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Determination of solute–polymer interaction constants via chromatography with polymer capillaries

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ABSTRACT

The interaction between model solutes and various polymeric materials was studied chromatographically by measuring dynamic solute absorption. Specifically, the solutes were injected into tubing "columns" manufactured by making thin pieces of tubing out of the polymers of interest. Polymers investigated in this manner included a di(2-ethylhexyl)phthalate-plasticized poly(vinyl chloride), a vinyl acetate–vinyl chloride copolymer and a blend of polypropylene and a styrene–butadiene block copolymer. Linear relationships could be established between the dynamic binding constant of the solute, determined chromatographically, and its equilibrium interaction constant, determined by conventional shake-flask means. Similarly, the dynamic binding constant could be directly related to the solvent–solvent partition coefficients of the solute. The proposed methodology provides a rapid means of assessing the magnitude of polymer–solute interactions.

INTRODUCTION

Developing polymeric containers for the food and pharmaceutical industries requires the establishment of container–product compatibility. Compatibility revolves around two issues: binding, wherein the container sorbs a component of the product, and leaching, wherein a container component becomes mobilized into the product. Both issues involve partitioning of the solute, regardless of its initial source, between the container and product phases.

Container–solution partition coefficients are usually determined by shake-flask methods wherein the container and solution are equilibrated under controlled conditions and the equilibrium concentration of the solute in the two phases is determined. Such an approach is time intensive (it may take several weeks to reach equilibrium) and must be rigorously controlled to establish (a) that solute loss observed from either phase is truly due to partitioning and not some other loss mechanism such as degradation and (b) that physical difficulties associated with the measurement [1–3] are minimized.

Alternatively, several more or less indirect chromatographic methods exist for assessing material–solute interactions. Inverse gas chromatography and high-performance liquid chromatography (HPLC), in which the polymer of interest essentially becomes the chromatographic support, has been used to study polymer–solute interactions [4–9]. The use of HPLC (reversed-phase) retention characteristics to determine the solvent–solvent partition coefficient of a solute is well documented [10–13]. As solvent–solvent partition coefficients can be directly correlated with polymer–water partition coefficients [14–16], such HPLC methods are directly applicable to the determination of polymer–solution interaction characteristics.

The ability of the chromatographic approaches to predict the polymer–solution interaction rests on how well the chromatographic system mimics the container–solution couple. For methods using a bonded polymeric stationary phase, it is probable that the polymer bonded to the stationary phase bears little resemblance to the material in its container form. This is especially true for the newer classes of container materials which represent mul-

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ti-layered structures. For the HPLC retention time methods, it is also unlikely that a conventional stationary phase could be found which would mimic the solution interaction of a significant number of the potential container materials, especially given the multi-modal container–solution interactions mechanism that occur.

In this research, container–solute interactions were measured directly by using thin tubes of the container material of interest as the stationary phase in a liquid chromatographic system. Changes in peak size are indicative of the magnitude of the material–solute interaction.

EXPERIMENTAL

Materials

Polymers studied included a di(2-ethylhexyl) phthalate (DEHP)-plasticized poly(vinyl chloride) (PVC) (Viaflex plastic, Baxter Healthcare, Deerfield, IL, USA), vinyl acetate–vinyl chloride copolymer (VA–VC) (Tygon tubing, Norton, Wayne, NJ, USA) and a blend of polypropylene and a styrene–butadiene block copolymer (PP). The VA–VC tubing had a I.D. of 2 mm and an O.D. of *ca.* 2.5 mm. PVC and PP tubing was extruded in-house; the PVC tubing had an I.D. of 1 mm and an O.D. of 1.5 mm and the PP tubing had an I.D. of 1.5 mm and an O.D. of *ca.* 3 mm. For both tubing types prepared in-house, the sizes prepared were dictated by practical processing constraints.

Test solutes were analytical-reagent grade (98% purity or better) and are listed, together with their solvent–solvent partition coefficients, in Table I. These solutes were chosen as they are analytically expedient, they encompass a fairly wide range in terms of their intrinsic lipophilicity, they exhibit a varying ability to interact with polymers via hydrogen bonding and their polymer diffusion coefficients are relatively large. Other reagents used to prepare mobile phases and other solutions were of analytical-reagent or HPLC grade as appropriate. Water was obtained from a Barnstead NANOpure II water purification system.

