International Journal of Pharmaceutics, 46 (1988) 95–102
Elsevier

IJP 01552

The liposome as a distribution model in QSAR studies

G.V. Betageri and J.A. Rogers

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alta. (Canada)

(Received 17 August 1987)
(Modified version received 7 January 1988)
(Accepted 16 February 1988)

Key words: Partitioning; Liposome; *n*-Octanol; β-blocker; Pharmacokinetic correlation; Corneal penetration

Summary

Quantitative structure–activity relationships (QSAR) were determined for β-adrenoceptor blocking agents based on their published pharmacokinetic properties and corneal penetrations, and experimental partition coefficients in the *n*-octanol-buffer and liposome systems. Apparent partition coefficient (K'_m) correlations were better than the intrinsic (or ion-corrected) values (K_m) in liposomes ($P < 0.01$) and in the *n*-octanol-buffer system ($P < 0.05$). The hydrophobic properties of these drugs appear to be the primary determinants of their pharmacokinetic and corneal penetration behaviour. Liposomes of various compositions yielded better correlations in all cases than the *n*-octanol-buffer system, but a DMPC/CHOL/DCP (7 : 2 : 1 mole ratio) liposome composition yielded the best results with pharmacokinetic parameters whereas a DMPC/CHOL (1 : 1 mole ratio) composition was superior in correlations of corneal penetration. When the values of the pharmacokinetic parameters and corneal penetration behaviour of the β-blockers were predicted from regression analysis of K'_m, the error was considerably less in the liposome system (9–29%) compared to the *n*-octanol-buffer system (24–192%). It is concluded that the model liposome partitioning system is more versatile and selective than the *n*-octanol-buffer system in predicting biological activities of the β-blocker drugs.

Introduction

The design of drugs having optimal activities requires an understanding of drug behaviour in biological systems as well as the experimental relationships between their chemical structure and physicochemical properties. The relationship between structure and activity (SAR) has been described in qualitative terms for some time. In 1963, Hansch and coworkers introduced structure–activity relationships in quantitative terms (QSAR) and the development of QSAR has been the subject of several reviews (McFarland, 1971; Redl et al., 1974; Cramer, 1976; Toplis and Fukunaga, 1978; Martin, 1979; Kubinyi, 1979). During the last two decades, lipophilicity has been the most frequently described property of compounds used in QSAR. Partition coefficients (K) have been measured extensively in the *n*-octanol–water system and various elaborate approaches have been developed to describe the activity of lipophilic group contributions (Rekker, 1977; Hansch and Leo, 1979). Other oil–water systems have been suggested but none of these appear to be as appropriate as the *n*-octanol–water system (Anderson et al., 1981).

Correspondence: J.A. Rogers, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alta., Canada T6G 2N8.

It is unclear what facet of overall drug activity is the basis of successful correlations of the *n*-octanol–water partition coefficient and it has been emphasized that various absorption phenomena involving the passage of drugs across biological membranes are not well modeled by the *n*-octanol–water distribution coefficient (Martin, 1981). Furthermore, the activity of a series of molecules as a function of hydrophobicity gives a parabolic response indicating that high levels of hydrophobicity can inhibit the desired biological response (Gillette and Pang, 1980).

As an alternative, phospholipid vesicles (liposomes) have been investigated as a model system to study solute distribution into membranes since these closely resemble the ordered structural features of biological membranes (Katz and Diamond, 1974a; Rogers and Davis, 1980; Ahmed et al., 1985). Depending on the nature of the solute, correlation with biological activity may occur above or below the phospholipid phase transition temperature (T_c) which clearly suggests that structure and order within the phospholipid bilayers is an important determinant of the extent of solute interaction (Wright and Bindslev, 1976).

