International Journal of Pharmaceutics, 45 (1988) 1–11
Elsevier

IJP 01497

Research Papers

The correlation of polymer–water and octanol–water partition coefficients: estimation of drug solubilities in polymers

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(Received 17 July 1987)
(Modified version received 4 November 1987)
(Accepted 20 November 1987)

Key words: Octanol–water partition coefficient; Polymer–water partition coefficient; Drug solubility; Polyethylene; Polydimethylsiloxane; Polyethylene-co-vinyl acetate; Poly-2-hydroxyethyl methacrylate; Poly-ε-caprolactone; Drug delivery

Summary

Extrathermodynamic relationships between the octanol–water and polymer–water partition coefficients of a number of solutes in 6 polymer–water systems were established:

$\log P$ (polymer–water) $= a \log P$ (octanol–water) $+ b$

The solutes were steroids, narcotic amines, and one barbiturate, with $\log P_{oct}$ values incrementally spanning the range from 1 to 4. The polymers were 5 rubbery polymers ($T_g < 37\,^\circ$C), polyethylene, polydimethylsiloxane, polyethylene-co-vinyl acetate, poly-ε-caprolactone, and poly-ε-caprolactam-co-ε-caprolactone, and one hydrogel, poly-2-hydroxyethyl methacrylate, with solubility parameters increasing from 15.1 to 25.5 $J^{1/2} \cdot cm^{-3/2}$. The slopes and intercepts of the correlation equations were shown to be proportional to the polymer polarity and to the logarithm of the solubility of water in the polymers, respectively. The log P correlations provided a means of estimating the relative solubilities of a new polymer ab initio. When combined with calculated or known aqueous drug solubilities, the correlations could be used to estimate absolute drug solubilities in a polymer.

Introduction

The controlled delivery of drugs from transdermal patches and subdermally implanted polymer capsules has become an accepted mode of drug administration, capable of enhancing the efficacy and acceptability of the medication (Chien, 1982). In the majority of systems now marketed or under development, it is intended that the rate of drug delivery be controlled by the rate of diffusion through a semipermeable polymer membrane. Provided the diffusion is Fickian, the drug flux is the product of the drug diffusion coefficient (D) and concentration gradient (dC/dx) in the polymer (Eqn. 1). The magnitude of D and dC/dx determines whether a practical delivery rate can be achieved with a particular drug/polymer combination.

$$dM/dt = -D \cdot dC/dx \quad (1)$$

A considerable body of evidence suggests that, for a given polymer, the value of D is determined

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primarily by the molecular volume of the solute or, for larger drugs, the molecular weight. This has been expressed as a log–log relationship, Eqn. 2.

$$\log D = a \log MW + b \quad (2)$$

In effect, this means that D can be treated as a constant for drugs in the molecular weight range 250–350, and the permeability is determined by dC/dx, the maximum value of which is the drug solubility (S_{pol}) in the polymer. Evidence supporting the validity of Eqn. 2, together with other methods of estimating D and S_{pol} from the molecular structure, has been reviewed (Pitt et al., 1987). The value of S_{pol} is more variable than D and, for solid drugs, its estimation requires knowledge of the enthalpy (ΔH_f) and entropy (ΔS_f) of fusion, or the assumption that ΔS_f can be treated as constant for a series of related structures. If the aqueous solubility (S_w) of the drug is known, it follows from Eqn. 3 that S_{pol} can be derived from the polymer–water partition coefficient (P_{pol}).

$$P_{pol} = C_{pol}\mu_{pol}/C_w\mu_w \simeq S_{pol}/S_w \quad (3)$$

The substitution of solubilities for thermodynamic activities in Eqn. 3 is an approximation, for it assumes that the activity coefficients (μ) of the solute in each phase deviate from unity to the same degree so that the value of P_{pol} is concentration independent The error associated with the use of concentration in place of activity is likely to be least severe at low concentrations, where $\mu \rightarrow 1$, and greatest at the saturation concentration. However, the use of partition coefficient to determine S_{pol} eliminates the need to consider heat of fusion terms, these already being embodied in the value of S_w.

