Examination of Data Relating to the Thermodynamic and Kinetic Interactions Between Nonvolatile Aqueous Solutes and Three Ethylene–Vinyl Acetate Copolymers

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ABSTRACT: Distribution coefficient (K_s) and diffusivity [diffusion coefficient (D)] values for 19 nonvolatile solutes were previously reported for three ethylene–vinyl acetate (EVA) copolymers. In this article, the interaction properties of these solutes are compared with their octanol/water partition coefficient ($P_{o/w}$) values. Adequate linear log/log correlations between K_s and $P_{o/w}$ are obtained for all three copolymers, once the effect of the solution pH on solute speciation is taken into account. The resultant correlations are similar for all three copolymers, suggesting that they share a common interaction mechanism. Inverse correlations between log D and log $P_{o/w}$ are established for all three materials. Although the relationship between log D and log $P_{o/w}$ is linear for the EVA polymers, the scatter in the poly(vinyl acetate) data is sufficiently large that a linear relationship cannot be unilaterally established. The utility of such a model in terms of assessing the potential interaction between a plastic container and its contained contents is demonstrated. © 2005 Wiley Periodicals, Inc. J Appl Polym Sci 99: 253–259, 2006

Key words: adsorption; compatibility; plastics

INTRODUCTION

An important facet in developing plastic container systems for aqueous products such as pharmaceutical preparations, foods, cosmetics, and others involves evaluating container/solution interactions. Two processes of interest include the sorption of ingredients of the solution product by the container (binding) and the migration of container components into the solution (leaching). These processes are of interest as they can materially impact the composition of the solution product. Both processes are thermodynamically and kinetically constrained, the former defining the absolute magnitude of the interaction and the latter defining the rate at which the interaction occurs.

The distributive and diffusive properties of solutes in a liquid/plastic system have been mathematically linked to fundamental solute properties such as liquid/liquid partition coefficients and pK_a.[1–5] Such mathematical relationships are useful in assessing the interaction potential of container systems that may be used in a large number of possible product configurations. This is true because such relationships can be used to extrapolate behavior observed in one test system to other systems of interest, precluding the need to perform repetitive and extensive testing of all possible product configurations.

The thermodynamic and kinetic interaction properties (distribution coefficients and diffusivities) of 19 nonvolatile solutes with three vinyl acetate type materials were recently reported.[6] Although the authors of the work noted a qualitative relationship between the observed behavior of the test solutes and the solutes' lipophilicity, the nature of the relationship was not quantified. In this article, this interaction data base is examined for the congruency of the findings, and the relationship between the solute properties and the reported interaction data is quantitatively examined.

EXPERIMENTAL

The experimental details associated with the generation of the films and the measurement of the distribution coefficients and diffusivities are described elsewhere.[6] No additional experimental work was performed for this article. The examined films included ethylene–vinyl acetate (EVA) copolymers with 33 or 45 wt % vinyl acetate (EVAc33 and EVAc45, respectively) and poly(vinyl acetate) (PVAc).

THERMODYNAMICS

The equilibrium distribution of a compound between a solution and a contact material can be expressed in terms of a partition coefficient, equilibrium distribu-

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TABLE I
Solute Identification and Interaction Properties

