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*Report*

# Estimating Human Oral Fraction Dose Absorbed: A Correlation Using Rat Intestinal Membrane Permeability for Passive and Carrier-Mediated Compounds

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Based on a simple tube model for drug absorption, the key parameters controlling drug absorption are shown to be the dimensionless effective permeability, $P^*_{eff}$, and the Graetz number, $Gz$, when metabolism or solubility/dissolution is not rate controlling. Estimating the Graetz number in humans and assuming that $P^*_{aq}$ is not rate controlling gives the following equation for fraction dose absorbed: $F = 1 - e^{-2P^*_w}$. The correlation between fraction dose absorbed in humans and $P^*_w$ determined from steady-state perfused rat intestinal segments gives an excellent correlation. It is of particular significance that the correlation includes drugs that are absorbed by passive and carrier-mediated processes. This indicates that $P^*_w$ is one of the key variables controlling oral drug absorption and that the correlation may be useful for estimating oral drug absorption in humans regardless of the mechanism of absorption.

KEY WORDS: carrier-mediated absorption; film model; fraction dose absorbed; passive absorption; permeability.

## INTRODUCTION

The estimation of human oral drug absorption based on *in vitro* and *in vivo* measurements is of considerable utility in the design of efficacious oral drug products. Drug solubility, partition coefficient, $pK_a$, stability, etc., affect drug absorption in ways that are qualitatively well understood. However, quantitative and semiquantitative approaches to the estimation of oral drug absorption still need to be developed. While the complexity and variability of the gastrointestinal (GI) tract are not fully understood, a rough estimation of human drug absorption is possible. Assuming that chemical stability and first-pass metabolism are not the cause of poor oral drug absorption, then the two key parameters controlling drug absorption are membrane permeability and dose-to-solubility ratio. The membrane permeability for passively absorbed compounds, using the simplest model for permeability (1,2), is a function of the partition coefficient and the $pK_a$ of the compound. However, for compounds whose absorption mechanism is not passive (e.g., α-methyldopa, β-lactam antibiotics), a simple relationship between membrane permeability and partition coefficient is not expected. In this report it is shown that the membrane permeability, determined using a perfused rat intestinal segment, can be correlated with the fraction dose absorbed in humans for both passive and carrier-mediated compounds.

## THEORY

For correlation purposes a simple tube model is used (1). For this model, the relevant differential equation is

$$v_z \frac{\partial C}{\partial z} = \frac{1}{r}\frac{\partial}{\partial r} r \frac{\partial C}{\partial r} \tag{1}$$

with boundary conditions

$$C = C_0, \quad z = 0, \quad t \geq 0 \tag{2}$$

$$\left.\frac{\partial C}{\partial r}\right|_{r=0} = 0$$

$$-D \left.\frac{\partial C}{\partial r}\right|_{r=R} = P_w C_w$$

where $r$ is the tube radius, $z$ the axial coordinate, $v_z$ the axial velocity profile, $C = C(r,z)$ the concentration profile, $D$ the solute aqueous diffusivity, $P_w$ the membrane (wall) permeability, and $C_w = C(R,z)$ the concentration along the tube wall. When this model is made dimensionless (1) the solution to the partial differential equation is a function of two parameters, $Gz$ and $P^*_w$.

$$Gz = \frac{\pi D L}{2Q} \tag{3}$$

$$P^*_w = P_w \frac{R}{D} \tag{4}$$

The Graetz number, $Gz$, is the ratio of axial convection to radial diffusion times. While it will vary with physiological variables, it is relatively independent of drug properties with

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the exception of its dependence on aqueous diffusivity. The membrane permeability, $P_w^*$, on the other hand is very dependent on drug properties. The simplest model, for example, for $P_w^*$ (2) gives:

$$P_w = PC\frac{D_w}{\delta_w} \tag{5}$$

i.e., a strong dependence on the partition coefficient between the fluid and the membrane wall, where $D_w$ is the membrane diffusion coefficient and $\delta_w$ is the membrane thickness. More realistic models for the wall permeability lead to a more complex dependence on drug properties (2).

However, for the purpose of this correlation we also need to consider a nonlinear Michaelis–Menten-type boundary condition. A more general boundary condition that Eq. (2), in dimensionless form, is

$$P_w^* = \frac{J_{max}^*}{K_m + C_w} + P_m^* \tag{6}$$

where $J_{max}^*$ is the maximal "carrier" flux, $K_m$ the apparent Michaelis constant, and $P_m^*$ the passive membrane permeability. Rearranging Eq. (6) results in

$$P_w^* = \frac{J_{max}^*}{K_m}\left(1 + \frac{C_w}{K_m}\right)^{-1} + P_m^* \tag{7}$$

where the $(1 + C_w/K_m)^{-1}$ term is the nonlinear term. When the concentration is below $K_m$ at the wall, Eq. (7) becomes

$$P_w^* = P_c^* + P_m^* \tag{8}$$

where

$$P_c^* = \frac{J_{max}^*}{K_m}$$

and is referred to as the carrier permeability.