Determination of equilibrium interaction constants

The equilibrium interaction constant (E_b) for a polymer–solute couple was determined by the shake-flask method. Specifically, a known amount of the polymeric material (cut into small pieces to hasten the attainment of equilibrium) was contacted with a known amount of solution which originally contained a known amount of one or more of the test solutes. Replicate polymer test articles and non-polymer-containing control samples was stored at 35°C for 2 weeks with constant gentle agitation. After this time, the solution phase concentration of the solute was determined by HPLC and E_b was calculated.

TABLE I

MODEL SOLUTES USED

Model solute	Abbreviation	Log P_{o-w}	Log P_{h-w}
Dimethyl phthalate	DMP	2.16	0.82
Diethyl phthalate	DEP	3.22	1.75
Dipropyl phthalate	DPP	4.05	2.67
4-Methylbenzoic acid	MBH	2.27	−0.4
4-Ethylbenzoic acid	EBH	2.97	0.4
4-Butylbenzoic acid	BBH	3.96	1.80
Aniline	AN	0.9	−0.1
4-Methylbenzyl alcohol	MBOH	1.6	0.3
Carbazole	CAR	3.59	2.18
Ethyl 4-aminobenzoate	ETBZ	2.24	−0.07
Butyl 4-aminobenzoate	BUBZ	3.37	1.14
Ethyl 4-hydroxybenzoate[a]	ETPB	2.57	−1.05
Butyl 4-butylbenzoate[b]	BUPB	3.59	0.5
n-Ethylhexylamine	NEHA	2.00	−1.80

[a] Ethyl paraben.
[b] Butyl paraben.

Preparation of tubing columns

The tubing was made into chromatographic "columns" as follows. For the VA–VC copolymer, the following "columns" were made: coiled, in which a 70-cm length of tubing was just loosely coiled; knotted, in which a 65-cm length of tubing was manually knotted (tightly but without flow stoppage); and knotted with beads, where a 70-cm length of tubing was filled with *ca.* 1 mm diameter glass beads and knotted. For PVC, a knotted "column" was made from a 70-cm length of this tubing. A knotted "column" of PP was made from a 90-cm piece of this material; however, owing to its rigidity, the knots were not a tight as those obtained for the other materials. The various polymer "columns" were fitted with conventional HPLC end fittings. An inert reference "column" was made by coupling two 0.5-ml stainless-steel sample loops together.

Generation of the dynamic binding chromatograms

The chromatographic system consisted of conventional HPLC components with the tubing serving as the analytical "column". Typical operating conditions included a mobile phase of 0.05% trifluoroacetic acid at a flow-rate of 0.3 ml/min, UV analyte detection at 215 nm and a sample size of 20 μl. The acidic mobile phase was necessary to ensure that the acidic model solutes were completely protonated. Although the system temperature was usually ambient, some experiments were performed at elevated temperature by placing the tubing in a conventional column oven and preheating the mobile phase in a water-bath.

Dynamic binding experiments were performed as follows. A given "column" was placed in the chromatographic system and equilibrated with the mobile phase. Duplicate injections of the test solutes (at concentrations of *ca.* 5 and 50 ppm) were made and the resulting chromatograms recorded. Sufficient time was allowed between injections so that the baseline was re-established. After elution of all the solutes, another "column" was put into the system and the experiment was repeated. Peak areas of the resulting chromatographic responses were determined by integrating computerized peak traces.

Definition and calculation of E_b and D_b

The equilibrium interaction constant, E_b, is the ratio of the equilibrium solute concentration in the polymer and solution:

$$E_b = (m_p/W_p)/(m_s/V_s) \quad (1)$$

where m is the mass of solute in either phase at equilibrium, W is the polymer weight (in grams), V is the solution volume (in liters) and s and p refer to the solution and polymer phases, respectively. The dynamic binding constant, D_b, is defined in a similar manner:

$$D_b = (m_c/W_c)/(m_s/V_s) \quad (2)$$

where m_c is the mass of solute bound by the column, W_c is the column weight, m_s is the mass of solute eluted from the column and V_s is the column void volume.

