Although the drug disposition in the GI tract is a dynamic situation, the simple model which considers absorption as a first order process is used routinely. In this model, the rate of absorption is controlled by the absorption rate constant, k_a, which is dependent upon the physicochemical properties of the absorbing species. In addition, the driving force of the passive absorption is the concentration gradient across the membrane which separates the GI lumen from the circulating blood. In most instances, the plasma concentration is much lower than the concentration in the GI tract due to the rapid removal of the absorbed drug by the circulating blood, making the rate of transport across the membrane proportional to the drug concentration C_g, in the intestinal lumen. In other words, the drugs are absorbed under sink conditions and the rate of absorption, dX/dt, is expressed by the equation:

$$\frac{dX}{dt} = k_a . C_g \tag{12}$$

Obviously, the parameters comprising the absorption potential are strongly related to the parameters k_a and C_g of equation (12). In reality, it is well known

that the parameter P is contained or subsumed in the constant k_a. Moreover, Martin[6] has analysed various absorption data from 193 compounds and showed that there is a linear relationship between $\log k_a$ and $\log P$ of the non-ionized form of the drug. It was found[6] and that this linearity levels off at a P value of approximately 100. Therefore, it is advisable to use a limiting value for the partition coefficient whenever quantitative predictions for very lipophilic drugs are attempted. Based on the data provided by Martin[6] (see Figure 1), a P value of 1000 should be considered as a reasonable maximum for the highly lipophilic compounds. Under these conditions the proportionality postulated between k_a and $(F_{non}.P)$ in equation (4) has a rational explanation and it is well documented.

The incorporation of the solubility-dose term, $S_o.V_L/X_o$, in the absorption potential is apparently linked to the driving force of the absorption process which is represented by the concentration term in the fundamental equation (12). Theoretically, it is a valid approximation to consider the absorption rate constant k_a which mirrors the rate of absorption, proportional to the term $S_o.V_L/X_o$ as has been done in equation (4). However, the doses used in practice did not always achieve saturation concentrations in the GI fluids.[7] Consequently, the use of the term $S_o.V_L/X_o$ in the calculations should only be applied whenever $S_o.V_L < X_o$; when this condition is met, the drug never reaches saturation concentration and the value of the term $S_o.V_L/X_o$ indicates the amount of drug which is actually dissolved. On the contrary, when $S_o.V_L > X_o$, the use of the term $S_o.V_L/X_o$ overestimates the contribution of the concentration factor in the final estimate of AP. For example, when S_o=1 mg ml^{-1} and X_o=25 mg then (SV_L/X_o)=10, although, the maximum concentration which can be achieved *in vivo* may be 0·1 mg ml^{-1} which is only 10 per cent of the solubility

Table 2. Absorption potential values

Drug	AP	
	Reported[1,5]	Calculated
Acyclovir	0·03	0·02*
Chlorothiazide	0·13	0·13
Griseofulvin	2·29	2·29
Captopril	4·57	0·003*
Hydrochlorothiazide	5·00	0·81*
Cimetidine	6·16	0·75*
Phenytoin	10·00	10·00
Mefenamic acid	18·62	0·08†
Prednisolone	79·43	25·97*
Digoxin	1348·96	55·94*

*The constraint for the term $S_o.V_L/X_o$ was taken into account.
†The constraint for the term P was taken into account. (The P value[5] for mefenamic acid is $2·3 \times 10^5$).

