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Intestinal absorption kinetics of various model drugs in relation to partition coefficients

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Summary

The kinetics of intestinal absorption of 9 drugs from aqueous solutions were studied in rats using an in situ perfusion technique. The results are discussed in the light of their partitioning behaviour, blood flow and the unstirred water layer. Correlations between absorption rate constants and partition coefficients were found to be either parabolic or hyperbolic and existing absorption models were applied to fit the data.

Introduction

Mechanisms of drug penetration in living cells have long been studied and have been interpreted in relation to lipophilicity (Overton, 1899; Collander and Bärlund, 1933; Collander, 1954) and size of the solute (Höber and Höber, 1937). Later, the diffusion of small molecules through pores in the membrane was demonstrated (Diamond and Wright, 1969; Smulders and Wright, 1971; Galey and Owen, 1973; Wright, 1974; Wright and Pietras, 1974) and the importance of molecular volume was confirmed (Diamond and Wright, 1969). The influence of the degree of ionization of drugs on their intestinal absorption (pH partition hypothesis) was demonstrated by Brodie and Hogben (1957), Shore et al. (1957), Schanker et al. (1957, 1958), Schanker (1959), Hogben et al. (1957, 1959) and Hogben (1960). Nowadays, the description of the intestinal barrier as a multilaminate composed of oily and aqueous phases is generally recognized and has been recently reviewed (Bernier, 1980).

Solute transfer experiments can be used either to describe the structure of the barrier or to define the ideal characteristics of a therapeutic agent for absorption and activity. Most investigations involve the determination of the so-called partition coefficient and several models have been proposed to fit the absorption data obtained with particular solutes. Unfortunately these studies did not consider the absorption kinetics of the drugs tested, which led to different theories concerning the relationship between absorption and partition. Using the absorption values of 9 model drugs and previously determined partition coefficients with two triglycerides (Nook et al., 1987), we examine here the kinetic aspects of drug absorption in relation to partitioning and cast some light on the ap-

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parent discrepancies between former publications in this field.

Materials and Methods

Materials

Nine products were chosen as model drugs, namely oxyphenbutazone (Ciba-Geigy, Switzerland), pyrazinamide (Fluka, Switzerland), theophylline, proxyphilline, diprophylline and isoniazid (Siegfried, Switzerland), pentifylline and pentoxifylline (Chemische Werke Albert, F.R.G.) and etofylline (Treupha, Switzerland).

The oily phases used for the determination of the partition coefficients, as reference media of different polarities, were tributyrin (TB) and tricaprylin (TC) (Fluka, Switzerland). These were formerly studied as perfusion vehicles of drugs in oily solutions (Nook et al., 1987) and appeared to give values similar to those obtained with *n*-octanol, the usual reference medium for partition coefficient measurements (Smith et al., 1975). Their acidity indices were assessed to be negligible, as measured by the Eur. Ph. method. All other chemicals were of analytical grade (Merck, F.R.G.).

Partition coefficient determination

Partition coefficients were determined at 37 °C by shaking 20 ml of the oily phase containing the drug at the concentration used for the perfusion experiments and 20 ml of an isotonic pH 6.0 Sørensen buffer. The drug concentration was measured at equilibrium by UV spectrophotometry in both phases. For this purpose, the oily phase was diluted with methanol and the aqueous phase with the phosphate buffer. The partition coefficient was calculated from:

$$K_{app} = \frac{C_o}{C_a} \quad (1)$$

where C_o is the concentration of the drug in the oily phase and C_a the concentration in the aqueous phase.

Drug absorption

The absorption of the drugs was investigated using the in situ perfusion technique of Hayton and Levy (1972) with the modifications proposed by Gabus (1984). The advantage of this method is that it maintains blood circulation, which is important for the integrity of the intestinal wall and preserves the concentration gradient encountered in vivo.

Sprague–Dawley rats weighing 200–250 g were restrained from food 12–16 h before the experiment, but had free access to water. Each animal was anaesthetized with urethane at a dose of 1.3 mg/g b. wt. Then, the small intestine was cannulated above the biliary duct and just before the ileo-caecal valve. The glass cannulas were then connected with silicone tubes to a peristaltic pump (Perpex Guldener Vario II, Werner Meyer, Switzerland) and to a reservoir stirred by a magnetic bar. The whole system was thermostatted at 37 °C and the rat was laid on a heating cushion at the same temperature.