Solute	CAS Registry number	Log $P_{o/w}$	K_s[f]			D[a,f]			
								PVAc[b]	
			EVAc33	EVAc45	PVAc	EVAc33	EVAc45	Extrapolation	Early time
1-Napthol	90-15-3	2.84	599	623	2203	0.13	0.46	4.36	1.08
2-Napthol	135-19-3	2.70	372	743	1693	0.44	0.66	6.6	1.34
2-Nitroaniline	88-74-4	1.85	66.3	140	350	2.85	3.86	9.28	3.38
3-Nitroaniline	99-09-2	1.43	36.5	80.1	264	4.29	5.11	11.3	5.87
4-Nitroaniline	100-01-6	1.35	25.2	65.9	322	4.60	6.21	12.3	4.69
2-Nitrophenol	88-75-5	1.77	93.7	122	185	1.15	10.2	14.5	6.86
3-Nitrophenol	554-84-7	2.00	44.1	94.2	314	3.00	2.51	12.3	2.39
4-Nitrophenol	100-02-7	1.91	33.9	87.3	374	4.62	1.55	13.2	6.85
2-Nitrotoluene	88-72-2	2.30	336	483	435	2.21	1.53	12.5	8.18
3-Nitrotoluene	99-08-1	2.45	105	249	386	2.87	2.92	15.6	5.62
4-Nitrotoluene	99-99-08	2.37	345	471	423	1.25	3.71	15.9	8.21
Acetophenone	98-86-2	1.63	38.7	41.5	55.7	4.61	12.8	12.5	10.8
Benzoic acid[c]	65-85-0	1.87	109	291	400	12	7.2	6.63	8.83
Benzonitrile	100-47-0	1.56	43.9	54.5	77.1	4.98	14.7	28.3	19.9
Benzophenone	119-61-9	3.18	1356	2231	1782	0.1	0.34	4.67	1.36
Benzyl alcohol	100-51-6	1.05	2.79[d]	10.8	23.4	56	15.9	145	10.5
Nicotine	54-11-5	1.17	1.42[d]	22	46	3.1	0.05	1.96	0.19
Nitrobenzene	98-95-3	1.85	91.5	145	172	2.63	5.53	17.4	18.7
Pyridine[e]	110-86-1	0.65	3.26	4.13	16.5	51.3	26.0	NM	NM

NM = not measured.
[a] units are 10^{-9} cm^2/s for the EVA polymers and 10^{-12} cm^2/s for PVAc.
[b] Extrapolation refers to the use of Fickian models to extrapolate the early time data to infinite time.
[c] pK_a = 4.3 per ref. 7. K_s was adjusted for solute pK_a with a solution pH of 5.5 assumed.
[d] These incongruent results were not utilized in the thermodynamic assessment.
[e] pK_a = 5.2 per ref. 8. K_s was adjusted for solute pK_a with a solution pH of 5.5 assumed.

tion coefficient, or interaction constant of the following form:

$$K_s = C_m/C_s$$

where C_m and C_s are the compound's equilibrium concentrations in the material and solution, respectively.

It is often desirable that available interaction data be extrapolated to other contact situations. One means of accomplishing this is to relate a compound's K_s value with a more readily available interaction indicator, such as the octanol/water partition coefficient ($P_{o/w}$). Such a model, if the relationship were linear, would take the following form:

$$\log K_s = \text{slope}(\log P_{o/w}) + \text{intercept}$$

The slope and intercept for this relationship can be obtained from the data set representing the test compounds. Specifically, the compound's log K_s can be regressed versus its log $P_{o/w}$, and the regression parameters obtained.

The measured distribution constants for all model compounds and the test material are summarized in Table I. Before the use of these data, it is useful to examine the data set for congruence. Because the examined materials are compositionally similar, it was anticipated that the data set would be internally consistent. The basic tenet is that the materials' similarities suggest that a fixed and reproducible difference should exist between their interaction properties. Anomalous relative behavior of a solute in two similar plastics reflects either the presence of a unique interaction mechanism or potential experimental issues.

The relationships between the reported distribution coefficients for the various pairs of the copolymers are shown in Figures 1 and 2. In general, an excellent correspondence is exhibited by the data sets obtained for the three polymers. Exceptions to this statement can be observed in Figure 1 for the EVAc33 material and the highly polar solutes benzyl alcohol and nicotine. The K_s values reported for these solutes are incongruous and thus are not used in further data analysis. The result of these deletions, also shown in Figure 1, is better agreement between the two EVAs in terms of their thermodynamic behavior.