This paper and earlier publications (Pitt et al., 1987; Bao et al., 1988) address the feasibility of deriving P_{pol} from the octanol–water partition coefficient (P_{oct}) of the drug using an extrathermodynamic relationship of the form of Eqn. 4 that has already been shown to apply to a variety of low-molecular-weight solute–solvent pairs (Leo and Hansch, 1971).

$$\log P_{pol} = a \log P_{oct} + b \quad (4)$$

An advantage of this method of estimating drug solubility in polymers is that S_w and log P_{oct}, together with the melting point, are the 3 most frequently reported of all drug properties (Yalkowsky and Morozowich, 1980). There is a large literature data base of experimental P_{oct} values (Leo et al., 1971; Hansch and Leo, 1988). Additionally, methods of calculating the P_{oct} of new structures are available, for example by the additive contributions of substituent groups or fragment constants (Hansch and Leo, 1979; Nauta and Rekker, 1977) (Eqn. 5), by semi-empirical calculations (Taft et al., 1985; Klopman and Iroff, 1979; Leahy, 1986), or by the use of HPLC retention times (Mirrlees et al., 1976; Unger et al., 1978; Caron and Schroot, 1984).

$$\log P(RX) = \log P(RH) + \Sigma\pi(X) \quad (5)$$

Even for drugs where S_w is not known, it can be accurately estimated from the melting point and/or P_{oct} using one or more semi-empirical relationships of the form of Eqn. 6, developed by Hansch et al. (1968) for liquids and by Yalkowsky et al. (1983) for solids.

$$\log S_w = A \text{ mp } (^\circ\text{C}) + B \log P_{oct} + C \quad (6)$$

The combination of Eqns. 4 and 6 permits the S_{pol} of a drug to be estimated solely from its mp and P_{oct}.

Materials and Methods

Materials

Polydimethylsiloxane (PDMS), medical grade 360 fluid, viscosity 100 cstk, M_n 28,000, was obtained from Dow Corning. Polyethylene (PE), low density, M_n 49,900, M_w 240,000, T_m 107.5, was obtained from NIHLB, NIH. Polyethylene-co-vinyl acetate (EVA), 40% VA, M_w 90,000, η_{inh} 0.73 dl/g ($C = 0.5$ g/dl toluene), was obtained from Aldrich Chemical Co. Poly-ε-caprolactam-co-ε-caprolactone (PCC), 40% ε-caprolactam, [η] 0.49 dl/g (chloroform), was prepared by the method of Goodman and Vachon (1984). Poly-ε-caprolactone (PCL), [η] 2.07 dl/g (toluene), M_w 220,000, M_w/M_n 1.8, was prepared by stannous

octoate catalyzed ring-opening polymerization of ε-caprolactone at 140 °C (Schindler et al., 1982). EVA, PCC and PCL were compression-molded into films. Poly(2-hydroxyethyl methacrylate) (PHEMA) was synthesized as films from the monomer (Polysciences, ophthalmic grade, further purified by passing through activated alumina), in the presence of 45% (v/v) water, according to Zentner et al. (1979).

Partition coefficients

The standard shake-flask method was employed. With the exception of PDMS fluid, each polymer film, approximate thickness 0.5 mm, was immersed in water at 37 °C. The aqueous reservoir was stirred and changed frequently until no leaching of oligomers could be detected by UV spectroscopy. The film was then dried in vacuo to constant weight. The purity and structure of the polymers were verified by GPC and ^{1}H-NMR. Aqueous solutions of the basic drugs were prepared from the free base or base hydrochloride, adjusting the pH by addition of aqueous hydrochloric acid or sodium hydroxide, respectively, and filtration through a 5 μm filter. Amobarbital solutions were prepared similarly. Filtration of solutions of steroids with low solubilities failed to remove micellar aggregates (Blomquist et al., 1978), even when a 0.5 μm filter was used. Therefore, after filtration, the solutions were diluted; the absence of a proportionate change in the UV absorbance was considered evidence of micellar forms remaining. The polymers were shaken mechanically in the aqueous solution of the drug at 37 °C. The change in the concentration of the drug in the aqueous phase was determined weekly by measurement of the absorbance at 220 nm (estradiol and nitrogen bases) or 240 nm (steroids and amobarbital). When no change in the absorbance was observed over a one week period, the drug distribution coefficient (DC) was calculated from the initial and final aqueous absorbance, and the known volumes of the polymer and aqueous phase. The volume of the polymer phase was determined from its gravimetric mass and reported density: PDMS 0.971; PE 0.917; EVA 0.965; PCL 1.142; PCC 1.146. In the case of PHEMA, the density of 1.166 for the swollen gel was used (Mark and Bikales, 1977). Measurements were generally conducted at two or more drug concentrations to rule out a dependence on the drug concentration. The partition coefficients of the neutral and ionized forms of the acids and bases were determined from the distribution coefficients measured at a series of pH's by the analytical method outlined by Horvath et al. (1977), Unger et al. (1978), and others and based on the relationship 7,