The quantities m_c and m_s cannot be measured directly but rather require detector calibration. The detector is calibrated by injecting the samples (containing a known concentration, C_i, of the solute) into the inert (*i.e.*, no solute absorption) column and noting the peak response (R_m) of the eluted solute. The same amount of solute is injected into the polymer columns, producing a detector response R_c. If the injection volume is V_i, then m_c and m_s from eqn. 2 can be calculated as follows:

$$m_c = (C_i V_i)(1\text{-}R_c/R_m) \quad (3)$$

$$m_s = (C_i V_i)(R_c R_m) \quad (4)$$

RESULTS AND DISCUSSION

Equilibrium interaction models

Equilibrium interaction models (shake-flask experiments) relate E_b to the solvent–water partition coefficient of a solute. For many polymers, a bivariant model is applicable and takes the form

$$\log E_b = a(\log P_{o-w}) + b(\log P_{h-w}) + c \quad (5)$$

where o–w refers to octanol–water and h–w refers to hexane–water. The binding model is obtained by linearly regressing known values of E_b *versus* known solute partition coefficients for a particular polymer and obtaining the coefficients in eqn. 5.

A typical equilibrium interaction model (VA–VC copolymer) is shown in Fig. 1 and regression coefficients are given in Table II. An excellent correlation between E_b and the partition coefficients is obtained for the three materials studied. As shown by the relative magnitude of the P_{o-w} and P_{h-w} coefficients,

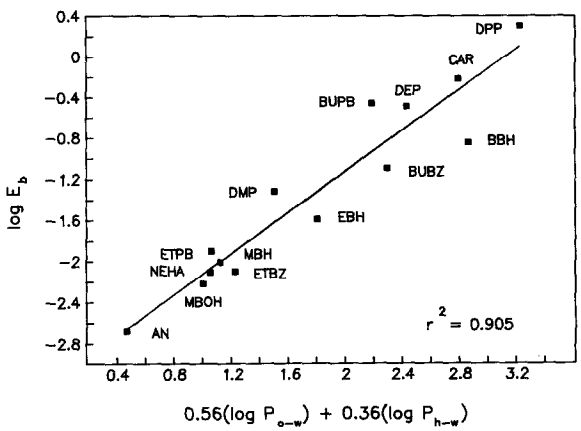

Fig. 1. Equilibrium interaction model for VA–VC copolymer. Plot of log E_b (from shake-flask methods) *versus* the linear combination of the octanol–water (o–w) and hexane–water (h–w) partition coefficients.

TABLE II

VARIOUS CURVE FIT PARAMETERS

Equilibrium interaction model constants[a], eqn. 5

Constant	PVC	VA–VC	PP
a	0.46 (0.09)	0.56 (0.13)	0.26 (0.19)
b	0.30 (0.07)	0.36 (0.11)	0.61 (0.12)
c	−2.80 (0.20)	−3.23 (0.30)	−3.41 (0.27)
r^2	0.940	0.905	0.925

Dynamic interaction model constants[a], $\log D_b = a(\log P_{o-w}) + b(\log P_{h-w}) + c$

Constant	PVC[b]	VA–VC[b]	VA–VC[c]	PP[d]
a	0.66 (0.12)	0.65 (0.12)	0.65 (0.11)	−0.01 (0.19)
b	0.35 (0.10)	0.21 (0.10)	0.27 (0.10)	0.63 (0.11)
c	−5.9 (0.28)	−5.47 (0.28)	−5.34 (0.26)	−5.30 (0.27)
r^2	0.929	0.904	0.926	0.904

Curve fit parameters[a], $\log D_b = a(\log E_b) + b$

Parameter	PVC	VA–VC[c]	PP[c]
a	1.28 (0.90)	0.94 (0.06)	0.83 (0.09)
b	−2.23 (0.23)	−2.14 (0.20)	−2.99 (0.26)
r^2	0.949	0.952	0.898

[a] Numbers in parentheses are the standard errors.
[b] 25°C, knotted column.
[c] 25°C, column with beads.
[d] 45°C, knotted column.

the VA–VC copolymer and PVC possess mixed interaction characteristics (classical lipophilic interaction plus hydrogen bonding) while the PP blend is dominantly hexane-like and possesses little hydrogen bonding ability.

When a model solute is injected onto the polymer column, two distinct effects are observed. For all but the most hydrophilic solutes, both peak shape and size (total area) are affected as the solute passes through the polymeric column. As the solute lipophilicity increases, the total peak response decreases and the peak develops a pronounced tail. While both peak response and shape could be related to the polymer's binding ability, peak area is used here as it is most easily and reproducibly measured.