Liposomes have been used previously as a model membrane system and the contributions of substituents to the thermodynamics of partitioning of alcohols, phenols, phenothiazines and β-blockers in dimyristoylphosphatidylcholine (DMPC)/physiological saline systems have been studied in some detail (Katz and Diamond, 1974a; Rogers and Davis, 1980; Anderson et al., 1983; Ahmed et al., 1985; Betageri and Rogers, 1987). Usually, a significant decrease in the K is observed upon cooling the liposomes below the T_c of the phospholipid. Wright and Bindslev (1976) demonstrated that permeation rates of solutes across the toad bladder were more closely related to vesicle–water distribution data when vesicles were below the T_c. In contrast, the liposome partitioning of a series of chloramphenicols has been reported to yield a better correlation with their biological activities above the T_c and also in comparison to the *n*-octanol–water system (Brown and Brown, 1984).

Thus, an objective of the present study was to determine the appropriateness of the *n*-octanol–water system versus the liposome system as a suitable membrane model for distribution studies of drugs using a series of β-adrenoreceptor blocking agents. Assessment has been made from correlations of their partition coefficients with pharmacokinetic parameters and corneal penetration behaviours.

Materials and Methods

Materials

The β-blockers used in this study were obtained as follows: propranolol hydrochloride, B.P. (PPL) (Ayerst Laboratories, Montreal, Canada); acebutolol hydrochloride (ABL) (May and Baker, U.K.); atenolol (ATL) (ICI, U.K.); metoprolol hydrochloride (MPL) and oxprenolol hydrochloride (OPL) (Ciba-Geigy Canada); nadolol (NDL) (Squibb Canada); pindolol (PDL) (Sandoz Canada); bupranolol hydrochloride (BPL) (Sanol Schwarz GmbH); toliprolol hydrochloride (TPL) (Boehringer-Ingelheim Canada); alprenolol hydrochloride (APL) (Hassle, Sweden). Petroleum ether (Fisher Scientific Co., NJ), methanol (Caledon Lab, Canada) and *n*-octanol (BDH, Toronto, Canada) were all reagent grade. L-α-Dimyristoylphosphatidylcholine, 99% (DMPC), L-α-dipalmitoylphosphatidylcholine, 98$^+$% (DPPC), cholesterol (CHOL) and dicetylphosphate (DCP) (Sigma Chemical Co., St. Louis, MO) were used as received. All other chemicals used were reagent grade and water was glass-distilled.

Methods

Distribution studies in the n-octanol-buffer system. Mutually-saturated aqueous phase (5 ml isotonic phosphate buffer, pH 7.4) to which drug was subsequently added (0.2–1.4 mM) and *n*-octanol (0.5 ml) were weighed into 25 ml round-bottom flasks and equilibrated for 4 h at 37 ± 0.5 °C (Dubnoff metabolic shaker-bath). Concentrations of drug in the aqueous phase were determined by UV spectrophotometry (Pye Unicam SP6-550 spectrophotometer) for each of the drugs at λ_{max}. The concentration of drug in the oil phase was determined from mass balance calculations. The determination of the distribution of each drug was

obtained from the average of duplicate determinations.

Distribution studies in liposome systems. Films were formed on the walls of 50 ml round-bottom flasks following rotary evaporation of 5 ml aliquots of a petroleum ether–methanol stock solution of lipids (10 mg/ml) and subsequent overnight drying in a vacuum oven at 30 °C. The resulting dried films were dispersed in 5 ml aliquots of isotonic, aqueous, phosphate buffer solution (pH 7.4) containing drug (0.2–1.4 mM) at 40–45 °C followed by vortex-mixing for 10 min. This resulted in the formation of multilamellar liposomes (MLVs). The distribution of the drug was determined in 24 h temperature-equilibrated MLVs (3.5 ml; 37 °C) following centrifugation (143,000 *g*, 30 min) (Beckman Model L8-55 Ultracentrifuge) at 37 °C from UV analysis and mass balance calculations. Determinations were made in duplicate and the results averaged. At these concentrations no evidence of adsorption of drug at liposome surfaces was found (Betageri and Rogers, 1987).