$$DC(1 + F) = P_{BH} + P_B \cdot F \tag{7}$$

where F is antilog(pH − pK_a) and P_{BH} and P_B are the partition coefficients of the conjugate acid and base, respectively. The DC of the base (or acid) between polymer and water was measured at a series of pH's generally within ± 1 unit about the pK_a. The P values of the protonated base (acid) and free base (acid salt) were derived from the intercept and slope, respectively, of a plot of DC $(1 + F)$ versus F. The P_{oct} values of the narcotic amines were determined by the same procedure using published DC data in the pH range 7.1 + 7.7 (Kaufman et al., 1975). In all cases the partition coefficient of the ionized form was zero within experimental error, and the partition coefficient was recalculated from Eqn. 7 with the P_{BH} term set to zero. There was no statistically significant difference in the values of P determined by the two methods.

The pK_a's of the amines at 37 °C were calculated from a least-squares fit of the literature DC vs pH data to Eqn. 7. The values were within 0.1 pH unit of the reported pK_a's (Kaufman et al., 1975), with the exception of methadone. A pK_a of 9.26 has been reported for methadone, based on extrapolation from the measured pK_a in 50% aqueous ethanol (Kaufman et al., 1975). The pK_a of 9.52 derived from the analysis of DC vs pH data was used in the present studies.

The log P_{oct} values of the steroids ketodesogestrel, norethindrone, 17α-hydroxyprogesterone, and estra-3,17β-diol were determined by the shake-flask method. The log P_{oct} values of other steroids and amobarbital were obtained from the literature, with those of progesterone and testosterone verified by remeasurement.

TABLE 1

Polymers studied, their solubility parameters and water content

Polymer	Solubility parameter ($J^{1/2} \cdot cm^{-3/2}$)		Water uptake (wt/wt%)
	From Hoy	From Fedors	
Polydimethylsiloxane (PDMS)	–	15.1	0.00183 ± 0.000
Polyethylene (PE)	16.7	17.5	0.00095 ± 0.00018
Polyethylene-co-vinyl acetate (EVA)	19.3	20.0	0.317 ±0.055
Poly-ε-caprolactone (PCL)	20.4	20.8	0.510 ±0.044
Poly-ε-caprolactam-co-ε-caprolactone (PCC)	22.2	22.7	11.0 ±0.1
Poly 2-hydroxyethyl methacrylate (PHEMA)	22.2	25.5	42.4 ±0.1

Solubility of water in polymers

The water content of PHEMA was determined gravimetrically. The other polymers were immersed in tritiated water until no change in the radioactivity in the polymer bulk was observed (2–3 weeks). Each polymer, approximately 100 mg, was washed with water quickly, blotted dry, and dissolved in 1 ml of toluene (PDMS, EVA, PCL), or immersed in 1 ml of water for 5 days (PE and PAE), before addition of Scintiverse II (Fisher Scientific) and determination of radioactivity by scintillation counting. The measurements were repeated at weekly intervals until constant counts were obtained. All measurements were made in triplicate.

Results

The polymers selected for study were PDMS, low-density PE, EVA, PCL, PCC, and PHEMA.

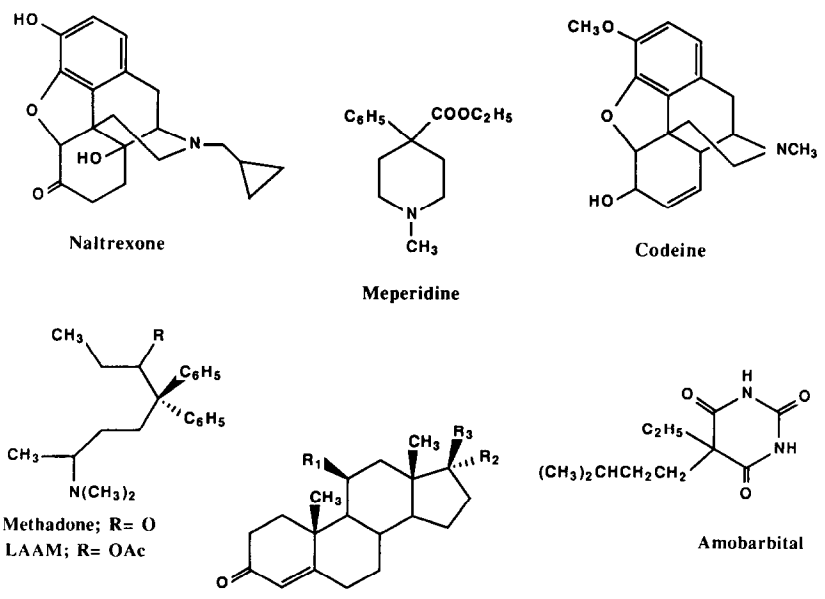

Fig. 1. Structures of solutes used for log P_{pol} – log P_{oct} correlations.