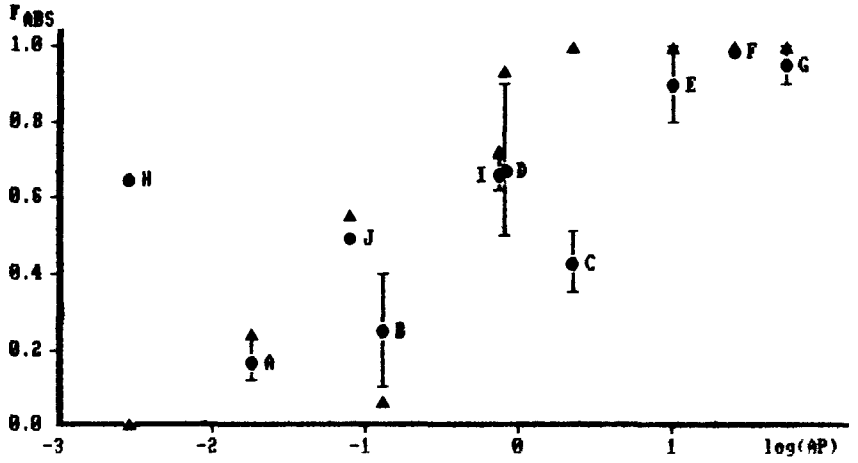

Figure 2. Plot of theoretical (Δ) and experimental (●) data for the fraction absorbed (F_{abs}) versus log AP. The calculation of AP was based on the values of parameters reported[1,5] taking into account the constraints for the terms P, and $S_o.V_L/X_o$. Key: the same as in Figure 1

imposed on the calculations. Hence, to avoid overestimations of AP, attributable to the solubility–dose term $S_o.V_L/X_o$, it is advisable to assign the value one to this term in cases where $S_o.V_L \geq X_o$. This agrees fairly well with the analysis of the dose dependency of absorption in relation to the solubility reported by Dressman *et al.*[7]

The AP values of the drugs considered were recalculated taking into account the constraints outlined above for the terms P and $S_o.V_L/X_o$ (Table 2). Using the recalculated AP values, captopril and mefenamic acid are now classified in the first category ($AP<0{\cdot}5$), while cimetidine is in the second category ($0{\cdot}5 \leq AP \leq 5$). The predicted F_{abs} values from equation (10) are plotted versus log AP in Figure 2. As can be seen, the predictive ability of equation (10) has been improved considerably for acyclovir, hydrochlorothiazide, cimetidine, and mefenamic acid. The drug which deviates remarkably from the asymptotic values is griseofulvin due to its dissolution rate limitation. It should be mentioned also that the great variability of the *in vivo* data for the poorly absorbed drug chlorothiazide (Figure 2) is in accordance with the theoretical considerations outlined above. The fraction of dose absorbed would be expected to be extremely susceptible to changes in F_{non}. This is verified theoretically by the fact that a perfect prediction for chlorothiazide absorption could be achieved by assuming a F_{non} value equal to 0·88. The corresponding pH at the absorption sites, calculated from the Henderson–Hasselbach equation is 5·8 which is close to the typical pH 6·5 assumed. Analogously, the appropriate pH for predicting the extent of absorption of another drug which deviates dramatically, captopril (Figure 2), is 4·0. Taking into account the extremely high solubility (170 mg ml^{-1}) of captopril[5] as well as its low pK_a value (3·7), it is plausible to conclude that

most of this drug is absorbed in the stomach. Generalizing the syllogisms, it can be concluded that the predictive ability of equation (10) for the hydrophilic category of drugs ($AP<0{\cdot}5$) is dramatically influenced by the pH value chosen as a 'typical pH' at the absorption sites. Bearing in mind the wide range of pHs encountered in the GI fluids, and the dynamic character of the absorption process, it is rather easy to conclude that the choice of the 'typical pH' is difficult but crucial for the theoretical estimation of F_{abs} of hydrophilic drugs. This is in absolute agreement with the relevant conclusions derived from the consideration of the two-tank perfect-mixing tank model.[7] According to the authors[7] ' ... day-to-day and patient-to-patient variation in intestinal pH profile can play a significant role in the determination of the extent of absorption for incompletely absorbed drugs. This explains in part the observation that drugs which are poorly absorbed often exhibit variable absorption'. For the purposes of the quantitative predictions of the present study, however, one should rely on the upper limits of the experimentally determined F_{abs} values since formulation factors which contribute toward lower absorption are not considered here. Thus, the upper limits of the variable absorption of acyclovir, hydrochlorothiazide, phenytoin, cimetidine, mefenamic acid, and digoxin have been predicted nicely by the approach developed here. That the actual absorption of chlorothiazide *in vivo* is greater than that expected on theoretical grounds (Figure 2), is probably attributable to our limited knowledge of the real F_{non} value predominating *in vivo*. This, in turn, arises from the uncertainty of the 'typical pH 6·5' at the absorption sites. Moreover, it is worthy of mention that a non-passive uptake mechanism for chlorothiazide has been suggested.[8] If this is a valid consideration then the higher absorption observed *in vivo* (Figure 2) could be attributed to the active mechanism. Undoubtedly, such a possibility can not be predicted or explained on the basis of the theory developed here.