Determination of partition coefficients. The apparent molal partition coefficients, K'_m, were calculated from the distribution results by employing Eqn. 1:

$$K'_m = \frac{(C_T - C_w)w_1}{C_w W_2} \quad (1)$$

where C_T = the total initial concentration of drug (mg/ml) in the aqueous buffer phase before equilibration, C_w = final aqueous phase concentration of drug (mg/ml), w_1 = weight (g) of aqueous phase, and w_2 = weight (g) of phospholipid in the sample. Intrinsic (or ion-corrected) partition coefficients were calculated from:

$$K_m = K'_m(1 + 10^{pK_a - 7.4}) \quad (2)$$

using published values of the pK_a of each beta blocker (Betageri and Rogers, 1987).

Statistical analysis

Statistics based on the two-sided *t*-test were used to evaluate the significance of the coefficient of determination obtained in the regressions. Levels of $P < 0.05$ were considered to be significant.

Results and Discussion

Values of K'_m and K_m of ten beta blockers in the *n*-octanol-buffer system and liposomes of different phospholipid compositions are given in Table 1. In all cases, it can be seen that in liposomes partition coefficients are considerably greater than in the *n*-octanol-buffer system. A K'_m of nadolol could not be detected in the *n*-octanol-buffer system and liposomes of DMPC/CHOL (1 : 1 mole ratio) whereas this drug partitioned into liposomes of other phospholipid compositions. Generally, it is expected that the addition of CHOL to liposomes or increasing the hydrocarbon chain length of the phospholipid will decrease the permeability to solutes (De Gier, 1970). In addition, it can be seen in Table 1, that decreased partitioning of the β-blockers in DMPC/CHOL and DPPC liposomes also occurs. In liposomes possessing a negative surface charge, as occurs by the addition of DCP, the partitioning is increased, likely due to electrostatic interaction between the cationic drug molecules and negative centres of charge on the liposome surfaces (Surewicz and Leyko, 1981). Hydrogen bonding interactions between water and atenolol and acebutolol which contain amido groups, and nadolol which has two additional hydroxy groups, could account for the low partition coefficient values obtained for these compounds. The relatively high partition coefficient of propranolol can be attributed mostly to the double aromatic ring in its structure.

Correlations between n-octanol-buffer and liposome partitioning

Regression analyses of (K'_m) and (K_m) in the *n*-octanol-buffer system and various liposome compositions were made and the results are presented in Table 2. The slope '*a*' from such a plot has previously been described as a selectivity constant (Katz and Diamond, 1974b). A low value is indicative of partitioning into a region of the lipid bilayers which is somewhat less hydrophobic than *n*-octanol. Generally, the intercept '*b*' (= log K'_m or log K_m) indicates the degree of affinity of the solutes for the bilayers compared to *n*-octanol. Correlation coefficients (r) were significant at the $P < 0.01$ level when either log K'_m or log K_m

TABLE 1

Apparent (log K'_m) and intrinsic (ion-corrected) (log K_m) partition coefficients of β-blockers in the n-octanol-buffer and liposome systems at 37°C and pH 7.4

β-blocker	log K'_m					log K_m				
	n-Octanol-buffer system	Liposome compositions [a]				*n*-Octanol-buffer system	Liposome compositions [a]			
		I	II	III	IV		I	II	III	IV
Nadolol	–	0.80	0.64	–	1.00	–	3.07	2.91	–	3.27
Pindolol	0.08	1.42	1.30	0.49	1.17	1.57	2.92	2.80	1.98	2.66
Atenolol	−0.11	1.09	0.32	0.56	0.37	2.04	3.24	2.41	2.72	2.53
Metoprolol	0.20	1.23	1.28	1.49	1.25	2.49	3.51	3.56	3.77	3.53
Acebutolol	0.48	0.65	0.66	0.69	0.90	2.75	2.92	2.93	2.96	3.16
Toliprolol	0.58	1.54	1.12	0.94	1.68	2.78	3.74	3.33	3.14	3.88
Oxprenolol	0.72	1.54	1.25	1.33	1.57	2.83	3.65	3.35	3.43	3.68
Bupranolol	1.25	2.51	1.86	1.55	2.48	3.45	4.71	4.06	3.75	4.68
Propranolol	1.49	2.62	2.00	1.52	3.03	3.54	4.68	4.06	3.58	5.09
Alprenolol	1.34	2.23	1.60	1.42	2.36	3.57	4.46	3.84	3.66	4.60