Dynamic binding constants and models

Dynamic binding constants for a variety of different tubing configurations are listed in Table III. For several of the materials, D_b data are not available for every solute. This illustrates a practical disadvantage of the dynamic binding approach, its limited dynamic range. As the determination of D_b rests on a differential measurement of solute elution between an inert and polymer column, it is constrained by either the ability to measure a difference between two peak areas or, in the case of a strongly interacting solute, to measure any peak response at all with the polymeric column.

Dynamic binding constant models for the three materials evaluated are illustrated in Figs. 2–4 and the regression constants are summarized in Table II. Although in general adequate correlations can

TABLE III

EQUILIBRIUM AND DYNAMIC BINDING CONSTANTS

Solute	PVC[a]		VA–VC[b]		PP[c]	
	Log E_b	Log D_b	Log E_b	Log D_b	Log E_b	Log D_b
DMP	−1.56	−4.28	−1.32	−3.62	−2.56	−5.11
DEP	−0.53	−3.16	−0.49	−2.65	−1.73	−4.31
DPP	0.05	−2.14	0.30	−2.08	−0.83	−3.30
NEHA	−[d]	−	−2.11	−4.20	−	−
MBH	−1.87	−4.36	−2.01	−4.00	−3.24	−5.51
EBH	−1.33	−4.22	−1.59	−3.43	−2.10	−4.84
BBH	−0.93	−3.20	−0.85	−2.62	−1.14	−4.30
AN	−2.41	−5.37	−2.68	−4.50	−	−
MBOH	−2.1	−4.80	−2.22	−4.45	−	−
CAR	−0.4	−2.65	−0.02	−2.20	−1.06	−3.60
ETBZ	−1.82	−4.88	−2.10	−4.21	−2.25	−4.99
BUBZ	−0.85	−3.57	−1.10	−2.96	−1.54	−4.70
ETPB	−1.76	−4.49	−1.69	−3.92	−3.46	−5.84
BUPB	−0.95	−3.11	−0.46	−2.36	−2.55	−5.20

[a] 25°C, knotted column.
[b] 25°C, knotted column with beads.
[c] 45°C, knotted column.
[d] − = Not measurable.

be obtained between D_b and the solvent–solvent partition coefficients of a solute, the correlations obtained with the dynamic binding constant are not as good as those obtained using the equilibrium interaction constants. However, the correlation between D_b and the partition coefficients are sufficiently strong that the dynamic binding models could be used to semi-quantitatively assess the relative behaviors of several polymeric materials.

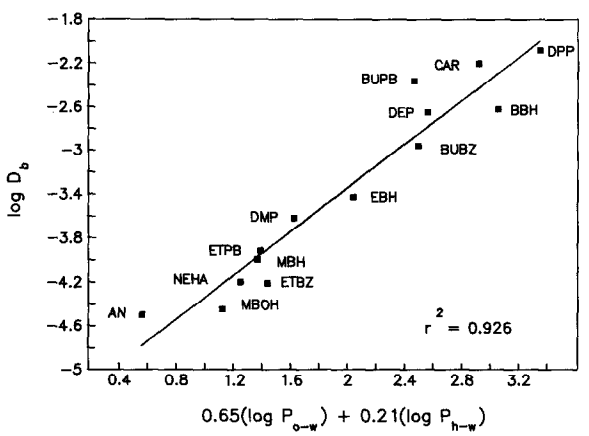

Fig. 2. Dynamic binding model for the VA–VC copolymer. Plot of log D_b (from the column experiments) *versus* the linear combination of the octanol–water (o–w) and hexane–water (h–w) partition coefficients of the solute at 25°C. The data were obtained with the knotted column.