For the purposes of this report, only the complete radial mixing or film model solution to Eq. (1) is considered (3). The solution for the ratio of outlet ($C_m$) to inlet ($C_0$) concentration is

$$\frac{C_m}{C_0} = e^{-4GzP_{eff}^*} \tag{9}$$

or

$$F = 1 - e^{-4GzP_{eff}^*} \tag{10}$$

where

$$P_{eff}^* = \frac{P_{aq}^* P_w^*}{P_{aq}^* + P_w^*} \tag{11}$$

$$Gz = \frac{\pi DL}{2Q} = \frac{DL}{2\langle v\rangle R^2}$$

$P_{aq}^*$ is the dimensionless aqueous permeability, $P_w^*$ is the dimensionless membrane permeability, and $P_{aq}^* = P_{aq}R/D$, $P_w^* = P_w R/D$; $D$ is the diffusivity; $L$ is the length of the perfused segment; $Q$ is the flow rate; and $F = 1 - C_m/C_0$ is the fraction dose absorbed.

The Graetz number of the human intestine can be estimated to be about 0.5 using an intestinal length of 500 cm, a flow rate of 0.5 ml/min, and a diffusivity of $5 \times 10^{-6}$ cm$^2$/sec. Consequently, Eq. (10) becomes

$$F = 1 - e^{-2P_{eff}^*} \tag{12}$$

If the assumption is made that $P_{aq}^*$ is not rate limiting (see below), i.e., the controlling resistance is $P_w^*$, then Eq. (12) becomes

$$F = 1 - e^{-2P_w^*} \tag{13}$$

This simple equation suggests the expected correlation between the rat intestinal membrane permeability and the fraction dose absorbed.

For compounds that are absorbed by a carrier-mediated process, a concentration-dependent permeability requires definition of a mean permeability to be used in correlations following Eq. (13). For this purpose we define

$$\overline{P_w^*} = \frac{\int_{C_0}^{0} P_w^*\, dC}{\int_{C_0}^{0} dC} \tag{14}$$

where $C_0 = D_0/V_L$, $D_0$ is the dose administered, and $V_L$ is the luminal volume. Substituting Eq. (7) into Eq. (14) and integrating gives

$$\overline{P_w^*} = P_m^* + P_c^*\frac{K_m}{C_0}\ln\left(1 + \frac{C_0}{K_m}\right) \tag{15}$$

## EXPERIMENTAL

Permeability values used in this report are intrinsic, dimensionless wall permeabilities as calculated from steady-state intestinal perfusion results in the rat small intestine (1). Fraction dose absorbed in humans is reported for each compound rather than bioavailability since the latter may be complicated by metabolic factors such as first-pass hepatic metabolism. The experimental details for the β-lactam antibiotics and α-methyldopa have been reported previously (4–6). Fractions dose absorbed were reported in Refs. 7–9

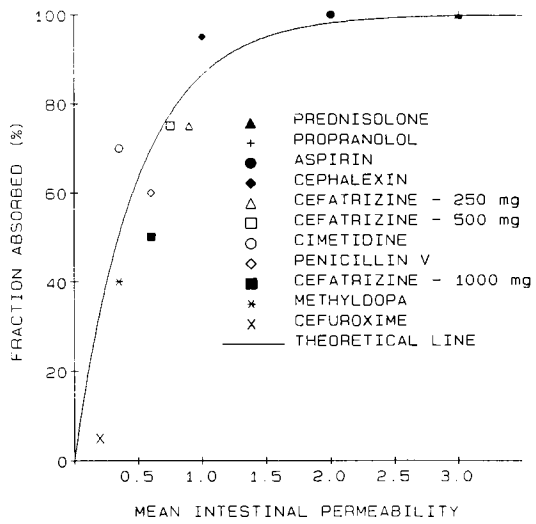


Fig. 1. Plot of the fraction dose absorbed (%) versus the mean dimensionless intestinal wall permeability. Wall permeabilities were calculated from steady-state rat intestinal perfusion experiments.

and 10, respectively. The wall permeability and fraction dose absorbed for the other compounds were taken from the following references: prednisolone (11,12), propranolol (13,14), aspirin (15,16), cimetidine (17,18), and cefuroxime (19,20).