[a] I = DMPC; II = DPPC; III = DMPC/CHOL (1 : 1 mole ratio); IV = DMPC/CHOL/DCP (7 : 2 : 1 mole ratio).

values were used, except for DMPC/CHOL (1 : 1 mole ratio) liposomes. In a similar manner, correlations have been shown between the *n*-octanol–water system and DMPC liposomes using chloramphenicol congeners (Brown and Brown, 1984). The best correlation with beta blockers was found between log K'_m values of *n*-octanol-buffer and DMPC/CHOL/DCP (7 : 2 : 1 mole ratio) liposomes.

TABLE 2

Linear regression parameters from correlations of apparent (K'_m) or intrinsic (ion-corrected) (K_m) partition coefficients of 9 β-blockers in the n-octanol-buffer system and various liposome compositions

Liposome composition [a]	log K'_m			
	b	*a*	*r*	*P*
DMPC	0.99	0.99	0.85	< 0.01
DPPC	0.75	0.76	0.81	< 0.01
DMPC/CHOL (1 : 1)	0.57	0.73	0.75	< 0.05
DMPC/CHOL/DCP (7 : 2 : 1)	1.38	0.72	0.94	< 0.01
	log K_m			
DMPC	1.25	0.90	0.87	< 0.01
DPPC	1.40	0.71	0.87	< 0.01
DMPC/CHOL (1 : 1)	1.22	0.72	0.83	< 0.01
DMPC/CHOL/DCP (7 : 2 : 1)	0.34	1.23	0.94	< 0.01

[a] Mole ratios in brackets.

Correlations between partition coefficients and pharmacokinetic parameters

Regression parameters from correlations of log K'_m or log K_m in the *n*-octanol-buffer system and pharmacokinetic parameters in humans (Hinderling et al., 1984) are listed in Table 3 and, similarly, regression parameters in liposomes of DMPC/CHOL/DCP are listed in Table 4. There was a significant correlation for 6 of 7 pharmacokinetic parameters in liposomes ($P < 0.01$) and *n*-octanol-buffer ($P < 0.05$) using log K'_m values. On the other hand, when log K_m values were used again 6 pharmacokinetic parameters gave significant correlations in liposomes; however, only one pharmacokinetic parameter gave a significant correlation in the *n*-octanol-buffer system (Table 3). The best correlation in the *n*-octanol-buffer and liposome systems was obtained using the ratio of the fraction of drug bound and unbound to albumin (r_A). Furthermore, correlations were better when log K'_m values were used in both the *n*-octanol-buffer and liposome systems. These results indicate that the hydrophobic property is the primary determinant of the pharmacokinetic parameters since the range of pK_as is 8.80–9.67. This is also in accordance with the results of published studies on structure and pharmacokinetic relationships (Craig and Welling, 1976; Jusko and Gretch, 1976; Seydel et al., 1980; Hinderling et al., 1984).

TABLE 3

Linear regression parameters from correlations of apparent (K'_m) or intrinsic (ion-corrected) (K_m) partition coefficients in the n-octanol-buffer system and pharmacokinetic parameters of β-blockers