As a preliminary, the intestine was washed with 500 ml of an isotonic solution (Doluisio et al., 1969), first at a low perfusion rate to expel hard residues, then at 45 ml/min for 10 min. The remaining solution was expelled by passing air through the intestine at 25 ml/min for 8 min. For the experiment, 40 ml of pH 6.0 isotonic Sørensen buffer containing the drug at a concentration of 0.12 mg/ml (oxyphenbutazone at 0.21 mg/ml) were perfused through the entire small intestine at a flow rate of 1.5 ml/min, in a closed circuit. The disappearance of the solute from the lumen was determined by UV spectrophotometry on samples taken in the reservoir at 10-min time intervals. For each drug 3–5 runs were performed. "Blank" experiments (without any drug) were made previously to check that there was no interference by intestinal secretions with the analytical method. Volume corrections due to water absorption were made according to the method of Gabus (1984), admitting linear water absorption kinetics between time zero and the end of the experiment (120 min), when the volume was measured precisely. This author reviewed the problems inherent in the use of so-called non-absorbable markers and demonstrated the accuracy of the linear regression method.

Results

Pharmacokinetics

Fig. 1 shows the plots of the mean drug concentrations remaining in the lumen as a function of time. Not only the rate of disappearance varies from drug to drug, but the kinetics of the process also differs. The individual experiments with di-

