A Simple Modified Absorption Potential

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INTRODUCTION

With the advent of combinatorial chemistry and high-throughput screening, a large number of pharmacologically active compounds are being synthesized without consideration of their biopharmaceutical properties. This can lead to the failure of promising new drug candidates because of inadequate absorption from the gastrointestinal (GI) tract.

It is generally assumed that the passive transport processes between various aqueous and organic phases are governed by a balance of the hydrophilicity and the lipophilicity of the compound. Therefore water solubility and partition coefficient are of primary interest in determining drug absorption.

Dressman *et al.* (1) have introduced an absorption potential (AP) term for predicting the fraction of drug absorbed via passive transport. The AP is a dimensionless number and is defined as

$$AP = \log\left[\frac{K_{ow}S_wF_{non}V_L}{D}\right] \quad (1)$$

where, K_{ow} is the partition coefficient, S_w is the intrinsic solubility in water, F_{non} is the fraction of non-ionized drug at pH 6.5, V_L is the volume of the lumenal contents (which is assumed to be 0.25 L), and D is the dose administered. (Note that S_w must have the same units as D/V_L.) They found a strong relationship between the values of the AP and the fraction absorbed (FA) for the seven drugs considered.

Equation 1 establishes a qualitative relationship between AP and the fraction of the dose absorbed passively. An alternative quantitative AP concept was proposed by Macheras and Symillides (2):

$$FA = \frac{(10^{AP})^2}{(10^{AP})^2 + F_{non}(1 - F_{non})} \quad (2)$$

with constraints that $K_{ow} = 1000$ when > 1000, and $S_wV_L/D = 1$ when $S_wV_L/D < 1$.

More recently, Balon *et al.* (3) utilized a more realistic AP based upon the distribution coefficient at pH 6.8 ($K^{6.8}{}_D$) and solubility at pH 6.8 ($K^{6.8}{}_T$) instead of the partition coefficient, solubility, and the fraction un-ionized:

$$AP = \log\left[\frac{K_D^{6.8}S_T^{6.8}V_L}{D}\right] \quad (3)$$

Using a data set of 21 compounds, they observed a weak correlation between the FA and the AP.

Boxembaum (4) recently proposed a modification to equation (1) with bounded limits (0–1):

$$F_L = \frac{(K_{ow})^{\alpha}}{(K_{ow}{}^{\beta}) + \left(\frac{D}{F_{non}S_oV_L}\right)} \quad (4)$$

where F_L is fraction of the intact drug available to the liver and α and β are constants.

All of the methods discussed above are based upon either the fraction of drug nonionized at pH 6.5 or the solubility and the distribution coefficient of drug at pH 6.8. It is well-known that both S_w and K_{ow} are pH-dependent for weak electrolytes. However, the increase in the total solubility (S_T) of a weak acid with increasing pH is equal to the accompanying decrease in the distribution coefficient (K_D). Therefore, the product of total solubility and the distribution coefficient is independent of pH and equal to the product of intrinsic values, that is,

$$K_D \times S_T = K_{ow} \times S_w \quad \text{(at any pH)} \quad (5)$$

On the basis of this relationship, it is no longer necessary to explicitly consider either the pK_a of the drug or the pH of the GI tract for calculating the AP.

Hence, the need to measure F_{non} at pH 6.5 does not arise because the pH of the GI tract does not affect the product of intrinsic solubility and the octanol-water partition coefficient. Therefore, a modified AP (MAP) can be defined as

$$MAP = \log\left[\frac{K_{ow}S_wV_L}{D}\right] \quad (6)$$

If the volume of fluid in the GI lumen (V_L) is 0.25 L,

$$MAP = \log\left[\frac{K_{ow}S_w}{4D}\right] \quad (7)$$

MAP differs from AP in that it essentially requires two parameters for its estimation, intrinsic solubility and octanol-water partition coefficient, compared to the three parameters required for determining AP. In this study, we tested the validity of this new model using experimental human GI absorption data and compared the result with that of Dressman *et al.* (1) and Balon *et al.* (3).

DATA COLLECTION

To have a reasonable comparison between AP and MAP, we selected the same drugs as used by Dressman *et al.* (1) and Balon *et al.* (3) in their respective studies. All octanol-water partition coefficients were calculated using CLOGP software (5). Aqueous solubility and melting point (MP) values were taken from the AQUASOL dATAbASE (6), the PHYSPROP database (7), the Log P/Log S Calculation software (8), or the Merck Index (9). For the compounds for which experimental intrinsic solubility in water were not reported, the S_w values were calculated from the general solubility equation of Jain and Yalkowsky (10) as:

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ABBREVIATIONS: AP, absorption potential; FA, fraction absorbed; GI, gastrointestinal; MAP, modified absorption potential; MP, melting point.