Before the comparison between K_s and $P_{o/w}$ can be evaluated, the effect of the solution pH on the interaction must be considered. This is true because several of the model solutes, most notably benzoic acid (pK_a = 4.21) and pyridine (pK_a = 5.2), will be in their dissociated form (nonbinding form) at the solution pH used

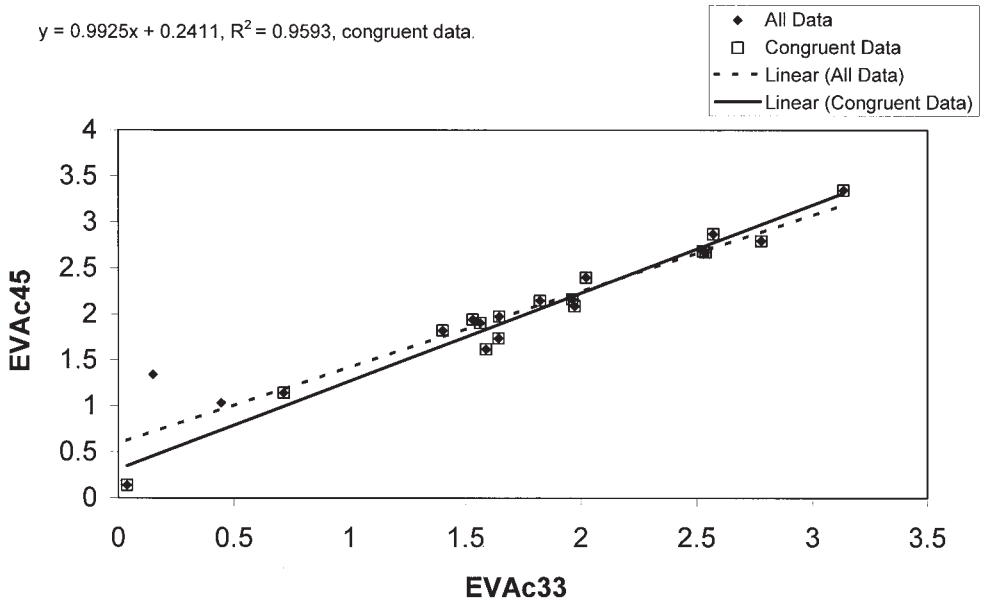

Figure 1 Comparison of reported K_s values for the two EVA copolymers. The K_s values for all the solutes are congruent, with the exception of the polar solutes benzyl alcohol and nicotine. The linear relationship between log K_s and log $P_{o/w}$ is improved if these incongruous analytes are eliminated from the data set.

in the interaction study (5.5–6.0 per ref. 6). The relationship between a solute's interaction constant and solution pH can be expressed as follows:[9]

$$K_{s,i} = K_{s,u}/(1 + 10^{pH-pK_a})$$

where $K_{s,i}$ is the distribution coefficient at the measured pH (ionized form) and $K_{s,u}$ is the coefficient for the neutral form of the solute. The K_s values for benzoic acid and pyridine that appear in Table I have been adjusted from the values reported in the original reference via this equation to account for dissociative effects. Although several other model solutes exhibit some ionic character at the pH of the donor solutions (e.g., 2-, 3-, and 4-nitrophenol and nicotine), their degree of ionization is not large and thus is not considered.