TABLE 2

Partition coefficients of drugs in octanol and 5 rubbery polymers

Drug	pK_a 37 °C	P_{oct}	P_{PDMS}	P_{PE}	P_{EVA}	P_{PCL}	P_{PCC}
Codeine	8.10	13.7 ± 0.0 [a]	0.0472 ± 0.0021	–	2.00 ± 0.13	3.26 ± 0.5	26.1 ± 1.6
Cortisone		29.5 [b]	–	–	1.71 ± 0.14	6.85 ± 0.13	37.9 ± 0.6
Naltrexone	8.13	83.3 ± 0.0 [a]	0.236 ± 0.05	–	18.3 ± 0.5	38.4 ± 0.4	88.2 ± 1.5
Corticosterone		87.1 [c]	0.569 ± 0.027	–	9.79 ± 0.99	21.3 ± 0.8	75.9 ± 0.6
Amobarbital	7.7	117 [d]	0.0936 ± 0.0032	–	18.7 ± 1.0	27.5 ± 0.5	97.6 ± 3.3
Meperidine	8.50	528 ± 0 [a]	16.8 ± 0.3	5.83 ± 0.80	95.5 ± 7.2	48.5 ± 3.7	140 ± 11
Androst-4-ene-3,17-dione		562 [b]	11.1 ± 1.8	2.30 ± 0.43	152 ± 2	89.9 ± 0.2	230 ± 12
Ketodesogestrel		1430 ± 40	–		506 ± 33	226 ± 2	–
Testosterone		2090 [b]	49.7 ± 3.0	2.00 ± 0.48	165 ± 4	135 ± 2	490 ± 4
Progesterone		7410 [b]	133 ± 1	52.3 ± 4.0	1620 ± 15	1250 ± 20	1650 ± 100
L-Methadone	9.52	15300 ± 0 [a]	1920 ± 20	524 ± 53	7800 ± 140	4360 ± 80	7860 ± 370
L-α-Acetylmethadol	8.61	20300 ± 0 [a]	–	208 ± 2	–	–	–

[a] From Eqn. 7 and Kaufman et al., 1975.

[b] From Leo et al., 1971 and Hansch and Leo, 1988.

[c] From Tomida et al., 1978.

[d] From Kakemi et al., 1967.

TABLE 3

Partition coefficients of drugs in octanol and the hydrogel PHEMA

Drug	P_{oct}	P_{PHEMA}
Codeine	13.7± 0.0 [a]	11.9±0.2
Hydrocortisone	40.7 [b]	27 [c]
Naltrexone	83.3± 0.0 [a]	25.5±1.6
Androst-4-ene-3,17-dione	562 [b]	62.7±2.1
Norethindrone	817 ± 7	70 [c]
17-α-Hydroxyprogesterone	1150 ±120	83 [c]
Testosterone	2090 [b]	77.7±1.0
Estra-3,17β-diol	2090 ±150	177 [c]
Progesterone	7410 [b]	129 [c]

[a] From Eqn. 7 and Kaufman et al., 1975.
[b] From Leo et al., 1971 and Hansch and Leo, 1988.
[c] From Zentner et al., 1979.

The latter was studied as an example of hydrogel; the remaining polymers are rubbery polymers with glass transitions below 37°C. With the exception of PCC, these polymers are used frequently as matrices in diffusion-controlled drug delivery studies. Their solubility parameters, which are a measure of their polarity, increase from 15.1 to 25.2 $J^{1/2} \cdot cm^{-2/3}$ (Table 1). This represents 80% of the polarity range of common synthetic polymers. Unfilled PDMS fluid, MW 28,000 Da, was used in preference to silicone rubber in order to eliminate the contribution of filler to the partition coefficient (Most, 1970).