Log pharmacokinetic parameters [a,b]	log K'_m			
	b	*a*	*r*	*P*
K_P	0.70	1.31	0.76	< 0.05 ($n = 7$)
r_A	−0.83	0.54	0.95	< 0.05 ($n = 7$)
r_G	−0.69	0.72	0.70	–
K_{BC}	−0.01	0.51	0.84	< 0.05 ($n = 7$)
V_{USS}	2.08	0.58	0.81	< 0.05 ($n = 7$)
r_T	0.43	0.61	0.85	< 0.05 ($n = 6$)
r	−0.29	1.40	0.87	< 0.05 ($n = 7$)
	log K_m			
K_P	−0.57	0.73	0.58	–
r_A	−1.39	0.35	0.79	–
r_G	−1.28	0.41	0.52	–
K_{BC}	−0.69	0.37	0.72	–
V_{USS}	1.36	0.40	0.66	–
r_T	−0.48	0.48	0.79	–
r	−2.42	1.11	0.81	< 0.05 ($n = 7$)

[a] K_P = partition coefficient of drug between plasma protein and plasma water; r_A = ratio of the fraction of drug bound and unbound to albumin; r_G = ratio of the fraction of drug bound and unbound to α_1-acid glycoprotein; K_{BC} = true erythrocyte partition coefficient; V_{USS} = steady-state volume of distribution referenced to the unbound drug in plasma; r_T = ratio of the fraction of drug bound and unbound to tissue; r = ratio of the fraction of drug non-renally and renally eliminated.

[b] Obtained from Hinderling et al. (1984).

Correlations between partition coefficient and corneal penetration behaviour

Regression analyses were performed using partition coefficients (K'_m) or (K_m) and corneal penetration behaviour (Schoenwald and Huang, 1983) of β-blockers in rabbits and the results are shown in Table 5. The best correlation was found with liposomes of DMPC/CHOL composition whereas there was no significant correlation when *n*-octanol-buffer values were used. In comparison, in the case of steroids and *n*-alkyl *p*-aminobenzoate homologues the correlation between partition coefficients in *n*-octanol/water systems and corneal penetration behaviour were parabolic (Schoenwald and Ward, 1978; Mosher and Mik-

TABLE 4

Linear regression parameters from correlations of apparent (K'_m) and intrinsic (ion-corrected) (K_m) partition coefficients in DMPC/CHOL/DCP (7:2:1 mole ratio) liposomes and pharmacokinetic parameters of β-blockers

Log pharmacokinetic parameters [a]	log K'_m			
	b	*a*	*r*	*P*
K_P	0.07	0.86	0.84	< 0.01 ($n = 8$)
r_A	−1.26	0.45	0.98	< 0.01 ($n = 5$)
r_G	−1.09	0.51	0.62	–
K_{BC}	−0.20	0.33	0.79	< 0.05 ($n = 7$)
V_{USS}	1.75	0.45	0.94	< 0.01 ($n = 7$)
r_T	0.11	0.45	0.92	< 0.01 ($n = 7$)
r	−1.07	1.02	0.88	< 0.01 ($n = 8$)
	log K_m			
K_P	−1.30	0.73	0.75	< 0.05 ($n = 8$)
r_A	−1.74	0.34	0.88	< 0.05 ($n = 5$)
r_G	−1.49	0.34	0.50	–
K_{BC}	−0.78	0.30	0.76	< 0.05 ($n = 7$)
V_{USS}	0.96	0.40	0.88	< 0.01 ($n = 7$)
r_T	−0.78	0.43	0.92	< 0.01 ($n = 7$)
r	−3.06	0.98	0.87	< 0.01 ($n = 8$)

[a] See footnote to Table 3 for definition of symbols.

TABLE 5

Linear regression parameters from correlations of apparent (K'_m) or intrinsic (ion-corrected) (K_m) partition coefficients in the n-octanol buffer or various liposome systems and corneal penetration behavior of β-blockers

Partitioning system [a]	log K'_m			
	a	*b*	*r*	*P*
n-Octanol-buffer	1.02	−5.70	0.68	–
DMPC	1.01	−6.62	0.81	–
DPPC	1.37	−6.68	0.94	< 0.01 ($n = 6$)
DMPC/CHOL (1:1)	1.97	−7.33	0.99	< 0.01 ($n = 5$)
DMPC/CHOL/DCP (7:2:1)	0.80	−6.35	0.82	< 0.05 ($n = 6$)
	log K_m			
n-Octanol-buffer	1.13	−8.21	0.68	–
DMPC	1.17	−9.37	0.83	< 0.05 ($n = 6$)
DPPC	1.46	−9.97	0.92	< 0.01 ($n = 6$)
DMPC/CHOL (1:1)	1.94	−11.50	0.93	< 0.05 ($n = 5$)
DMPC/CHOL/DCP (7:2:1)	0.85	−8.27	0.81	< 0.05 ($n = 6$)