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Table I. Calculation of Modified Absorption Potential for Representative Drugs

Drug	FA	MP (°C)	Dose (mg)	log K_{ow}	log S_w	log MAP	log AP
Acetylsalicylic acid	0.9	135	500	1.02	–1.59	1.38	–2.40[b]
Acyclovir	0.2	255	200	–2.52	–2.14	–2.21	–1.30[b]
Acyclovir	0.2	255	200	–2.52	–2.14	–2.21	–1.50[c]
Allopurinol	0.9	350	300	–0.88	–2.38	–1.21	–0.60[b]
Amiloride	0.5	241	5	–0.69	–0.97[d]	2.40	0.40[b]
Atenolol	0.6	147	50	–0.11	–0.61[d]	2.40	0.40[b]
Chlorothiazide	0.3	342[e]	250	–0.31	–3.05	–0.89	–0.89[c]
Diclofenac	1.0	157	50	4.32	–4.37	3.12	2.30[c]
Digoxin	0.9	249[e]	0.25	2.27	–4.08	4.08	3.13[b]
Famotidine	0.5	164	40	0.26	–2.53[d]	1.05	–0.50[b]
Fluoxetine	0.8	158	30	4.57	–5.40[d]	2.58	3.30[b]
Furosemide	0.7	295	40	1.87	–3.66	1.53	–0.10[b]
Griseofulvin	0.4	220	250	1.75	–4.61	–0.31	0.36[c]
Hydrochlorothiazide	0.7	274	25	–0.40	–2.62	0.46	0.70[c]
Ibuprofen	0.8	76	200	3.68	–3.99	2.10	1.60[b]
Miconazole	0.3	NA[a]	250	5.81	–7.10[f]	1.33	3.10[b]
Moxonidine	1.0	218	0.3	1.42	–2.85[d]	3.87	3.10[b]
Nizatidine	1.0	131	300	–0.20	–0.36[d]	1.88	0.50[b]
Olanzapine	0.8	195	10	4.02	–5.22[d]	2.69	1.70[b]
Paromomycin	0.0	NA[a]	250	–6.52	–0.53[f]	–4.26	–1.00[b]
Phenytoin	0.9	286	100	2.08	–3.90	0.98	1.00[c]
Prednisolone	1.0	235	20	1.38	–3.21	1.83	1.90[c]
Propranolol	1.0	96	80	2.75	–2.96[d]	2.70	2.90[b]
Rifabutine	0.5	NA[a]	150	NA[a]	NA[a]	NA[a]	2.80[b]
Terbinafine	0.8	NA[a]	250	5.96	–6.06[f]	2.36	3.50[b]
Xipamide	0.7	256	20	1.89	–3.70[d]	1.84	1.50[b]
Zidovudine	0.9	109	100	0.04	–1.03	1.83	1.60[b]
Zopiclone	0.8	178	8	1.17	–2.20[d]	3.05	1.50[b]

[a] NA, not available.
[b] log AP values from Balon *et al.* (3).
[c] log AP values from Dressman *et al.* (1).
[d] log S_w calculated using the general solubility equation of Jain and Yalkowsky (10).
[e] Drug decompose at melting point.
[f] log S_w calculated from Log P/Log S Calculation Software.

$$\log S_w = 0.5 - \log K_{ow} - 0.01(MP - 25)$$

where MP is the melting point of a given compound in °C.

Table I lists the names of the drugs considered and the values for each parameter.

RESULTS AND DISCUSSION

A total of 27 structurally diverse compounds were used for the model validation. Figure 1 shows the plot between the logarithm of FA vs. the logarithm of AP as reported by Dressman *et al.* (1) and Balon *et al.* (3). Figure 2 shows FA as a function of the logarithm of MAP for the same compounds. It is clear that the reported fractions of drug absorbed (i.e., the FA) and MAP is correlated as well as or better than are FA and AP. The use of $K_{ow}S_w$ instead of K_DS_T provides a more pronounced relationship of FA to MAP (Fig. 2) than AP (Fig. 1). Possible reasons for the greater scatter in Fig. 1 could be the inaccuracies of measuring distribution coefficients and solubilities as functions of pH and the inability to model the GI tract with a specific pH value. (It is well-known that the pH in the GI tract varies considerably over the length of the small intestine and proximal colon [the major absorptive sites], and it is therefore a coarse approximation to use a single pH value, as is used in various models.) It is even more difficult to know the pH at the surfaces of the dissolving particle and the gut wall. Because MAP is based on intrinsic partition coefficients and solubility values, it is not subject to these errors. Also it is easier to measure or calculate intrinsic