TABLE 4

Summary of correlations of log P_{oct} vs log P_{pol}

log P_{DMS}	$=1.52(\pm0.15)$ log $P_{oct} - 3.37(\pm0.43)$
	$n=9$ $r=0.97$ $s=0.43$
	$F=99.1$ (99.99% conf. level)
log P_{PE}	$=1.32(\pm0.33)$ log $P_{oct} - 3.28(\pm1.19)$
	$n=6$ $r=0.98$ $s=0.52$
	$F=15.7$ (98.34% conf. level)
log P_{EVA}	$=1.16(\pm0.08)$ log $P_{oct} - 1.17(\pm0.21)$
	$n=11$ $r=0.98$ $s=0.23$
	$F=235$ (99.99% conf. level)
log P_{PCL}	$=0.91(\pm0.07)$ log $P_{oct} - 0.50(\pm0.20)$
	$n=11$ $r=0.97$ $s=0.23$
	$F=154$ (99.99% conf. level)
log P_{PCC}	$=0.73(\pm0.06)$ log $P_{oct} + 0.45(\pm0.18)$
	$n=10$ $r=0.97$ $s=0.20$
	$F=129$ (99.99% conf. level)
log P_{PHEMA}	$=0.39(\pm0.05)$ log $P_{oct} + 0.71(\pm0.13)$
	$n=9$ $r=0.95$ $s=0.12$
	$F=68.9$ (99.99% conf. level)

The solutes (Fig. 1) were chosen to span incrementally the most populated log P_{oct} range from 1 to 4, representing a change of 3 orders of magnitude in lipophilicity. The narcotic amines, steroids, and one barbiturate provided examples of both hydrogen-bonding donor and acceptor functional groups. The measured partition coefficients for these solutes and the 6 synthetic polymers are listed in Tables 2 and 3. The low rate of diffusion of the solutes in polymers, relative to low molecular weight solvents, increased the equilibration time required for each partition coefficient measurement to 2–3 weeks, compared with less than 1 h for a typical octanol-water shake-flask determination. The least squares fit of each set of data to Eqn. 4 are summarized in Table 4.

Discussion

The linear free-energy relationships that exist between the octanol-water partition system and other low-molecular-weight solvent–water pairs have been reviewed by Leo and Hansch (1971). These authors analyzed an extensive amount of literature data to show that the partition coefficients of solutes in 20 solvent–water systems could be correlated with the corresponding octanol–water partition coefficient by linear equations analogous to Eqn. 4. For a number of solvent–water pairs, correlations were improved by separating the solutes into hydrogen bonding donor (Class A) and acceptor (Class B) categories. A "sole" equation sufficed to correlate the partition coefficients of some solutes, while for $CHCl_3$/water and CCl_4/water an equation for solutes with both donor and acceptor groups (N class) was considered necessary.

Of the solutes characterized in this study, methadone, androst-4-ene-3,17-dione, and progesterone, fall in Class B, while the remainder are characterized by the presence of both donor and acceptor groups. Despite this diversity of solutes, and the fact that their octanol–water partition coefficients span 3 decades, the correlation coefficients of the regression analyses for all of the

polymers except polyethylene are 0.95 or greater (Table 4). The lower correlation coefficient observed for polyethylene may be partly the result of experimental difficulties with this polymer. The low *P*-values for all but the more lipophilic drugs require a disproportionate amount of the polymer to achieve a measurable change in the aqueous drug concentration. The lower permeability of polyethylene, relative to the other polymers, increases the equilibration time. These difficulties did not apply to PDMS although this polymer has similarly low *P*-values. PDMS is more permeable and, as a fluid, has greater surface contact with the aqueous phase. It may be significant that, in the earlier studies of low-molecular-weight solvent pairs (Leo and Hansch, 1971; Yalkowsky and Morozowich, 1980), only the hydrocarbons heptane and cyclohexane exhibited poor correlations. The importance of matching the solvent characteristics was tested by determining whether the correlation with log *P* (polyethylene–water) was improved by substituting heptane for octanol. For the limited number of solutes evaluated (testosterone, androst-4-ene3,17-dione, progesterone and meperidine), the correlation with log *P* (heptane–water) was worse.