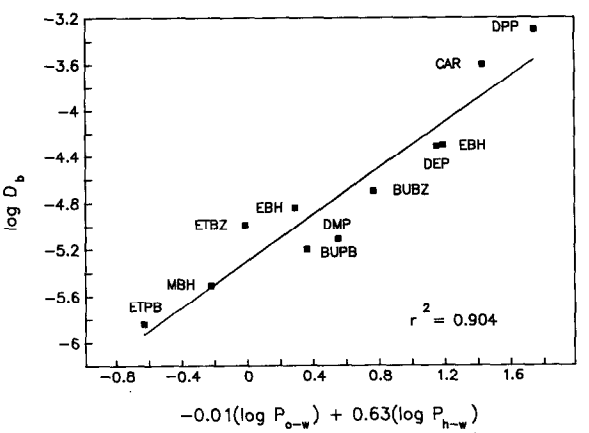

Fig. 3. Dynamic binding model for the polypropylene blend. Plot of log D_b (from the column experiments) *versus* the linear combination of the octanol–water (o–w) and hexane–water (h–w) partition coefficients of the solute at 45°C. The data were obtained with the knotted column.

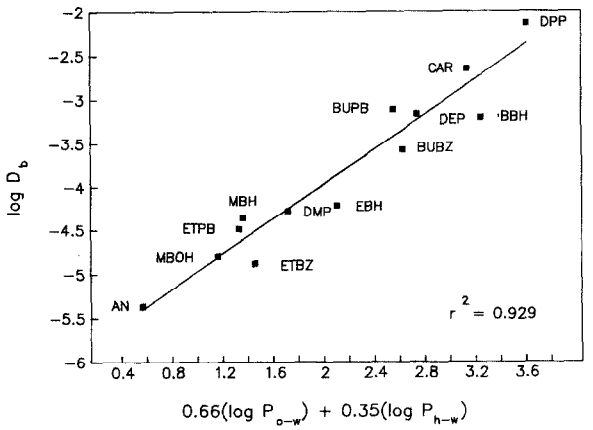

Fig. 4. Dynamic binding model for PVC. Plot of log D_b (from the column experiments) *versus* the linear combination of the octanol–water (o–w) and hexane–water (h–w) partition coefficients of the solute at 25°C. The data were obtained with the knotted column.

Factors influencing the magnitude of the dynamic binding constant

The dynamic binding process is not reversibly chromatographic in the sense of producing varying retention times as a function of column material and solute identity. Rather, the dynamic binding process is essentially an "on-the-fly" approximation of the equilibrium polymer–solute interaction, wherein a fraction of the solute is irreversibly bound to the polymeric stationary phase. The absolute amount of a solute which will partition irreversibly on to the binding column will be impacted by factors that control the length of time the solute is in the column (*e.g.*, flow-rate and column length), by factors that promote turbulent mixing in the column (and thus promote column–solute interactions, *e.g.*, column geometry) and by factors that influence the rate of diffusion of the solute into the column (*e.g.*, temperature).

The mobile phase flow-rate directly affects the magnitude of solute absorption by the binding column. As the flow-rate decreases, the amount bound by the column increases and in general the peak shape becomes more skewed. The 0.3 ml/min flow-rate applied used here represents the practical lower limit for the polymeric materials and solutes used. Even at this flow-rate, it takes nearly 20 min for the baseline to become re-established after a strongly bound solute is injected into the system.

In many respects, the polymer binding column is similar to a post-column reactor used in HPLC detection. For such reactors, the effect of reactor geometry (*e.g.*, coiled, knotted, knitted) on the efficiency of mixing and the turbulence of the flow within the reactor is well established (*e.g.*, ref. 17). As the polymer binding columns used have large inner diameters, any column configuration which promotes turbulent flow will maximize solute–wall interactions and thus the amount of solute bound by the column. By inducing turbulent flow (knotting the column) and reducing the inner void volume of the column (by filling the column with inert glass beads), one dramatically improves the column's solute binding efficiency. For the more efficient columns, the solute peak is smaller and less skewed.

While changing the column geometry will change the absolute magnitude of D_b, the effect should be similar for all solutes. Thus, while the absolute value of D_b would be different for two different column configurations, the regression constants for D_b interaction models for the same column material in two different column configurations should be comparable. Dynamic binding models generated with knotted VA–VC columns either empty or filled with inert glass beads are statistically identical (Fig. 5). The unit slope of the best fit line relating D_b obtained from both column configurations confirms that the column configuration does not impact the