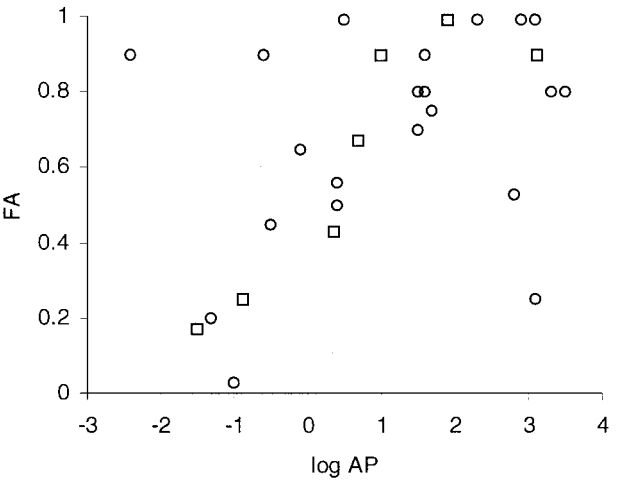

Fig. 1. Relation of FA vs. log AP. (□) Dressman *et al.* (1). (○) Balon *et al.* (3).

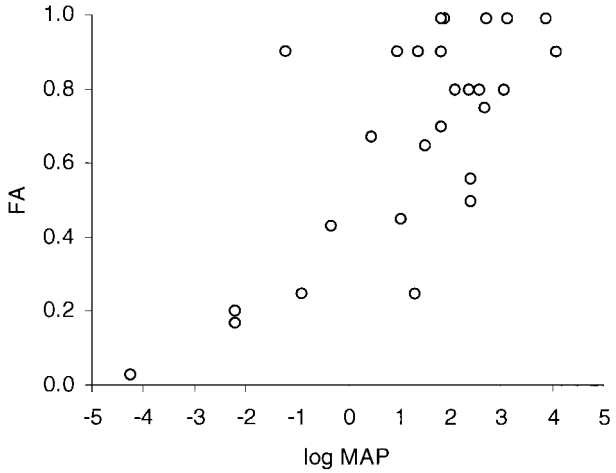

Fig. 2. Relation of FA vs. log MAP.

solubility and intrinsic partition coefficient values accurately. Therefore, MAP can be used to predict the FA for orally administered drugs that are passively transported. However, because the calculation is thermodynamically based, it may not account for the kinetics of dissolution vs. transit.

CONCLUSION

The MAP, based on the relationship that $K_{ow}S_w = K_DS_T$, can be used instead of the original APs of Dressman *et al*. (1) and Balon *et al*. (3) to predict the FA by passive diffusion for orally administered compounds. Because the MAP incorporates intrinsic values of solubility and the partition coefficient, it saves experimental time and reduces errors associated with the measurement or calculation of both solubility and the distribution coefficient or the fraction of drug left un-ionized at a particular pH. Also, both solubility and the octanol-water partition coefficient can be estimated from the structure with reasonable accuracy, making the model very user friendly. Therefore, the MAP model is not only simpler but also more accurate and more reliable than the AP model.

REFERENCES

1. J. B. Dressman, G. L. Amidon, and D. Fleisher. Absorption potential: estimating the fraction absorbed for orally administered compounds. *J. Pharm. Sci.* **74**:588–589 (1985).
2. P. E. Macheras and M. Y. Symillides. Toward a quantitative approach for the prediction of the fraction of dose absorbed using the absorption potential concept. *Biopharm. Drug Dispos.* **10**:43–53 (1989).
3. K. Balon, B. U. Riebesehl, and B. W. Muller. Drug liposome partitioning as a tool for the prediction of human passive intestinal absorption. *Pharm. Res.* **16**:882–888 (1999).
4. H. Boxenbaum. Absorption potential and its variants. *Pharm. Res.* **16**:1893 (1999).
5. Bio Byte Corp. ClogP for Windows, version 4, Bio Byte Corp., the QSAR specialists, Claremont, California.
6. S. H. Yalkowsky (ed.). *AQUASOL dATAbASE of Aqueous Solubility,* University of Arizona, Tucson, Arizona, 1999.
7. P. H. Howard and W. M. Meylan (eds.). *Handbook of Physical Properties of Organic Chemicals,* Lewis Publishers, New York, 1997.
8. I. V. Tetko, V. Y. Tanchuk, T. N. Tamara, and A. E. P. Villa. Internet software for the calculation of the lipophilicity and aqueous solubility of chemical compounds. *J. Chem. Inf. Comput. Sci.* **41**:246–252 (2001).
9. S. Budavari (ed.). *The Merck Index,* Merck & Co., New Jersey, 1996.
10. N. Jain and S. H. Yalkowsky. Estimation of the aqueous solubility. I: Applications to organic nonelectrolytes. *J. Pharm. Sci.* **90**: 234–252 (2001).