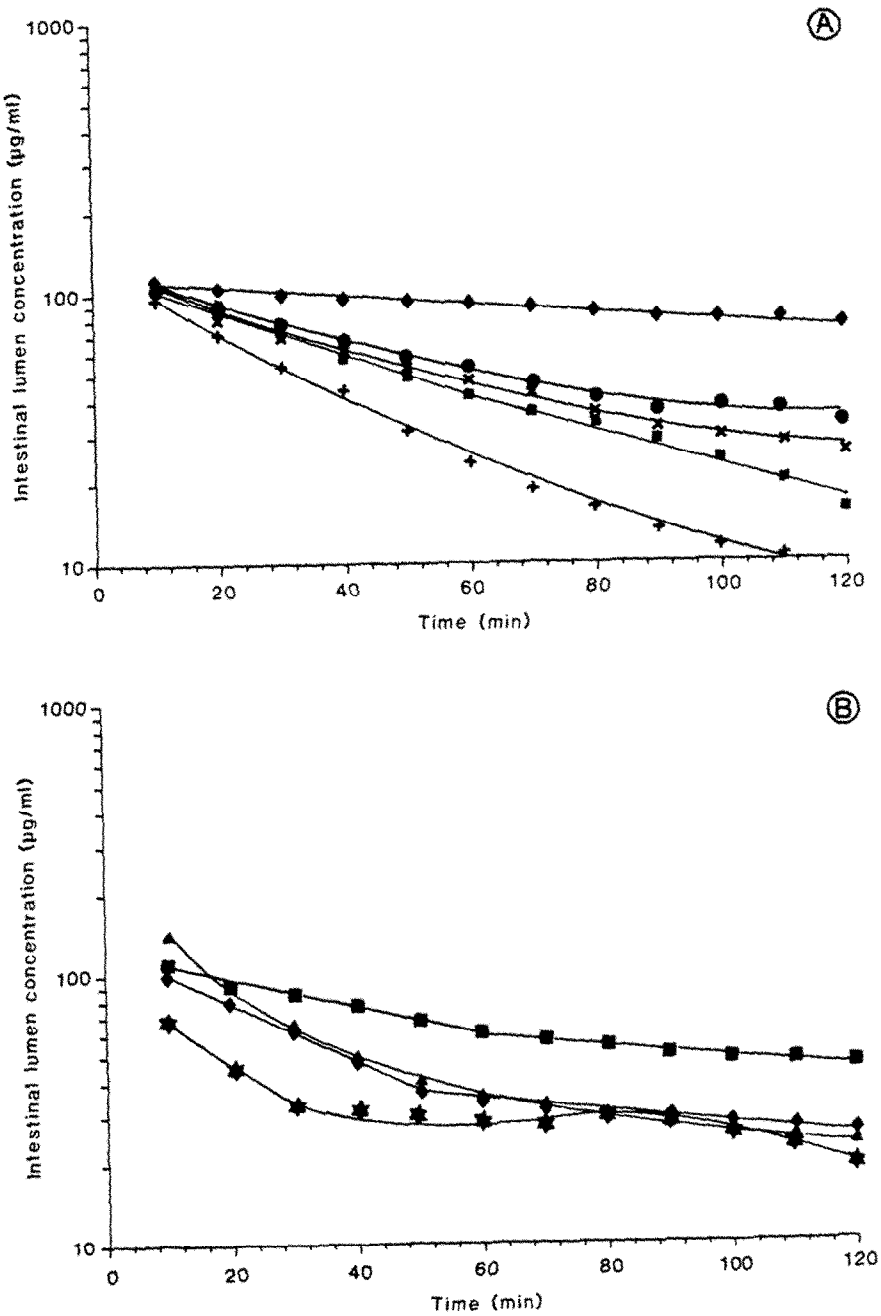

Fig. 1. Absorption profiles of: (A) diprophylline (◆), etofylline (●), proxyphylline (×), isoniazid (■), pyrazinamide (+) and (B) oxyphenbutazone (▲), theophylline (■), pentoxifylline (◆), pentifylline (★) from solutions in pH 6.0 Sørensen phosphate buffer.

prophylline, etofylline, proxyphylline, isoniazid and pyrazinamide are well described (Fig. 1A) by a simple exponential term (model 1):

$$C_t = Ae^{-k_1 t} \quad (2)$$

With oxyphenbutazone (Fig. 1B) a typical biexponential behaviour (model 2) is observed which can be fitted by the following expression (Gibaldi and Perrier, 1975):

$$C_t = Ae^{-k_1 t} + Be^{-k_2 t} \quad (3)$$

In these equations, C_t is the drug concentration remaining in the gut at time t and k_1 and k_2 are rate constants. A and B represent preexponential constants (A is the concentration at time 0).

Theophylline and pentoxifylline, although showing a concentration decay with two phases (Fig. 1B), do not fit well to model 2 and correspond better to a pseudo-model 1 described by equation 2 with a change of k_1 after a certain time. This phenomenon is quite common in biology (Geller, 1973), although it has seldom been described in pharmacokinetics. The reasons for such a change will be discussed later on.

Finally, pentifylline shows a particular pattern, as a rebound of its luminal concentration occurs at 80 min (Fig. 1B). This has been attributed to the marked enterohepatic circulation of this substance (Sjöstrand and Schmiterlöw, 1968). Because of the limited data available, an extensive modelling was not possible and absorption rate constants were approximated by linear regression of the first 3 and last 3 measurements.

To choose the right model for oxyphenbutazone, pentoxifylline and theophylline, a statistical analysis of the fit was undertaken on the sum of squared residuals, using an F-test (Yamaoka et al., 1978, Boxenbaum et al., 1974) and the Akaike information criterion, AIC (Akaike, 1974). When the sum of the squared residual becomes smaller through the application of the non-linear regression (model 2) the F-test is applied to check the significance of this reduced value. The AIC gives a similar indication through a different formula and also weights the sum of the squares by the number of parameters of the model. Table 1 summarizes this statistical analysis for all individual runs.

The second experiment with pentoxifylline seems to correspond to model 2 according to the slight reduction of AIC_{nlin}, whereas the other experiments with this drug show a clear tendency towards model 1. This is also confirmed by the F-test. The first perfusion with theophylline seems to obey model 2; however, this hypothesis was rejected because of the typical model 1 behaviour of this substance in the two other experiments.