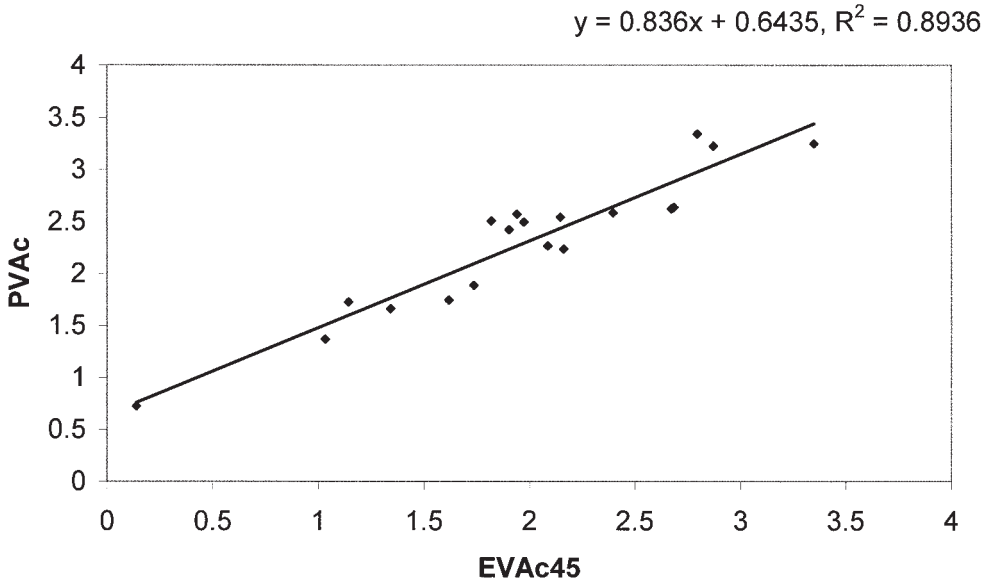

Figure 2 Comparison of reported K_s values for one of the EVA copolymers and PVAc. The K_s values for all the solutes are congruent. Based on Figures 1 and 2, the K_s values for the polar solutes benzyl alcohol and nicotine in EVAc33 are not used in the data analysis documented in this article.

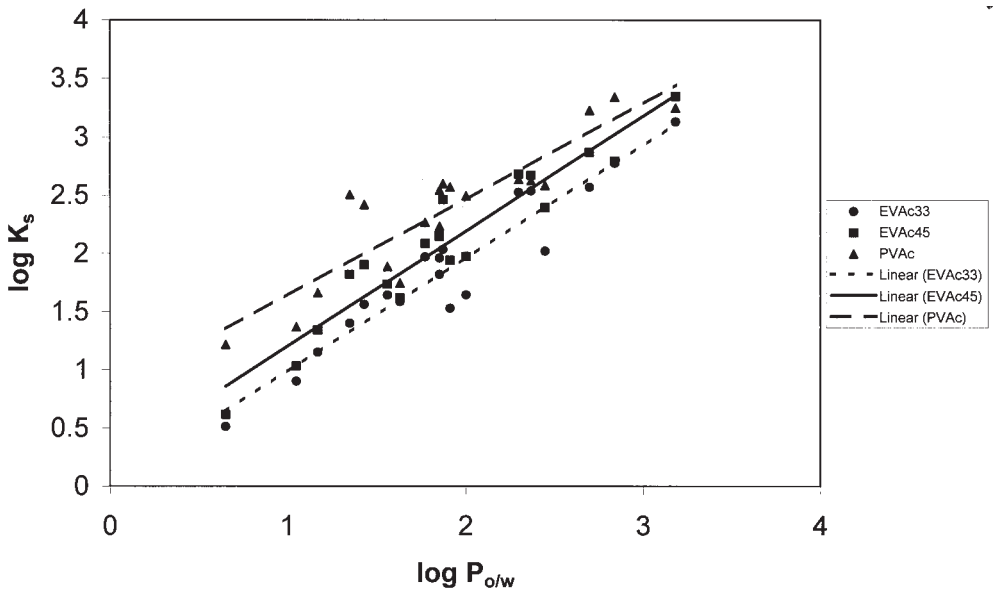

Figure 3 Thermodynamic interaction models for the three polymers studied: the relationship between K_s and $P_{o/w}$. In all cases, an excellent linear relationship can be established between these two variables.

The relationship between the distribution coefficients and the test solutes' $P_{o/w}$ values for all three films is shown in Figure 3. In general, the distribution coefficients (log K_s) are linearly related to the model compound's log $P_{o/w}$. Curve-fit parameters are given in Table II. Although multivariant relationships, which consider paired solvent systems [e.g., octanol/water and hexane/water], have been used in other investigations[10,11] to consider secondary interaction mechanisms, the octanol/water relationships are sufficiently rigorous that this additional mathematical thoroughness is unnecessary. Thus, to a first approximation, one can account for the impact of the compound identity on the material/solution interaction via the compound's log $P_{o/w}$. The slopes of the relationships for the three materials examined are similar, and this indicates that in general the materials share a common interaction mechanism. The intercepts of the interaction models roughly approximate the materials' intrinsic interaction capacity, with the larger intercept reflecting a material that will interact with solutes to a greater extent. The trend observed (PVAc > EVAc45 > EVAc33) matches that discussed by the authors of the previous investigation.[6]

