Absorption Potential: Estimating the Fraction Absorbed for Orally Administered Compounds

To the Editor:

Estimating the oral bioavailability for new chemical entities or modifications of established drugs is of considerable pharmaceutical importance. However, correlation of in vivo with in vitro dosage form performance is impeded by the wide range of factors that influence release from the dosage form and/or drug absorption[1-4] in the GI tract. Important drug/dosage form related properties include solubility, dissolution rate, particle size, density, ionization, chemical stability, etc. Important physiological variables include GI motility patterns, volume and flow rate of contents, pH, membrane permeability to the drug, blood flow, etc. Any model for predicting oral drug absorption which attempts to account for all the factors involved will, by necessity, be extremely complex. A number of approaches have been taken which focus on one or another of the drug or physiological factors listed above.[5-9] Each of these approaches is limited to the range of conditions under which the factor studied is of primary impact on absorption. For instance, dissolution rate considerations become important for poorly soluble drugs, while intestinal wall permeability may become rate controlling if the drug is polar.

In our approach we have attempted to include as many key variables as possible, yet keep the model and its analysis simple.[10] This approach and its extension[11] have led us to a simple dimensionless number, absorption potential (AP), that appears to function well as a first approximation for predicting oral absorption of a given compound. Its strength (and weakness) lies in the fact that it is based entirely on readily obtained physicochemical measurements. Conceptual development and application of the absorption potential to several drug examples follows.

Neglecting lumenal degradation and first-pass metabolism, the fraction of a dose absorbed is a function of:

$$F_{abs} = f\ (P_w,\ P_{aq},\ S_o,\ X_o,\ F_{non},\ V_L,\ \text{etc.}) \qquad (1)$$

where P_w is the permeability of gut wall to drug, P_{aq} is the aqueous permeability of drug, S_o is the intrinsic solubility (aqueous solubility of the nonionized species at 37°C), X_o is the dose administered, F_{non} is the fraction in nonionized form at pH 6.5, and V_L is the volume of the lumenal contents.

Solubility and dissolution rate are obviously important since the drug must be in solution in order for uptake to occur. Since dissolution rate is in part governed by solubility, as well as by volume of the lumen, motility (hydrodynamics), diffusivity, particle size, density, wettability, etc., the key parameter is solubility. As far back as the 1950's, the concept of ionization-limited absorption was proposed by Brodie and co-workers[12] in their pH partition hypothesis. The work of Winne,[13] among others, suggests that there is a shift in the pH–permeability relationship when the partition coefficient is large. In addition, changing surface area and different residence times in different regions of the GI tract may attenuate the ionization effect. In general, though, the concept that the drug is primarily absorbed in the nonionized form is valid for the majority of cases. For a few examples where there is an active transport mechanism for uptake, or where the drug is small enough to be absorbed by paracellular routes, or where ion-pairing may effectively disguise an ionic site, the foregoing assumption may not apply. Since the main site of absorption, due to its high surface area:volume ratio, is the small intestine, the appropriate parameter to account for ionization effects is the fraction nonionized at a pH typical of the small intestine, namely pH 6.5.[14]

The variable of interest can be arranged into dimensionless groups:

$$F_{abs} = f\left[\left(\frac{P_w}{P_{aq}}\right),\ (F_{non}),\ \left(\frac{S_o \cdot V_L}{X_o}\right)\right] \qquad (2)$$

Dimensional analysis implies that a correlation of the form:

$$F_{abs} \propto \left(\frac{P_w}{P_{aq}}\right)^a (F_{non})^b \left(\frac{S_o \cdot V_L}{X_o}\right)^c \qquad (3)$$

can be expected.[15] Taking the simplest case, we allow a = b = c = 1:

$$F_{abs} \propto \left[\left(\frac{P_w}{P_{aq}}\right)(F_{non})\left(\frac{S_o \cdot V_L}{X_o}\right)\right] \qquad (4)$$

Furthermore, in many cases the permeability ratio is proportional to the membrane–water partition coefficient[16,17] which can be correlated to the 1-octanol–water partition coefficient, P. We can then define:

$$AP = \log\left(P \cdot F_{non} \cdot \frac{S_o \cdot V_L}{X_o}\right) \qquad (5)$$

as a simpler relationship, using the logarithmic function to produce a convenient scale of values.

Several drug examples were chosen to evaluate the utility of the absorption potential (AP) as a predictor of fraction absorbed. The parameter values, calculated AP, and fraction absorbed for these drugs are listed in Table I and the correlation is shown graphically in Fig. 1.