TABLE 1

Statistical analysis of the proposed pharmacokinetic models

Drug	R_{lin}	R_{nlin}	F_{ij}	$F_{0.05\,[1,8]}$	AIC_{lin}	AIC_{nlin}	Model
Oxyphenbutazone	67.0	24.4	14.0	5.32	56.4	46.3	2
	95.1	43.5	9.5	5.32	60.6	53.3	2
	96.9	24.8	23.2	5.32	60.9	46.5	2
Pentoxifylline	330	494	–	–	75.6	82.4	1
	44.3	29.9	3.9	5.32	51.5	48.8	1
	82.6	159	–	–	59.0	68.8	1
Theophylline	11.1	6.3	6.1	5.32	34.8	30.0	2
	8.6	9.0	–	–	31.8	34.4	1
	2.5	15.6	–	–	15.2	35.5	1

R_{lin} = sum of squared residuals obtained by using model 1.
R_{nlin} = sum of squared residuals obtained by using model 2.
F_{ij} = calculated value of F.
$F_{0.05\,[1,8]}$ = value of F for 95% confidence and degrees of freedom of 1 and 8.
AIC_{lin} = Akaike information criterion using model 1.
AIC_{nlin} = Akaike information criterion using model 2.

TABLE 2

Pharmacokinetic models and partition coefficients of the perfused drugs

Drug	Model (equation no.)	$k_1 \pm$ S.D. (10^{-1}/h)	$k_2 \pm$ S.D. (10^{-1}/h)	K_{app} TB	K_{app} TC
Oxyphenbutazone	2 (3)	36 ±6	3 ±2	360	63
Pentifylline	1, two slopes approx. (2)	22 ±8	8 ±2	14.2	6.6
Pentoxifylline	1, two slopes (2)	15 ±4	2.4 ± 0.6	1.7	0.5
Pyrazinamide	1 (2)	14 ±2	–	0.25	0.087
Theophylline	1, two slopes (2)	7 ±1	3.3 ± 0.1	0.21	0.06
Proxyphylline	1 (2)	10 ±2	–	0.16	0.033
Isoniazid	1 (2)	10 ±1	–	0.019	0.084
Etofylline	1 (2)	8 ±1	–	0.085	0.018
Diprophylline	1 (2)	2.0 ± 0.5	–	0.014	0.006

This inconsistency shows that it is risky to accept or reject a pharmacokinetic model on the basis of a single statistical information criterion and that great care should be taken with the sum of squared residuals, F-values and AIC values of several experiments before making a decision. F- and AIC tests have been shown previously to be helpful in preventing over-modelling (Yamaoka et al., 1978; Boxenbaum et al., 1974).

Finally, the absorption of pentifylline shows a special behaviour (Fig. 1B). The rebound of the luminal concentration observed at 80 min can be explained by the marked enterohepatic circulation of this drug (Sjöstrand and Schmiterlöw, 1968). Again, because of the limited number of data available, no model was developed that represents this phenomenon and the absorption constants were approximated by linear regression of the first and last values of each profile.

Table 2 summarizes the models observed for the 9 drugs tested with the corresponding pharmacokinetic constants and lists the apparent partition coefficient K_{app} values between pH 6.0 phosphate buffer and tributyrin or tricaprylin. The K_{app} values would be somewhat lower than if octanol had been used as an oily phase as indicated by the higher value measured for theophylline with this solvent ($K_{app} = 1.06$). The pH 6.0 phosphate buffer appropriately simulates the pH conditions of the intestinal lumen. However, a more acidic environment is created by the glycocalyx at the surface of the enterocytes (Lucas et al., 1975; Lei et al., 1977; Swanston et al., 1977; Schurgers and De Blaey, 1984). Therefore, the unionized fractions of the drugs were calculated both at the luminal pH of 6.0, and at pH 5.5, the value measured at the absorbing surface under the present conditions (Schurgers, 1983). It appears that oxyphenbutazone is much less ionized at the latter pH value, while the other drugs remain unionized at both values, as shown in Table 3. The pK_a of the remaining xanthines were unknown

TABLE 3

Unionized fractions of the studied drugs at pH 6.0 and 5.5

Drug	pK_a	pK_b	pH 6.0		pH 5.5	
			$1-\alpha_a$	$1-\alpha_b$	$1-\alpha_a$	$1-\alpha_b$
Oxyphenbutazone	4.7	–	0.05	–	0.14	–
Pyrazinamide	–	0.5	–	0.99	–	0.99
Isoniazid	–	2.2	–	0.99	–	0.99
	–	3.8	–	0.99	–	0.98
Theophylline	8.8	3.5	0.99	0.99	0.99	0.99

but were assumed to be similar to that of theophylline (Herzfeldt, 1980):

As oxyphenbutazone is 3 times less ionized at the surface pH, its partition coefficient was corrected using Eqn. 4 (Wang and Lien, 1980).

$$K_{app_{5.5}}/1 - \alpha_{5.5} = K_{app_{6.0}}/1 - \alpha_{6.0} \quad (4)$$

These corrected values for oxyphenbutazone are in Table 2.