TABLE II
CurveFit Parameters: Relationship Between K_s and $P_{o/w}$

Material	Regression constants, interaction model		
	Slope	Intercept	Correlation coefficient (r^2)
EVAc33	0.977	0.010	0.912
EVAc45	0.988	0.216	0.908
PVAc	0.828	0.812	0.809
Composite model, both EVAs	0.983	0.113	0.882
Composite model, all materials	0.931	0.346	0.783

The relationship took the form log K_s = Slope(log $P_{o/w}$) + Intercept. The interaction constants for the charged solutes (benzoic acid and pyridine) were adjusted for solution pH and solute pK_a.

KINETICS

As was the case for K_s, the diffusion coefficient (D) data set was first examined for congruence between similar materials (EVAc33 vs EVAc45) and, in the case of PVAc, for congruence between the early time and extrapolated data. Pertinent plots are shown in Figures 4 and 5. Although the D values for many of the solutes varied consistently with respect to EVAc33 versus EVAc45 (Fig. 4), a significant exception was benzyl alcohol, whose result [appearing in the lower right-hand corner of Fig. 4(A)] is clearly out of trend. As shown in Figure 5, there is a good general agreement in the D values for PVAc calculated via the short-time and extrapolated methods. Given this behavior, all the D data were considered to be appropriate for further evaluation.

Although thermodynamics establishes the absolute distribution of a solute in a plastic/solution system, the rate at which the equilibrium distribution is attained is important in pharmaceutical applications as pharmaceutical products have well-defined shelf lives. It is relevant to examine the diffusivity data in the context of any relationship that can be established