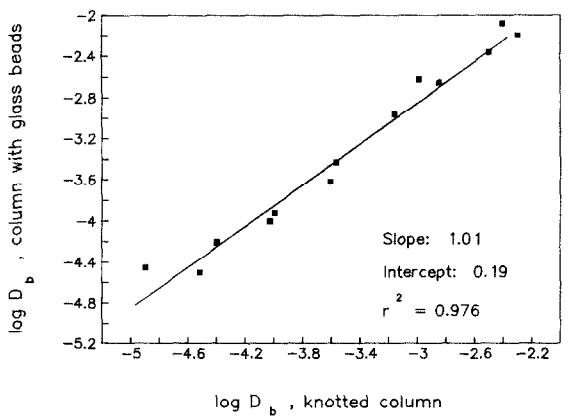

Fig. 5. Comparison of the calculated dynamic binding constants obtained on two different column configurations from the same material. The material used was the VA–VC copolymer and the experiment was performed at a column temperature of 25°C.

trend observed in D_b as a function of solute identity. As shown by the non-zero intercept, the column configuration merely impacts the absolute magnitude of the D_b constant.

Temperature impacts the ability of the solute of diffuse to the surface of the polymer column through the mobile phase and to diffuse into the polymeric material and thus be irreversible bound by the polymer column. One would expect that an increase in column temperature would result in a larger measured D_b. As shown in Fig. 6, an increased column temperature results in a reproducible increase in the measured D_b.

As the polymeric "column" irreversibly binds a fraction of the solute with each injection, one would expect that after a certain period of time the polymer would become saturated and additional solute binding would cease. Repetitive injections of high concentration sample did not cause a change in the solute's elution response. Replicate injections of one solute, separated by the injection of other solutes, were equivalent in terms of shape and response. Thus column saturation was not observed in this research.

Relationship between equilibrium and dynamic interaction constants

The most useful application of D_b would be to provide a rapid estimate of E_b, which in turn is a parameter critical to polymer–solute interaction calculations. While the two factors are defined in a similar manner, one suspects that they will not be numerically equivalent because the solution volumes associated with both types of experiments are radically different. Whereas in the case of a shake-flask experiment used to determine E_b the solution interaction volume is known and fixed, in the case of D_b the assignment of the column void volume as the interaction volume is more a matter of convenience (providing internal consistency for D_b) than a matter of strict theoretical correctness. This difference between E_b and D_b, being a matter of definition, should be species independent and constant and would be reflected as a non-zero intercept in a plot of log D_b *versus* log E_b.

Another reason why E_b and D_b might be different is the variable uptake rates of the model solutes themselves. In the dynamic experiment, the solute is in contact with any given portion of the column for a relatively short period of time. For especially the more lipophilic solutes, one could envision a scenario in which there was insufficient interaction time at any given plate to allow for an instantaneous equilibrium between the solution and the column material in the plate to be established. If equilibrium is not established at each plate within the column, then D_b will be inherently less than E_b. As one would expect that this effect would be most prevalent for the highly bound, lipophilic solutes, one would expect that a log D_b *versus* log E_b plot would have a slope of less than unity.

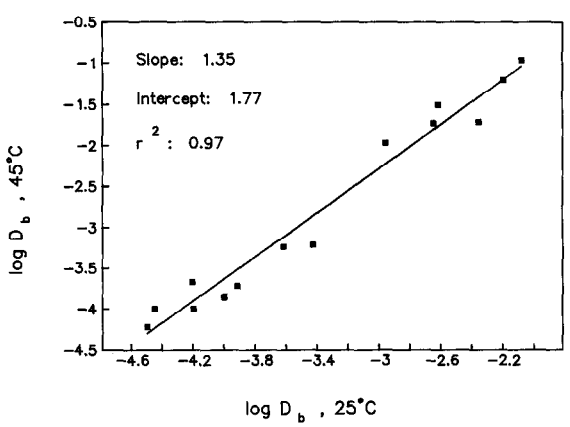

Fig. 6. Comparison of the dynamic binding constants as a function of column temperature. The column used was the knotted configuration of the VA–VC copolymer.

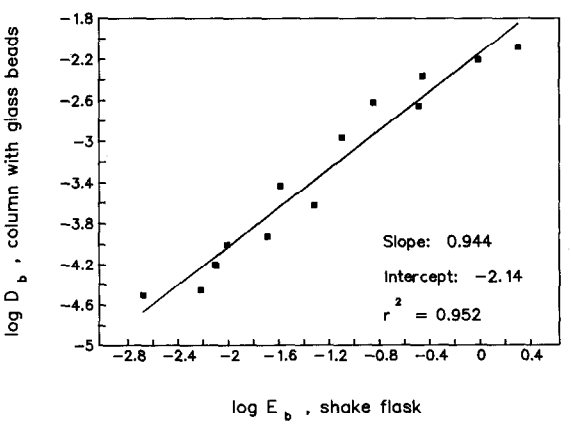

Fig. 7. Comparison of the equilibrium interaction constants and dynamic binding constants for the VA–VC copolymer. The column used was knotted with beads and the experiment was performed at 25°C.