The application of the correlations in Table 4 to estimate the absolute solubilities in polymers was tested with codeine, naltrexone, L-methadone, androst-4-ene-3,17-dione and progesterone. Using experimentally determined water solubilities, it was possible to calculate the absolute solubilities of these 5 drugs to within a factor of two or better (Table 5). The solubilities of these drugs were also estimated by procedures described by Michaels et al. (1975) and, for EVA, by Lee et al. (1985). The latter method is based on the linear correlation of the melting points of a series of steroids and their solubilities in EVA and several other polymers, Eqn. 8, a relationship which has also been discussed by Chien (1976).

$$\log S_{pol}\ (\mathrm{mg/ml}) = 2.75 - 0.0086\ \mathrm{mp}\ (^{\circ}\mathrm{C}) \qquad (8)$$

The method of Michaels et al. (1975) utilizes Eqn. 9, which is derived from Hildebrand's theory of microsolutes and Flory–Huggins theory. It requires as input, values for the entropy of fusion (ΔS_f), the solubility parameters of the polymer (δ_{pol}) and solute (δ_a), and the solute melting point (mp), density (ρ), and molar volume (V_a).

$$\ln S_{pol} + (1 + X) - \ln \rho = -\Delta S_f\ (\mathrm{mp}/T - 1)/R$$

$$X = V_a(\delta_a - \delta_{pol})^2/RT \qquad (9)$$

The results of these two methods of calculating solubilities are less satisfactory than the present method (Table 5). However, because these methods were developed and tested exclusively with steroids, reparameterization may improve their accuracy.

The log *P* correlations may be compared graphically, as shown in Fig. 2 for PDMS and PCC versus octanol–water. The advantage of presenting the results in this format is that, because

TABLE 5

Calculated solubilities (mg/ml) of codein, naltrexone, androst-4-ene-3,17-dione, progesterone, and L-methadone in PCL and EVA

Drug	PCL			EVA			
	Expt. [a]	Eqn. 4	Eqn. 9	Expt. [a]	Eqn. 4	Eqn. 8	Eqn. 9 [c]
Codeine	29.3	31.0	13.5	18.0 [b]	12.8	26.1	7.8
Naltrexone	16.9	7.8	0.18	8.1 [b]	5.0	19.8	5.8×10^{-2}
Androst-4-ene-3,17-dione	4.4	4.9	10.2	7.4	5.1	18.1	8.8
Progesterone	17.6	14.8	36.2	22.8	29.4	51.2	35.5
L-Methadone	30.5	14.4	46.0	36.6 [b]	34.3	80.9	53.7

[a] Except where noted, determined from experimental partition coefficients and the following water solubilities (37 °C); codeine, 9.0 mg/ml; naltrexone, 0.44 mg/ml; androst-4-ene-3,17-dione, 4.87×10^{-2} mg/ml; progesterone, 14.1×10^{-3} mg/ml; L-methadone, 7.0×10^{-3} mg/ml.

[b] Determined directly.

[c] Calculated using solubility parameters derived from Fedors' group constants (Fedors, 1974).

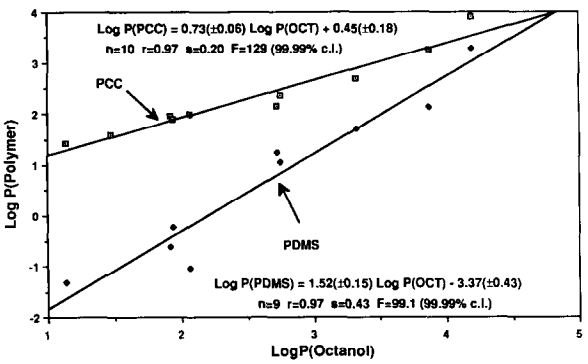

Fig. 2 Linear correlation of log P_{oct} and log P_{pol} for various solutes, PDMS and PCC.

of the relationship (Eqn. 10), it is not necessary to know the water solubility of the drug to make use of the partition coefficient data.

$$\log P - \log P' = \log(S_{pol}/S_w)/(S_{pol'}/S_w)$$

$$= \log(S_{pol}/S_{pol'}) \qquad (10)$$

That is, for any solute, the vertical separation of the two correlation lines in Fig. 2 is equal to the relative solubility of a drug in the two polymers. This figure shows how the log of the ratio of the solubilities of a drug in the two polymers can be expected to vary with the log P_{oct} value or lipophilicity of the drug. For a hydrophilic drug, e.g. log $P_{oct} = 0$, the $S_{pol}/S_{pol'}$ ratio for the two polymers is antilog 3.82, i.e. 6610. If the relative diffusion coefficients of the two polymers are known, it is possible to estimate their relative permeabilities to any drug with a log P_{oct} of zero. Comparison of the other correlations in Table 4 shows that, for the 5 rubbery polymers studied, there is a small difference in the relative solubilities of lipophilic drugs ($P_{oct} = 4$–5), but substantial discrimination for hydrophilic drugs ($P_{oct} = 0$). The slope of the correlation lines is smaller for the more polar polymers, reflecting less discrimination between the polar and non-polar drugs.