[a] Mole ratios in brackets.

kelson, 1979). Again, correlation coefficients were higher when log K'_m values were used (Table 5), suggesting that hydrophobicity is the primary factor for their corneal penetration. These results also indicate a limitation in the use of the *n*-octanol-buffer system in QSAR studies whereas the liposome system has been demonstrated as having better overall usefulness in QSAR studies. The advantage of the liposome system is that its structure can be altered in terms of charge, permeability and size which is not possible in an oil/water system. Correlation studies with pharmacokinetic properties or corneal penetration behavior clearly indicate the differences in the interactions of β-blockers with different biological membranes. The charged liposome model gave the best correlation with pharmacokinetic parameters whereas liposomes having decreased fluidity and a more ordered structure better described corneal penetration behaviour.

Predictability of pharmacokinetic parameters and corneal penetration behaviour

Predictions of the values of the pharmacokinetic parameters, V_{USS}, r_A, and corneal penetration behaviour were attempted in the *n*-octanol-buffer and liposome systems of different phospholipid compositions (Tables 6–8). The predictions were made by using previously obtained regressions of the pharmacokinetic parameters and corneal penetration behaviour with K'_m or K_m. If this procedure allowed estimates of sufficient precision, the biological properties of a new compound could be predicted in vivo provided that in vivo–in vitro relationships were known for a sufficient number of congeners and that the in vitro characteristics of new compounds were within the boundaries of the tested congeners. Rational drug design would then be possible.

Comparison of predicted values of pharmacokinetic parameters with literature values (Hinderling et al., 1984) shows that DMPC, DPPC and DMPC/CHOL/DCP liposome systems are superior to the *n*-octanol-buffer system for predicting V_{USS} while DPPC and DMPC/CHOL/DCP were better in predictions of r_A. The least average % error was found with liposomes of DMPC/CHOL/DCP. These results indicate that the pharmacokinetic behaviour of a new β-blocker can be reasonably predicted when a negatively-charged liposome system is used in distribution studies.

In addition, the prediction of the corneal penetration behaviour of β-blockers in rabbits was best obtained from liposomes of any composition studied rather than the *n*-octanol-buffer system. Furthermore, the corneal penetration behaviour of

TABLE 6

Comparison of membrane-predicted and literature values of steady-state volumes of distribution (V_{USS}) of β-blockers

β-Blocker	Predicted (V_{USS}, L) [a]					Lit. values [b]
	n-Octanol-buffer system	I	II	III	IV	
Propranolol	864	1606	941	567	1271	1950
Alprenolol	708	226	514	483	636	316
Metoprolol	156	226	316	540	202	240
Pindolol	133	295	326	109	186	200
Nadolol	–	123	120	–	156	186
Acebutolol	226	100	124	150	141	126
Atenolol	103	185	74	122	82	79
Ave. % error	59	33	39	78	23	

[a] Using regression equations from Table 3 and 4.
[b] Hinderling et al. (1984).

I = DMPC liposomes; II = DPPC liposomes; III = DMPC/CHOL (1 : 1 mole ratio) liposomes; IV = DMPC/CHOL/DCP (7 : 2 : 1 mole ratio) liposomes.