As the partition coefficient increases, it appears that the model that better fits the absorption data becomes more complicated; highly lipophilic drugs (oxyphenbutazone, pentifylline) probably show a distribution phase in the intestinal wall, while hydrophilic ones (isoniazid, etofylline, diprophylline) do not. Drugs with intermediate character, like pentoxifylline or theophylline, show high absorption rates which strongly depend on external factors, such as changes in mesenteric blood flow or bile salt secretion and micelle formation. Such phenomena might explain the sudden reduction of the absorption rate of this kind of solute during our experiments, and have been reported by Schurgers and de Blaey (1984) for theophylline.

Relation between absorption and partitioning

As mentioned before, oxyphenbutazone exhibits two-compartment kinetics and can be assumed to penetrate quickly into the intestinal wall, to distribute in it and then to reach the blood at a much slower rate. Therefore, its "true" absorption rate constant k_2 will correspond to the second step, k_1 being called the "apparent" absorption rate constant. For the other drugs, the "true" absorption constant can be considered as being k_1 because their disappearance from the intestinal lumen corresponds to their appearance in the blood. In the case where two slopes were observed, k_2 was assumed to depend on physiological modifications and not on real physicochemical properties of the drug and was disregarded.

Fig. 2 shows the relation between the apparent partition coefficients and the "true" absorption constants. Such parabolic relations were previously described by Lien (1970, 1975) and Lien et al. (1971) and correspond to Eqns. 5 and 6 for tributyrin and tricaprylin, respectively:

$$\log k = 0.205 + 0.102 \log K_{app} - 0.140 \log^2 K_{app} \quad (5)$$

$$(r = 0.808, \quad P \leqq 0.05)$$

$$\log k = 0.296 - 0.035 \log K_{app} - 0.206 \log^2 K_{app} \quad (6)$$

$$(r = 0.909, \quad P \leqq 0.01)$$

The correlation is less satisfactory with the partition coefficients obtained with tributyrin (Fig. 2A) than with tricaprylin (Fig. 2B) and is due to the outlier isoniazid. Without the latter, the correlation coefficient would be 0.955 and the significance $P \leqq 0.01$. The values of the optimal partition coefficient K_{opt} can be calculated from the two equations above and are 0.66 (0.29–1.51, 95% confidence interval) for tributyrin and 0.36 (0.16–0.76, 95% confidence interval) for tricaprylin. The scatter of the points around the parabola is responsible for the wide confidence intervals.

When only the "apparent" absorption constants k_1 of oxyphenbutazone are included, the relations between K_{app} values and absorption constants take a hyperbolic shape (Fig. 3A and 3B).

This type of relation was analysed by Wagner and Sedman (1973) and Wagner (1975), and is described by Eqn. 7:

$$k_1 = \frac{k_{um}(K_{app})^n}{Q + (K_{app})^n} \quad (7)$$

where k_{um} is the maximum rate at which the drug is extracted from the membrane and n and Q are constants for the specific solvent system used in the determination of K_{app}. With increasing lipophilicity k_1 tends towards a plateau represented by k_{um}. The initial values of the parameters can be estimated by iteration, using the logarithmic form of Eqn. 7:

$$\log \frac{k_1}{k_{um} - k_1} = n \log K_{app} - \log Q \quad (8)$$

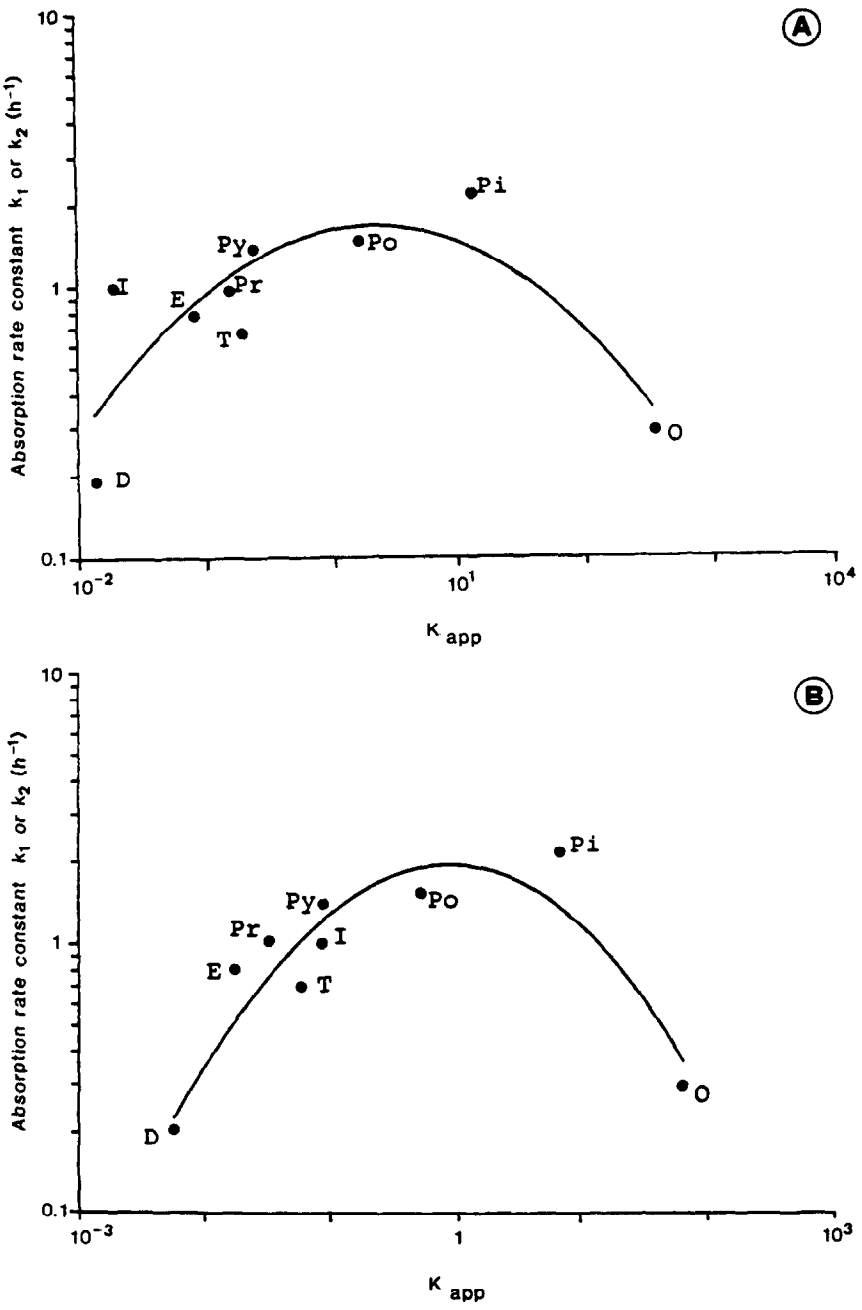

Fig. 2. Relationship between K_{app} values measured with (A) tributyrin, (B) tricaprylin, and "true" intestinal absorption rate constants. D, diprophylline; I, isoniazid; E, etofylline; T, theophylline; Pr, proxyphylline; Py, pyrazinamide; Po, pentoxyfylline; Pi, pentifylline; O, oxyphenbutazone.