Prediction of new correlating equations

Leo and Hansch (1971) observed that the intercept of the correlating equations for low-molecular-weight solvent–water pairs could be predicted from the molar solubility of water in the solvents. The correlation observed for "N" class solutes was:

$$\log[H_2O] = 1.077\ [\text{intercept}] + 0.249 \qquad (11)$$
$$n = 17 \qquad r = 0.979$$

The possibility that such a relationship might extend to polymeric solvents was tested by measuring the solubility of water in the 6 polymers (Table 1). Because of the low solubility in the more hydrophilic polymers, the equilibrium water content of all of the polymers except PHEMA was determined by measuring the incorporation of high specific activity tritium labeled water. By this means it was possible to measure as little as 0.00095 wt% water uptake. The water content of PHEMA was determined gravimetrically to be 42.4 wt%, which is in good agreement with the reported (Kim et al., 1980) value of 43 wt%. NMR studies (Kim et al., 1980; Sung 1978) have shown that 22.8% of this amount is pore water; that is, the water uptake by the polymer bulk is 32.7 wt%.

A high correlation was observed when the molar concentration of sorbed water was plotted against the intercept of the log P_{oct} correlations of the 6 polymers (Fig. 3, Eqn. 12).

$$\log[H_2O] = 1.09\ (\pm 0.07)\ [\text{intercept}]$$
$$+ 0.411\ (\pm 0.14) \qquad (12)$$

$n = 6$, $r = 0.99$, $s = 0.27$,

$F = 257$ (99.99% confidence level)

This correlation, the coefficients of which are not

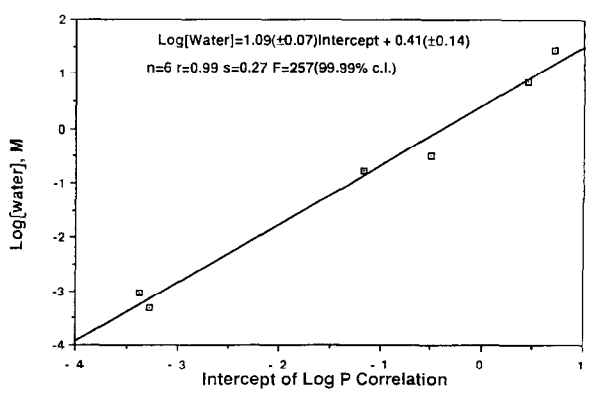

Fig. 3. Plot of the molar solubility of water in 6 polymers vs the intercept of the log P_{pol} − log P_{oct} correlations.

greatly different from those observed with low-molecular-weight solvents (cf. Eqn. 11), permits the a priori estimation of the intercept of the log P_{oct} correlation for new polymers using either the experimentally determined solubility of water in the polymer or the solubility estimated from the structural group contributions of the polymer by the method of Van Krevelen and Hoftyzer (1976). The correlation was slightly improved when the total water content of PHEMA was replaced by its bulk water content.

PE, PCL, and PCC are semicrystalline polymers, the crystallinity of which will vary with their molecular weight and chemical structure. Because the crystalline phase is generally inaccessible to solutes, the experimental partition coefficients and solubilities will be directly proportional to the amorphous content of the polymer. As a result, changes in the crystallinity of the polymers can be expected to alter the intercept of Eqn. 12 in a predictable manner. The slope of Eqn. 12 should not be dependent on the degree of polymer crystallinity.

The apparent relationship between the slope of the log P_{oct} correlation equations and the polarity of the polymers was noted above. This relationship was tested quantitatively by examining the correlation of the slope with the polymer solubility parameter (δ). The latter property, derived from Hildebrand's theory of solubility, is known for a large number of polymers and can be estimated from tables of group contributions. The

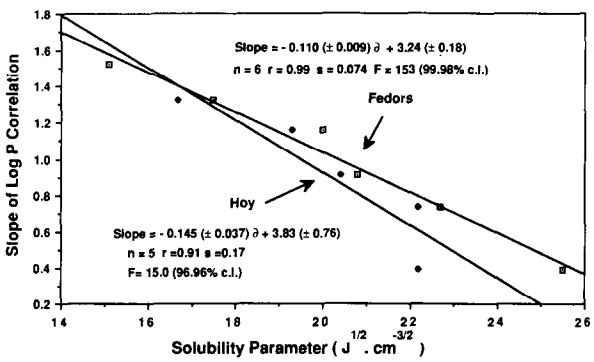

Fig. 4. Plots of the slopes of log P_{pol} − log P_{oct} correlations vs the solubility parameters of the polymers calculated from the tables of Hoy (1970) and Fedors (1974).