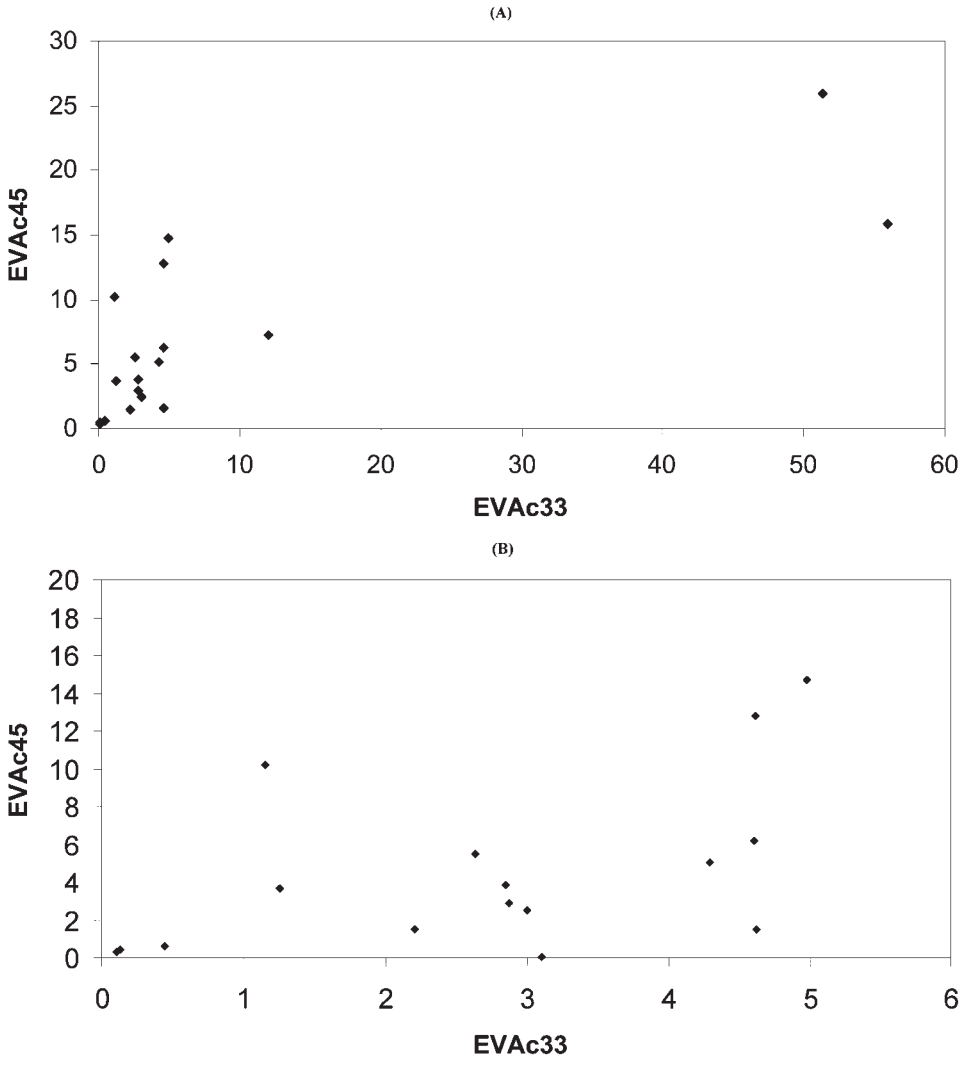

Figure 4 Comparison of reported D values (units of 10^{-9} cm^2/s) for the two EVA copolymers studied: (A) the entire data set and (B) the majority of solutes with D values less than 20.

between kinetic and thermodynamic (e.g., $P_{o/w}$) solute properties as such relationships have been demonstrated by several authors.[1,12–17] In general, acceptable log/log relationships are suggested or reported between the thermodynamic and kinetic coefficients. Such log/log relationships for the EVA and PVAc polymers considered in this study are shown in Figure 6. A strong inverse linear relationship is evident between log D and log $P_{o/w}$ for both EVA copolymers (Fig. 6), with the only significantly out-of-trend result being that of nicotine in EVAc45. Although there is appreciably more scatter in the PVAc data, an inverse relationship between log D and log $P_{o/w}$ can be inferred from Figure 6(B). As was the case for the EVA materials, the only significant out-of-trend result for PVAc was for nicotine. The behavior of nicotine may reflect the relatively large experimental errors associated with this analyte.[6]

UTILIZATION OF THE RELATIONSHIPS

The utility of the thermodynamic equation is considered as follows. Consider the case where one desires to assess the compatibility of drug X in the packaging/delivery system studied. If log $P_{o/w}$ for the drug can be obtained, then its log K_s value can be calculated via the interaction model. Once the drug's K_s value is known, its fractional binding (F_b) by the container can be calculated if the container weight (W_c) and fill volume (V_s) are specified:

$$F_b = f(K_s, W_c, V_s)$$

Similarly, the model can be used to estimate the level that a container leachable will accumulate in solution (C_s) if the leachable's K_s and total pool (P_T) values in the container are known and W_c and V_s are specified:

$$C_s = f(P_T, W_c, V_s, K_s)$$

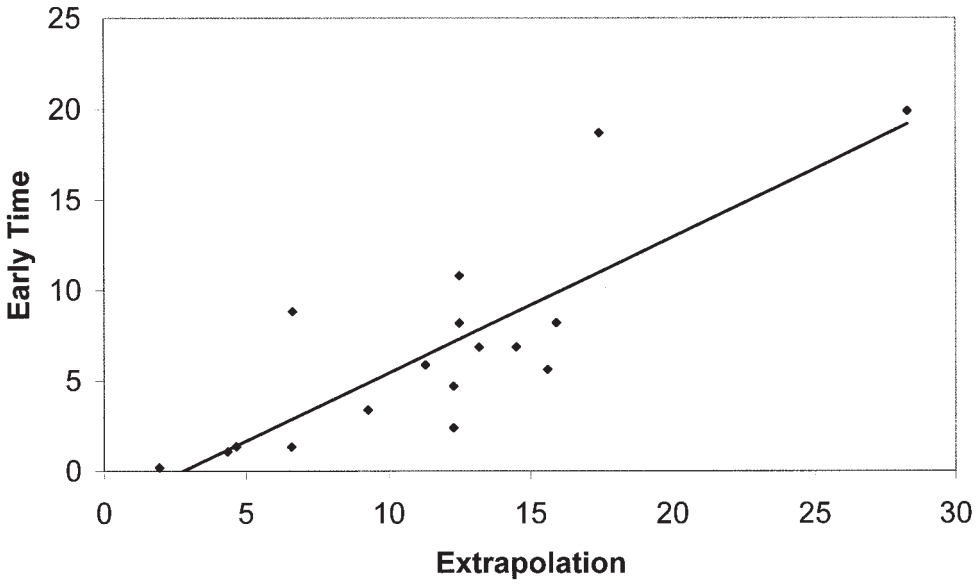

Figure 5 Comparison of reported D values (units of 10^{-12} cm^2/s) for the PVAc copolymer studied: early time versus extrapolation data. The pyridine D values are not included in this plot as they were not reported, and the reported D values for benzyl alcohol are not included as they are clearly anomalous, differing by a factor of 10 between the early time and extrapolation.

The concentration convention used to calculate K_s is important in terms of its practical utility in the aforementioned functions. As the relevant characteristic of a plastic container is most readily expressed in terms of its weight and the relevant characteristic of a contained solution is most readily expressed in terms of its volume, a distribution coefficient is most directly useful when it is derived and expressed in a manner directly compatible with such units of measure. The expression of K_s as a ratio of volume fractions, as was done in ref. 6, complicates its practical application in terms of assessing the magnitude of binding or leaching. Alternatively, an equilibrium interaction constant (E_b) has been proposed:[18,19]

$$E_b = (m_c/W_c)/(m_s/V_s)$$

Although E_b and K_s are both distribution coefficients, their magnitudes will be different as their expression of solute concentrations in the plastic and solution phases is different. Because E_b is calculated on a material weight and solution volume basis, it can be directly used in the calculation of F_b and C_s as follows:[18,19]

$$F_b = (W_c \times E_b)/[V_s + (W_s \times E_b)]$$

$$C_s = (P_T \times W_c)/[V_s + (E_b \times W_c)]$$

As an example of the utility of such expressions, consider the following scenario. For a particular plastic material, the relationship between a compound's E_b and $P_{o/w}$ values has been determined to be (by the generation of a plot such as that shown in Fig. 3)

$$\log E_b = 0.8 \log P_{o/w} - 0.95$$

The product configuration under consideration is 50 mL of a drug product in a container weighing 5 g, where the drug substance has a $P_{o/w}$ value of 10. F_b of the drug by the container can be calculated as follows:

$$\log E_b = 0.8(\log P_{o/w}) - 0.95 = 0.8(1) - 0.95 = -0.15,\ E_b = 10^{-0.15} = 0.708$$

$$F_b = (W_c \times E_b)/[V_s + (W_c \times E_b)] = (5 \times 0.708)/[50 + (5 \times 0.708)] = 0.066$$

Thus, in this example, approximately 7% of the drug is bound by a container made from the plastic, whose E_b–$P_{o/w}$ relationship was experimentally determined.

Alternatively, if the same plastic material contains a leachable X with a $P_{o/w}$ value of 10 and a P_T value of 5 μg/g (ppm), the equilibrium concentration of X in the drug product can be calculated as follows:

$$C_s = (P_T \times W_c)/[V_s + (E_b \times W_c)] = (5 \times 5)/[50 + (0.708 \times 5)] = 0.47\ \mu\text{g/mL}$$

In this example, the equilibrium concentration of X is virtually its entire P_T value of 0.5 μg/mL.