TABLE 7

Comparison of membrane-predicted and literature values of the ratio of fraction of β-blocker bound and unbound to albumin (r_A)

β-Blocker	Predicted r_A [a]					Lit. values [b]
	n-Octanol-buffer system	I	II	III	IV	
Propranolol	0.94	1.13	1.36	0.47	1.26	1.23
Alprenolol	0.78	0.26	0.51	0.44	0.63	0.66
Oxprenolol	0.36	0.36	0.21	0.41	0.28	0.29
Pindolol	0.16	0.31	0.24	0.21	0.19	0.22
Metoprolol	0.19	0.26	0.23	0.46	0.20	0.16
Ave. % error	24	50	23	62	9	

[a] Using regression equations from Tables 3 and 4.
[b] Hinderling et al. (1984).

I = DMPC liposomes; II = DPPC liposomes; III-DMPC/CHOL (1:1 mole ratio) liposomes; IV = DMPC/CHOL/DCP (7:2:1 mole ratio) liposomes.

a new beta blocker can be predicted best from DMPC/CHOL liposomes.

It is concluded that both the *n*-octanol-buffer and the liposome system can be employed to measure the relative hydrophobicities of congeners of drugs in a series but the oil/water system is too simplified a model to describe the properties of drug–membrane interactions which are important in membrane uptake and transport of drugs. Also, the structure and composition of liposomes provide for a more versatile model of the biological behavior of drugs than the *n*-octanol-buffer system even though each may possess a similar hydrophobic environment.

TABLE 8

Comparison of membrane-predicted and literature values of the corneal penetration (P_T) behavior of β-blockers

β-Blocker	Predicted (P_T; cm/s×10^6) [a]					Lit. values [b]
	n-Octanol buffer system	I	II	III	IV	
Propranolol	66.4	110.0	116.0	45.5	115.0	57.5
Oxprenolol	10.8	8.84	10.8	19.3	7.9	27.5
Metoprolol	3.19	4.29	11.9	39.8	4.39	24.0
Nadolol	–	1.57	1.57	–	2.78	1.02
Acebutolol	6.17	1.11	1.67	1.06	2.31	0.85
Atenolol	1.54	3.09	0.57	0.59	0.88	0.68
Ave. % error	192	142	70	29	149	

[a] Using regression equations from Table 5.
[b] Schoenwald and Huang (1983).

I = DMPC liposomes; II = DPPC liposomes; III = DMPC/CHOL (1:1 mole ratio) liposomes; IV = DMPC/CHOL/DCP (7:2:1 mole ratio) liposomes.

Acknowledgements

An award of an Alberta Heritage Foundation for Medical Research Studentship to G.V.B. is gratefully acknowledged. Gifts of β-blockers from the pharmaceutical companies identified under Materials and Methods are greatly appreciated.

References

Ahmed, A.M.S., Farah, F.H. and Kellaway, I.W., The thermodynamics of partitioning of phenothiazines between phosphate buffer and the lipid phases of cyclohexane, *n*-octanol and DMPC liposomes. *Pharm. Res.*, (1985) 119–124.

Anderson, N.H., James, M. and Davis, S.S., Pharmaceutical applications of solvent extraction and ion exchange. *Chem. Ind.*, (1981) 677–680.

Anderson, N.H., Davis, S.S., James, M. and Kojima, I., Thermodynamics of distribution of *p*-substituted phenols between aqueous solution and organic solvents and phospholipid vesicles. *J. Pharm. Sci.*, 72 (1983) 443–448.

Betageri, G.V. and Rogers, J.A., Thermodynamics of partitioning of β-blockers in the *n*-octanol-buffer and liposome systems. *Int. J. Pharm.*, 36 (1987) 165–173.

Brown, R.E. and Brown, B.J., Liposome/saline partitioning for the chloramphenicol family of drugs. *QSAR Des. Bioact. compd., Prous Publ.*, Barcelona, 1984, pp. 13–24.

Craig, W.A. and Welling, P.G., Protein binding of antimicrobials, clinical pharmaokinetics and therapeutic implications. *Clin. Pharmacokin.*, 2 (1976) 252–268.

Cramer, R.D. III., Quantitative drug design. *Annu. Rep. Med. Chem.*, 11 (1976) 301–310.

De Gier, J., Regulation of membrane permeability by lipids. *Proc. 4th Int. Congr. Pharmacol., Basel*, 1970, pp. 102–106.