values obtained vary somewhat with the particular tables used, and with the weighting of hydrogen bonding that is employed. However, assuming no hydrogen bonding and using the data of either Fedors (1974) or Hoy (1970), listed in Table 1, there is an acceptable correlation between the slope of the log P_{oct} − log P_{pol} correlations listed in Table 4 and the solubility parameter. This is expressed by Eqns. 13 and 14 and illustrated in Fig. 4.

$$\text{Slope} = -0.145\ (\pm 0.037)\ \delta + 3.83\ (\pm 0.76)\ \text{(Hoy)} \quad (13)$$
$n = 5,\ r = 0.91,\ s = 0.17,$
$F = 15.0$ (96.96% confidence level)

$$\text{Slope} = -0.110\ (\pm 0.009)\ \delta + 3.24\ (\pm 0.18)\ \text{(Fedors)} \quad (14)$$
$n = 6,\ r = 0.99,\ s = 0.074,$
$F = 153$ (99.98% confidence level)

The lower correlation coefficient obtained using solubility parameters from Hoy's group constants is due to the value for PHEMA. The value of 22.2 $J^{1/2} \cdot cm^{-3/2}$ for PHEMA calculated using Hoy's tables is considerably lower than the experimental value of Hourston and Satgurunathan (1984) of 25.2 $J^{1/2} \cdot cm^{-3/2}$, whereas Fedors' value of 25.5 $J^{1/2} \cdot cm^{-3/2}$ is in good agreement.

The relationships 12–14 provide simple means by which the slope and intercept of the log P_{pol} − log P_{oct} correlations for new polymers may be estimated using readily accessible data.

Poly-2-hydroxyethyl methacrylate

Transport in PHEMA and other hydrogels has been attributed to dual diffusion mechanisms. The pore mechanism invokes diffusion through aqueous channels composed of bulk-like water. The solute-diffusion mechanism invokes dissolution and transport via a domain composed of polymer, interfacial water, and bound water (Jhon and Andrade, 1973). This dual model has been sup-

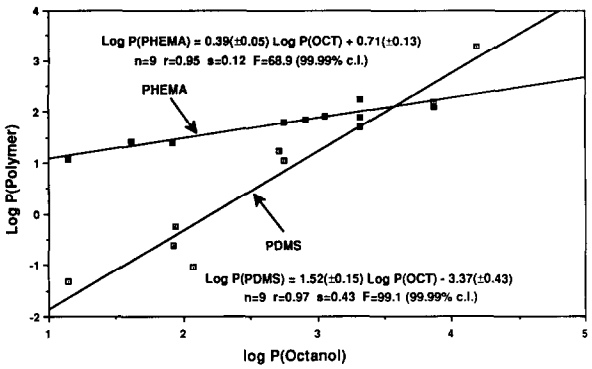

Fig. 5. Linear correlation of log P_{oct} and log P_{pol} for various solutes, PDMS and PHEMA.

ported by measurements of the flux and the partition coefficients of solutes with different lipophilicities (Zentner et al., 1979; Kim et al., 1980), although DTA measurements have been reinterpreted (Roorda et al., 1987). To test the correlation of the PHEMA partition coefficients with log P_{oct} values, the series of solutes was expanded and, where data were absent, the log P_{oct} values were determined. The results of these measurements, combined with those of Zentner et al. (1979), are shown in Table 3 and Fig. 5. The high correlation coefficient of the log P_{oct} − log P_{PHEMA} regression analysis and the fact that the slope and intercept of the correlation equation conform to the trends exhibited by rubbery polymers provides quantitative evidence of solute partitioning into the polymer bulk. It is evident from the correlation equation in Table 4 that preferential partitioning into the polymer bulk will occur for all but the most hydrophilic solutes, i.e., log $P_{oct} < -2$, but will not increase greatly with the drug lipophilicity.

Acknowledgements

This work was supported by the National Institute on Drug Abuse, Grant DABB 5-R01-DA-3616-03. It was presented in part at the 190th Meeting of the American Chemical Society, New York, NY, April, 1986.

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