The choice of drugs was made to cover a wide range of absorption characteristics, from poorly absorbed compounds to those with virtually complete absorption (prednisolone, etc.). Individual parameters such as dose (from 0.25 mg for digoxin to 250 mg for chlorothiazide), solubility (from 0.01 mg/mL to 1.3 mg/mL), and partition coefficient (from 0.018 to 295) also covered a wide spectrum of values. Lumenal volume was set at 250 mL for all compounds based on available information in the literature concerning volume, flow rates, and transit time.[25-27]

From Fig. 1 it is clear that, for the compounds chosen, the dimensionless parameter AP exhibits a strong relationship to the fraction absorbed. Negative values of AP correspond to poor drug absorption. Between zero and one, an increase in AP is correlated with an increase in fraction absorbed, while values above one appear to correspond to virtually complete absorption. This means that when the absorption potential exceeds one, there is no limitation on absorption due to the equilibrium physicochemical properties of the drug.

Notice that the absorption potential is mainly concerned with the physicochemical properties of the drug and cannot be used as the sole indicator of bioavailability. Factors such as degradation in the lumen, nonpassive uptake mechanisms, first-pass metabolism, and enterohepatic cycling can substantially influence bioavailability. Absorption of erythromycin, for example, is precluded by acid decomposition in the stomach.[28] Substantial first-pass metabolism of many drugs, e.g., methyldopa[29] and propranolol,[30] results in a discrepancy be-

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Table I—Calculation of Absorption Potential for Representative Drugs

Drug	P	Solubility, mg/mL	Dose, mg	pK_a	F_{non} (pH 6.5)[a]	AP	%ABS (range)[a]	Ref.
Acyclovir	0.018	1.3	200	9.5	1	−1.5	17 (12–23)	18
Chlorothiazide	0.54	0.4	250	6.7	0.6	−0.89	25 (10–40)	19
Griseofulvin	151	0.015	250	—	1	0.36	43 (35–51)	20
Hydrochlorothiazide	0.85	0.6	25	8.8	0.95	0.7	67 (50–90)	21
Phenytoin	295	0.014	100	9.2	0.99	1.0	90 (80–100)	22
Prednisolone	26	0.235	20	—	1	1.9	99	23
Digoxin	56	0.024	0.25	—	1	3.13	>90	24

[a] % ABS = percentage of drug absorbed following an oral dose in human subjects.

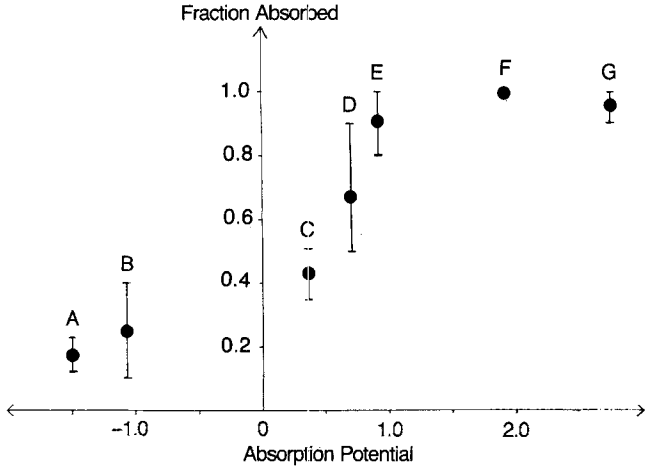

Figure 1—*Relationship between absorption potential and fraction absorbed for seven compounds. Key: (A) acyclovir; (B) chlorothiazide solution; (C) micronized griseofulvin; (D) hydrochlorothiazide; (E) phenytoin; (F) prednisolone; (G) digoxin (Lanoxicaps).*

tween fraction absorbed from the lumen and systemic bioavailability. On the other hand, absorption can appear to be greater than 100% of the dose for drugs which undergo enterohepatic cycling. An example in this category would be indomethacin.[31] Therefore, the absorption potential will not accurately predict the bioavailability for drugs prone to the above effects. In addition, particle size may be a significant influence on the dissolution rate and, if this is slow compared to transit rate in the GI tract,[32] the fraction absorbed will be lower than predicted by the absorption potential.[11]

In summary, although the absorption potential does not account for all processes influencing oral drug absorption, the parameter calculation is simple and has the merit of combining several key physicochemical properties into one number. The AP appears to correlate strongly with fraction absorbed, and, for poorly absorbed compounds, it is possible to identify the critical limiting physicochemical property. More refined analysis using the dynamic models[10,11] can then be used to determine the most appropriate chemical/formulation/administration strategy for improving the fraction absorbed. Poor absorption combined with an AP in excess of one suggests that factors other than the equilibrium physicochemical properties of the drug are limiting absorption.

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32. Dissolution rate will not be a limitation for drugs having reasonable aqueous solubility (~0.1 mg/mL or greater) but, when solubility is in the microgram/milliliter range, it will be a significant factor in determining fraction absorbed. Well-documented examples of drugs with dissolution rate limited absorption include digoxin and griseofulvin. For these cases the absorption potential is an indicator of how well the drug might be absorbed provided dissolution rate limitations are circumvented by micronizing the drug, using a solid solution formation, or delivering a solution form using a soft gelatin capsule preparation.

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