Gillette, J.R. and Pang, K.S., In M.E. Wolff (Ed.), Burger's Medicinal Chemistry, Part I, Wiley, New York, 1980, pp. 55–105.

Hansch, C., Muir, R.M., Fujita, T., Maloney, P.P., Geiger, F. and Streich, M., The correlation of biological activity of plant growth regulators and chloromycetin derivatives with Hammett constants and partition coefficients. *J. Am. Chem. Soc.*, 85 (1963) 2817–2824.

Hansch, C. and Leo, A., *Substituent Constants for Correlation Analysis in Chemistry and Biology,* Wiley, New York, 1979, pp. 18–43.

Hinderling, P.H., Schmidlin, O. and Seydel, J.K., Quantitative relationships between structure and pharmacokinetics of β-adrenoreceptor blocking agents in man. *J. Pharmacokin. Biopharm.,* 12 (1984) 263–287.

Jusko, W.J. and Gretch, M., Plasma and tissue protein binding of drugs in pharmacokinetics. *Drug. Metab. Rev.,* 5 (1976) 43–140.

Katz, Y. and Diamond, J.M., Thermodynamic constants for nonelectrolyte partition between dimyristoyl lecithin and water. *J. Membr. Biol.,* 17 (1974a) 101–120.

Katz, Y. and Diamond, J.M., Interpretation of nonelectrolyte partition coefficients between dimyristoyl lecithin and water. *J. Membr. Biol.,* 17 (1974b) 121–154.

Kubinyi, H., Lipophilicity and drug activity. *Prog. Drug. Res.* 23 (1979) 97–198.

Martin, Y.C., *Drug Design, Vol. VIII,* Academic, New York, 1979.

Martin, Y.C., A practitioner's perspective of the role of quantitative structure activity analysis in medicinal chemistry, *J. Med. Chem.,* 24 (1981) 229–237.

McFarland, J.W., On the understanding of drug potency, *Prog. Drug. Res.,* 15 (1971) 123–146.

Mosher, G.L. and Mikkelson, T.J., Permeability of the *n*-alkyl *p*-aminobenzoate esters across the isolated corneal membrane of the rabbit. *Int. J. Pharm.,* 2 (1979) 239–243.

Redl, G., Cramer, R.D. III and Berkoff, C.E., Quantitative drug design. *Chem. Soc. Rev.,* 3 (1974) 273–292.

Rekker, R.F., *The Hydrophobic Fragmental Constant,* Elsevier, Amsterdam, 1977, pp. 25–36.

Rogers, J.A. and Davis, S.S., Functional group contributions to the partitioning of phenols between liposomes and water. *Biochim. Biophys. Acta,* 598 (1980) 392–404.

Schoenwald, R.D. and Huang, H.S., Corneal penetration behavior of beta blocking agents I: Physicochemical factors. *J. Pharm. Sci.,* 72 (1983) 1266–1272.

Schoenwald, R.D. and Ward, R.L., Relationship between steroid permeability across excised rabbit cornea and octanol–water partition coefficients. *J. Pharm. Sci.,* 67 (1978) 786–792.

Seydel, J.K., Trettin, D., Wassermann, O. and Maliusz, M., Quantitative struktur-pharmacokinetik-beziehungen am biespiel von sulfonamidobenzolen und sulfanilamidopyridinen. *J. Med Chem.* 23 (1980) 607–613.

Surewicz, W.K. and Leyko, W., Interaction of propranolol with model phospholipid membranes. *Biochim. Biophys. Acta,* 643 (1981) 387–397.

Toplis, J.G. and Fukunaga, J.Y., Quantitative structure–activity relationships in drug design. *Annu. Rep. Med. Chem.,* 13 (1978) 292–303.

Wright, E.M. and Bindslev, N., Thermodynamic analysis of nonelectrolyte permeation across the toad urinary bladder. *J. Membr. Biol.,* 29 (1976) 289–312.