The exact values of the parameters are then determined by non-linear regression (Wood, 1979). With the present data, the values of the parameters for tributyrin and tricaprylin were, respectively:

$k_{um} = 5.1$ and 6.6 min $^{-1}$

$n = 0.29$ and 0.27

$Q = 2.6$ and 2.8

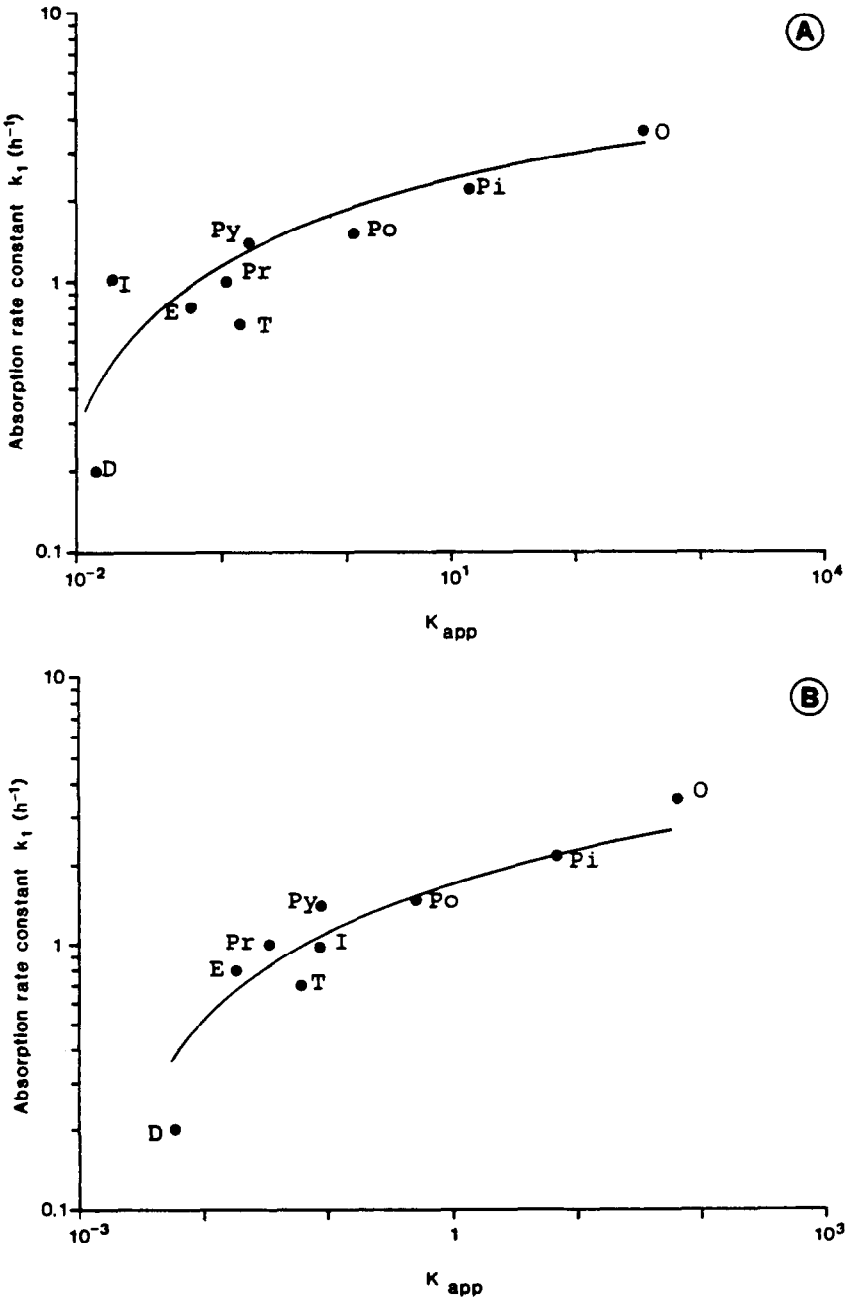

Fig. 3. Relationship between K_{app} values measured with: (A) tributyrin, (B) tricaprylin, and "apparent" intestinal absorption rate constants. Abbreviations: see Fig. 2.

