Absorption Potential and Its Variants

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In a cogent and innovative 1985 paper, Dressman, Amidon and Fleisher (1) posited the concept of "absorption potential," a predictor of percent oral drug dose available intact to the human liver (assuming no lumen degradation, first-pass effects, efflux transporting, etc.). Based solely on physicochemical drug and gut properties, the equation is:

$$AP = \log\left(P \times F_{NON} \times \frac{S_0 V_L}{X_0}\right) \quad (1)$$

where AP is absorption potential (capable of negative values and those exceeding unity), P is drug 1-octanol-water partition coefficient, F_{NON} is fraction of drug nonionized at pH 6.5, S_0 is aqueous drug solubility of nonionized species at 37° C, V_L is luminal content volume (250 mL) and X_0 is drug dose.

Other significant contributions have appeared since 1985. Amidon *et al.* (2), for example, developed a biopharmaceutics drug classification scheme in which F_L (no lumen degradation, first-pass effects, efflux transport, etc.) is expressed as a function of solubility and permeability. The impact of particle size on drug dissolution and absorption has also been investigated (3).

Physicochemical data could be fit to hundreds of equations to obtain estimates of intact drug available to the liver (per conditions discussed above). One such modification of equation 1 with bounded limits (0 to 1) is:

$$F_L = \frac{P^\alpha}{P^\alpha + \left(\frac{X_0}{F_{NON} S_0 V_L}\right)^\beta} \quad (2)$$

where F_L is fraction of intact drug available to the liver, α and β are constants, and for convenience, the 4 variables in the right-hand term of the denominator are termed dose-solubility complex. Equation 2 was fit (4) to 7 unweighted data-sets from Dressman, Amidon and Fleisher (1), where partition coefficient and dose-solubility complex were independent variables, and F_L was the dependent variable. Figure 1 illustrates the theoretical three dimensional plot of the three variables and provides goodness-of-fit indicators. As required by theory and observation, when dose-solubility complex becomes very large (dose >> solubility capability), dissolution is rate-limiting, and large P values have a minor impact on liver availability. When dose-solubility complex is small (solubility capability >> dose), permeability is the major controlling variable.

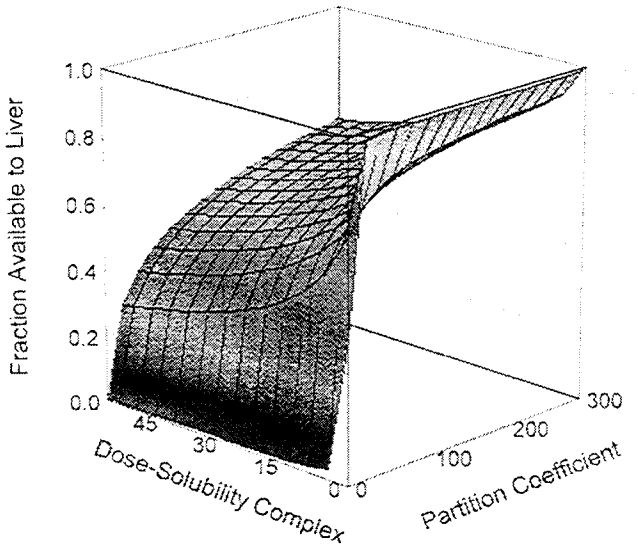

Fig. 1. Theoretical three dimensional relationship between drug partition coefficient (P), drug dose-solubility complex $[X_0/(F_{NON}S_0V_L)]$ and intact drug fraction available to the liver (F_L). See text for necessary assumptions. Using the Levenberg-Marquardt algorithm, $R^2 = 0.9185$, $\alpha = 0.5767$ ($p = 0.00744$) and $\beta = 0.6459$ ($p = 0.01446$). Observed and calculated F_L data, respectively, were: (0.17, 0.119), (0.25, 0.218), (0.67, 0.737), (0.99, 0.929), (0.9, 0.988), (0.43, 0.545) and (0.9, 0.752).

In cases where solubility and dissolution are not absorption rate-limiting, CACO-2 permeability *per se* frequently predicts F_L (see Yee (5) for example). With the advent of technologies capable of rapidly determining CACO-2 cell permeability coefficients, equations such as those discussed herein (theoretical or empiric) would probably be improved by substituting permeability values for partition coefficients. Rapid calculation of F_L values should expedite routine screening of new chemical entities during drug discovery. However, estimates of projected human doses will be required.

Correlates of permeability are now rapidly determinable, e.g., immobilized artificial membrane (IAM)-HPLC partition data, and these may be utilized under appropriate conditions. Even prior to chemical synthesis, partition coefficients may be estimated utilizing commercially available software. A plethora of equations could be derived, evaluated and utilized to characterize drug absorption characteristics.

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