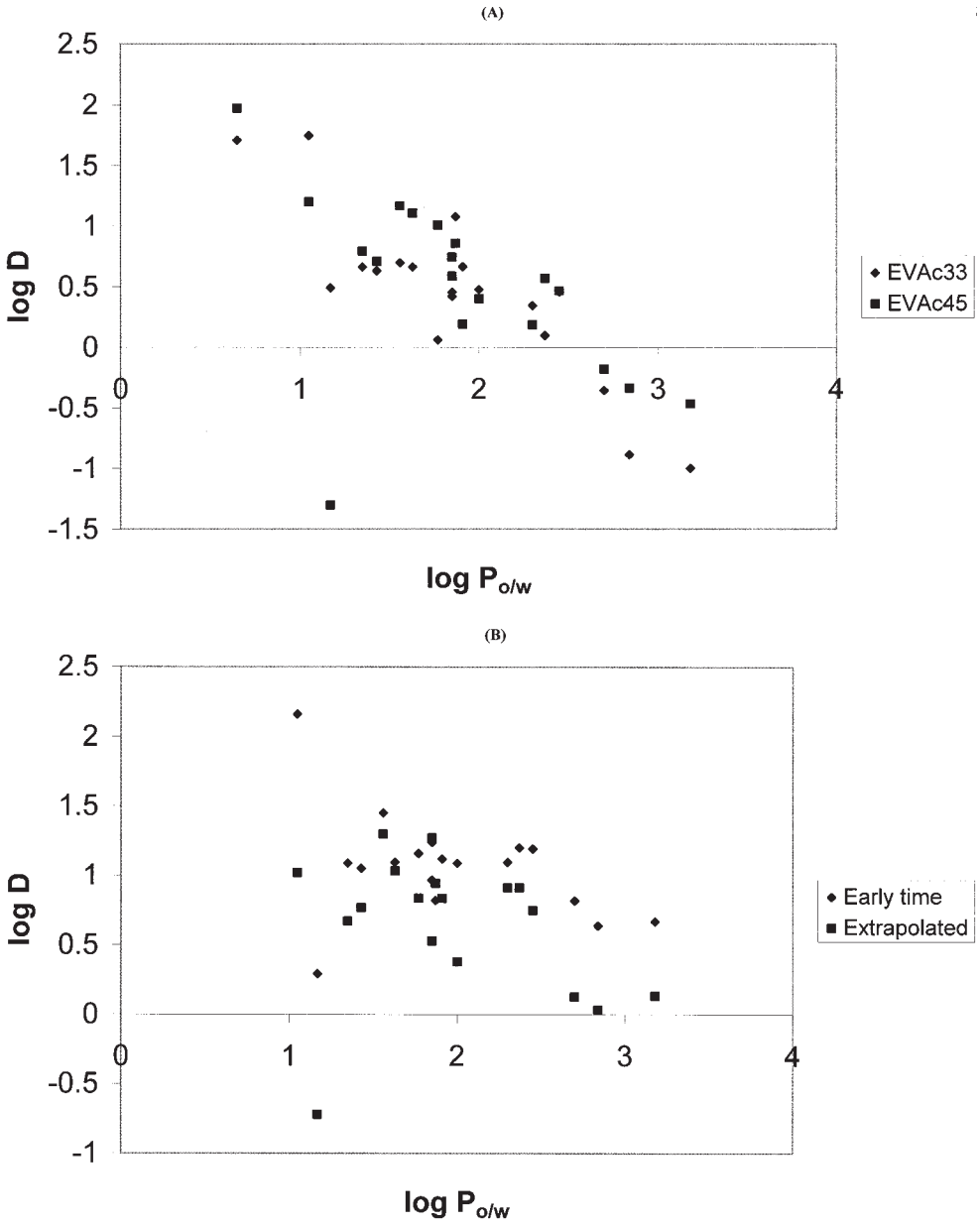

Figure 6 Relationships between log D and log $P_{o/w}$: (A) the two EVA copolymers and (B) the PVAc material (both early times and extrapolations are shown). Although in general the log D value decreases with increasing log $P_{o/w}$, there is a considerable deviation from a strictly linear mode, especially for PVAc. In both parts, the clearly anomalous data point belongs to nicotine.

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