Discussion

Two types of correlation were observed between the partition coefficients and the absorption constants, depending on the nature of the latter parameter measured in situ. The penetration constant k_1 of a drug into the intestinal wall increases with the partition coefficient K_{app} until it becomes limited by blood extraction on the serous side, as suggested by Wagner and Sedman (1973) and Wagner (1975) or by the increasing influence of the unstirred water layer as proposed by Suzuki et al. (1970), Ho et al. (1972), Higuchi et al. (1979) and Taylor et al. (1985). Strongly lipophilic drugs, like oxyphenbutazone, exhibit a distribution phase inside the intestinal wall. This two-compartmental behaviour has been observed with other drugs of this category (Doluisio et al., 1969; Crevoisier, 1974; Schurgers, 1983; Schurgers and de Blaey, 1984). In this case, the "true" absorption rate constant k_2 is much smaller than the penetration rate constant k_1. Solutes possessing an intermediate oil affinity, like theophylline or pentoxifylline, are quickly absorbed by one-compartment kinetics but absorption strongly depends on intestinal blood flow and on the aqueous unstirred layer which may change during in situ perfusion experiments. The concentration decay in the lumen is monoexponential but may show an inflexion during the experiment. Absorption of hydrophilic drugs, like diprophylline, etofylline, isoniazid, proxyphylline or pyrazinamide, is controlled by the penetration step into the intestinal barrier, which therefore determines the true absorption constant.

When "true" absorption constants of lipophilic drugs are measured from the final portion of the profile, the relation with the partition coefficient takes the form of a parabola with an optimal lipophilicity value. The latter depends of course on the organic solvent used as a reference for the lipophilic phase. Linear relations between these parameters have been described for example with xanthines (Sanvordeker et al., 1977; Blanchard et al., 1984; Kakemi et al., 1967; Augustine and Swarbrick, 1972), sulfonamides or cardiac glycosides (Hempelmann et al., 1978). However, Hansch and Clayton (1973), Lien (1975) and Kubinyi (1979) agree with the opinion that linear relations are portions of non-linear relationships where only a small group of representative partition coefficients has been considered. A false interpretation of the first disappearance constant observed in situ as the "true" absorption constant may also be an explanation for this discrepancy. With "true" absorption constants of lipophilic drugs and over a large scale of partition coefficients, over 5 powers of 10 as in the present study, an optimal partition coefficient is observed. Hansch and Clayton (1973) and Kubinyi (1979) ascribe this phenomenon to an optimal lipophilicity of a solute enabling it to diffuse through successive oily and aqueous barriers, whereas Pla-Delfina and Moreno (1981) explain it by a sudden attainment of a critical molecular size. As a matter of fact, there is a relation between the molecular size and the partition coefficient. When very different chemical species are studied, as in this case, molecular size and steric hindrance may overimpose their influence on the general effect of the partition coefficient, even if corrections are made for local pH and ionization, and may produce a larger scatter around the observed correlations. Indeed, more satisfactory correlation coefficients are obtained with drugs belonging to the same basic structure as was demonstrated with carbamates (Houston et al., 1975; Wood et al., 1979; Yoshimura and Kakeya, 1983). More heterogeneous groups lead frequently to a greater scatter of points around the observed model, as for sulfonamides or a series of basic drugs (Lien, 1975) and more developed models have been proposed, with limitation of the necessary number of observations (Hwang et al., 1976; Higuchi et al., 1979; Pla-Delfina and Moreno, 1981). Nevertheless, more simple models, as used in this study, well describe the observed data and help understand or predict the behaviour of these drugs when administered in conjunction with lipidic vehicles.

Finally, the choice of the oily phase to simulate physiological membranes should not influence the general scheme but changes only the K_{app} value of each model drug in a certain direction, depending on its polarity. For example, using octanol as a solvent would have led to a somewhat higher K_{opt}. However, as demonstrated here with two different

triglycerides, k_{um} values would probably have been identical. Similar conclusions have been drawn by Martin (1981).

Conclusion

Until now, numerous studies have investigated the relationship between the absorption of drugs and their partitioning into oily phases. Different theories were advanced to explain the observed data. To our opinion, these discrepancies are mainly due to insufficient pharmacokinetic analysis of the drug profiles measured in situ. When "true" absorption constants are determined, there appears to be an optimum partition coefficient, whose value depends on the nature of the oily phase chosen to simulate the lipidic components of membranes. However, great efforts still have to be made to evaluate such factors as blood perfusion and interaction with mucus, in order to achieve better correlations and more precise predictions on drug absorption with an intestinal in situ perfusion model.

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