A typical plot of log D_b *versus* log E_b for the three polymers studied is shown in Fig. 7. For all three, the two interaction constants can be linearly related with a modest degree of accuracy. Curve fit parameters are given in Table II. In all instances, the intercept of the best fit line is negative, indicating that E_b tends to be larger than D_b. This results was anticipated in the previous discussion. Slopes of the best fit line were less than 1 for the VA–VC and PP materials (although the standard error is sufficiently large that the confidence interval for the slope includes 1.0). For PVC, however, the slope is significantly larger than 1. No explanation for this behavior is apparent.

CONCLUSIONS

Dynamic interaction constants can be reproducibly determined for various model solutes via a chromatographic method involving a column made from capillaries of polymeric materials. The method requires the comparison of peak sizes when the solute is injected on to a "column" of an inert material and a "column" made from the polymer of interest. The magnitude of the measured D_b is influenced by the conditions employed during the experiment (*e.g.*, column length, flow-rate, column geometry, temperature) but is relatively insensitive to solute concentration over the range 5–50 ppm. Thus, although D_b may change as a function of changing operating conditions, it has proved to be reproducible when the operating conditions are rigidly controlled.

A material's D_b can be linearly correlated with its equilibrium binding constant, thus establishing the dynamic binding approach as a rapid means of determining E_b. Once E_b has been determined, one can directly determine the magnitude of a solute–polymer interaction, for example, in a typical container configuration.

REFERENCES

1 M. S. Mirrlees, S. J. Moulton, C. T. Murphy and P. J. Taylor, *J. Med. Chem.*, 19 (1976) 615–619.
2 T. Yamana, A. Tsuji, E. Miyamota and O. Kubo, *J. Pharm. Sci.*, 66 (1977) 747–749.
3 M. L. Bieganowska, *J. Liq. Chromatogr.*, 5 (1982) 39–48.
4 P. J. Carillo, S. G. Gilbert and H. Daun, *J. Food Sci.*, 53 (1988) 1199–1203.
5 U. Coelho, J. Miltz and S. G. Gilbert, *Macromolecules*, 12 (1988) 1226–1230.
6 J. E. Guillet, M. Romansky, G. J. Price and R. Van der Mark, *ACS Symp. Ser.*, 391 (1989) 20–32.
7 P. Munk, P. Hattam, Q. Du, A. Abdel-Azim, *J. Appl. Polym. Sci., Appl. Polym. Symp.*, 45 (1990), 289–316.
8 G. Schomburg *Trends Anal. Chem.*, 10 (1991) 163–169.
9 A. L. Khurana and C. Ho, *J. Liq. Chromatogr.*, 12 (1989) 1679–1686.
10 J. E. Garst and W. C. Wilson, *J. Pharm. Sci.*, 73 (1984) 1616–1929.
11 A. Bechalany, T. Rothlisberger, N. El Tayar and B. Testa, *J. Chromatogr.*, 473 (1989) 115–124.
12 C. Yamagami, T. Ogura and N. Takao, *J. Chromatogr.*, 514 (1990) 123–136.
13 D. R. Jenke, D. S. Hayward and R. A. Kenly, *J. Chromatogr. Sci.*, 28 (1990) 609–612.
14 L. Illum, H. Bundgaard and S. S. Davis, *Int. J. Pharm.*, 17 (1983) 183–192.
15 C. G. Pitt, Y. T. Bao, A. L. Andrady and P. N. K. Samuel, *Int. J. Pharm.*, 45 (1988) 1–11.
16 D. S. Hayward, R. A. Kenley and D. R. Jenke, *Int. J. Pharm.*, 59 (1990) 245–253.
17 B. Lillig and H. Engelhardt, in I. S. Krull (Editor), *Reaction Detection in Liquid Chromatography*, Marcel Dekker, New York, 1986, pp. 1–61.