For the sake of completion, some comments should be made on the actual value of the quotient μ/λ appearing in equation (9). Apparently, whatever the actual value of the dimensionless quotient μ/λ may be, the analysis presented in Table 1 is still valid. Depending on the real value of μ/λ, it will probably be necessary to adjust the absolute values of AP quoted in Table 1. However, the general conclusions derived will not change. A reliable estimation of μ/λ would be possible if more data were available. Using the upper limits of F_{abs} data reported[1,5] for all drugs except griseofulvin and captopril, and nonlinear fitting was attempted to evaluate μ/λ by monoparameterizing equation (9), i.e.

$$F_{abs} = \frac{R^2}{R^2 + (\mu/\lambda)} \tag{13}$$

where $R=AP[\,F_{non}(1-F_{non})\,]^{-1/2}$. Caution was exercised in using equation (13) by adjusting the value of F_{non} to 0·999 when the reported[1,5] value was equal to one. The calculated AP values quoted in Table 2 were utilized and the results of the

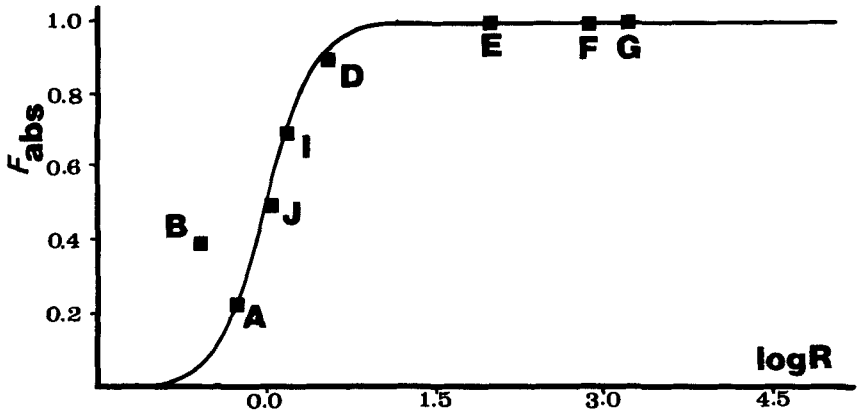

Figure 3. Theoretical curve fitted by a non-linear regression according to equation (13) to the upper limits of F_{abs} reported[1,5]. Key: the same as in Figure 1

curve fitting are shown in Figure 3. The estimated value for μ/λ was 1·05 which is almost identical to the value (one) postulated above. Even though the curve describes the data nicely, it is difficult to draw conclusions about the significance of the 1·05 value for μ/λ because it is based on only eight data points (drugs).

In conclusion, the development of an equation based on the absorption potential concept enables us to establish an approach for the quantitative prediction of the fraction absorbed, and gave an insight into the relevance and interrelationships of the variables AP, F_{abs}, and F_{non}. The classification of drugs into three broad categories, according to their AP values in relation to the fraction of dose absorbed, provides a new approach for considering bioavailability problems which do not arise from dissolution rate limitations. In view of the complexity of the *in vivo* system and the numerous *in vitro* models used to simulate individual *in vivo* processes, the present approach for the prediction of fraction of dose absorbed is simple. Keeping in mind the limitations (non-passive uptake mechanisms, dissolution rate limitations, the decisive role for hydrophilic drugs of the 'typical' pH assumed at absorption sites) it is hoped that the present approach will provide valuable preformulation information about the extent of absorption.

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