## RESULTS AND DISCUSSION

Figure 1 shows the correlation between the percentage dose absorbed in humans versus the (dimensionless) intestinal wall permeability measured in the perfused rat intestinal segment. The line is the theoretical line based on Eq. (13). The overall correlation is very good using an approximated Graetz number in humans, which is estimated to be about 0.5. Fitting the data to Eq. (10) to determine the best value for the overall correlation in humans gives 0.44 ($\pm 0.05$) ($R^2 = 0.76$), very close to the approximation used in these correlations. The correlation suggests that compounds with a dimensionless intestinal wall permeability of 1 or greater will be well absorbed in humans, while compounds with a $P_w^*$ of less than 0.1 will be very poorly absorbed in humans, in agreement with the simple model of Eq. (13). One of the model assumptions, that $P_{aq}^*$ is not rate limiting, can now be justified since

$$P_{aq}^* = \frac{D}{\delta}\frac{R}{D} = \frac{R}{\delta}$$

where $\delta$ is the film thickness of the aqueous boundary layer. In general, the film thickness can, at most, be equal to $R$, $\delta \leq R$, hence $P_{aq}^* \geq 1$. In the case where $\delta = R$ the fluid would be completely stagnant. Convective mixing, normally present in the intestine, would considerably reduce $\delta$ making $P_{aq}^* \gg 1$. Consequently, the aqueous permeability is always above the critical value of 1 and would not be rate limiting.

Other investigators (21) have suggested that the relationship between the apparent *n*-octanol/water partition coefficient (PC) and passive membrane permeability is complex and that a simple correlation usually cannot be realized. However, there may be a relationship between permeability and lipophilicity within a given structural class of compounds of homologs (21). Given the diverse physical properties of the compounds presented in this paper, including acidic, basic, neutral, and zwitterionic compounds, a simple relationship between absorption and PC is not expected. Furthermore, nonpassively absorbed compounds would not be expected to follow a simple relationship with PC since they are absorbed by a carrier mechanism (22) of unknown structural specificity. While the traditional approach of correlating PC to absorption has significant limitations, one of the real advantages of the correlation in Fig. 1 is that it is independent of mechanism and structural class. That is, the membrane permeability is the fundamental parameter of interest and the key parameter to measure. Other parameters such as partition coefficient and $pK_a$ are useful as guides but they are not the fundamental parameters of interest.

For the nonpassively absorbed compounds, cefatrizine has the lowest $K_m$ (5), consistent with its observed oral dose dependency (23). Table I gives the dose-dependent permeabilities calculated from Eq. (15). Cefatrizine's calculated dose-dependent permeabilities are consistent with its lower oral availability in humans as the dose was increased from 250 to 1000 mg. This compared well to the other cephalosporins and was consistent with the overall correlation in Fig. 1.

Table I. Mean Permeability of Cefatrizine Calculated Using Eq. (15)[a]

| Dose (mg) | $\bar{P}_w^*$ |
|---|---|
| 250 | 0.90 |
| 500 | 0.75 |
| 1000 | 0.60 |

[a] The intrinsic membrane parameters are $P_c^* = 1.25$, $P_m^* = 0.17$, and $K_m = 0.58$ m$M$.

With regard to the generality of the correlation, the main factor not included in this analysis (aside from chemical stability and metabolism) is the dose-to-solubility ratio as included in the absorption potential parameter (24). When the dose-to-solubility ratio becomes large the dissolution rate may limit absorption, as has been discussed by other authors (25). In a sense this represents an aqueous permeability limitation since it is the aqueous boundary layer around the particles that is now the rate-limiting step. In this case $P_m^*$ would not likely be rate limiting since water insoluble compounds are generally nonpolar and expected to have a high passive membrane permeability. Other factors affecting the absorption of low-solubility compounds that need to be considered such as micelle transport, $pK_a$, dissolution rate profile, etc., are beyond the scope of this study, as well as metabolism factors that effect oral availability.

In summary it has been shown that the intestinal membrane permeability determined in a perfused rat intestinal segment correlates very well with the human oral availability for compounds that are absorbed by passive as well as nonpassive (carrier-mediated) mechanisms. It can be used to estimate oral absorption in humans assuming that solubility or metabolism factors are not significant and does not rely on an assumed membrane model or absorption mechanism (i.e., it is applicable to both passive and carrier-mediated absorption mechanisms). This correlation can be used to optimize the oral absorption in a series of analogues or homologs of a lead active compound.

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