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Interactions between polymer containers and parenteral solutions: Correlating equilibrium polymer-water interaction constants with solute partition coefficients

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Summary

The interaction between six polymeric materials (current or candidate parenteral product containers) and eight test marker solutes was evaluated. Test marker compounds used possessed variable ability to act as hydrogen bond donors. Polymers studied included two plasticized PVCs, two rubber materials and two polyolefin composites. Correlation between the equilibrium interaction coefficients (E_b) and solute octanol-water ($P_{o\text{-}w}$) or hexane-water ($P_{h\text{-}w}$) partition coefficients was poor for all materials studied. However, when the Collander-type relationship between E_b and the partition coefficients are augmented with a term relating to an empirically determined secondary interaction constant (targeting hydrogen bond interactions) excellent correlations between E_b and the partition coefficients are obtained. Alternatively, a bivariate linear interaction model relating E_b and both partition coefficients is proposed:

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

Such a model effectively mimics the interaction behavior of all polymers evaluated; however, the fit is somewhat poorer for the PVC materials. Apparently the two model solvent systems used interact with the acidic test marker compounds via a mechanism which is unavailable to the PVC. The utilization of the model to facilitate container compatibility assessments is demonstrated.

Introduction

A polymer's usefulness and lifetime as a container for aqueous parenteral formulations may be strongly influenced by the polymer's interaction with the solution phase. Two interaction mechanisms are pertinent; leaching, wherein a minor chemical component of the polymer migrates into the solution and sorption (binding), wherein the polymer takes up solutes from solution. Regardless of the specific interaction mechanism, the establishment of container/solution compatibility rests on the demonstration that the magnitude of the effect falls within acceptable limits. For leaching, the maximum permissible accumulation is typically determined by the toxicity of the extractable material or other product use constraints (e.g., solution color, clarity, etc.). For sorption, the maximum permissible amount of solute loss is determined by product efficacy considerations

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(that is, how much solute can be lost before product function is compromised).

Certainly container compatibility assessments can be performed by evaluating the exact nature of the container/solution interaction for all possible product configurations; however, as the number of configurations becomes large (due to a large number of formulation types, solutes of interest or candidate container materials) such an approach becomes prohibitive. Alternately, an interaction model, relating the interaction property of test marker solutes to some solute fundamental property, can be used to estimate the magnitude of the container/solution interaction. In the case where the interaction is partition mediated, several researchers have demonstrated that polymer-solution partition coefficients ($P_{\text{p-s}}$) can be correlated with a solute's solvent-water partition coefficient ($P_{\text{s-w}}$) via a Collander-type expression:

$$\log P_{\text{s-s}} = a(\log P_{\text{s-w}}) + b \tag{1}$$

where

$$P_{\text{s-w}} = C_{\text{s}}/C_{\text{w}} \tag{2}$$

and C_{s} and C_{w} are the equilibrium solute concentrations in the solvent and water phases (Jordon and Pollack, 1972; Nasim et al., 1972; Serota et al., 1972; Pollack et al., 1979; Illum et al., 1983; Pitt et al., 1988).

The effectiveness of the Collander expression as an interaction model hinges on the ability of the model organic solvent to mimic the interaction properties of the container material. In point of fact, several researchers have observed that for most polymeric materials the interaction with aqueous solutes occurs via several mechanisms and thus that a single solvent system is generally a poor model of polymer-solution partitioning (Jordon and Pollack, 1972; Illum and Bundgaard, 1982; Jenke et al., 1989). In such cases, the Collander expression can be modified to include a secondary interaction term (B):

$$\log P_{\text{p-w}} = a(\log P_{\text{s-w}}) + b(\log B) + c \tag{3}$$

This convention is similar in concept to the factorization of partition coefficients into two terms, a volume (cavity) term accounting for hydrophobicity and dispersion terms and an electronic/polarity term accounting for electrostatic interactions (Van de Waterbeemd and Testa, 1987). For the correlation of partition coefficients across solvent systems, the ability of the solute to interact with the solvent via a hydrogen bond mechanism represents a commonly cited secondary interaction used to modify the Collander expression (Higuchi et al., 1969; Leo et al., 1971; Seiler, 1974; Rekker, 1977; Van de Waterbeemd and Testa, 1987; Gryllaki et al., 1989).

As an alternative to $P_{\text{p-w}}$, the equilibrium interaction coefficient (E_{b}) is defined as follows:

$$E_{\text{b}} = (m_{\text{p}}/W_{\text{p}})/(m_{\text{s}}/V_{\text{s}}) \tag{4}$$

where m represents the mass of solute in a phase at equilibrium, w is the weight of polymer (g), v denotes the volume of solution (l), s is the solution phase, and p is the polymer phase.

E_{b} is analogous to $P_{\text{p-w}}$ differing as a gravimetric (as opposed to a volumetric) expression of the concentration of the solute in the polymer and thus can replace $P_{\text{p-w}}$ in Eqns 2 and 3. In a practical sense, E_{b} relates more conveniently to common container/solution design parameters than does the partition coefficient.

This research focuses on establishing the nature of the interaction of six polymers (all of which are current or candidates for parenteral product containers) and various test solutes. The resulting interaction data are used to generate interaction models for each polymer based on solvent-water partition behavior; the nature of the resulting models is discussed in the context of the polymer's composition. Finally, the developed models are used to determine the relative utility of two polymers as container materials.

Materials and Methods

Materials

The polymers used in this study included two plasticized PVC materials, two rubber materials and two polymer composites. The PVC materials differ in terms of the plasticizer; PVC no. 1 contains approx. 25% (by weight) dioctylphthalate (DOP) while PVC no. 2 contains approx. 33% by weight of a hexylcitrate-based plasticizer. Both rubbers used herein are representative of thermoset solution contact components of parenteral product containers/delivery systems. Polymer composite no. 1 consists primarily of polypropylene with minor amounts of low density polyethylene and other components while polymer composite no. 2 is primarily linear low density polyethylene with polycaprolactam tie layers.

Test solutes used are summarized in Table 1 and were obtained as reagent grade compounds. Other reagents used to prepare diluents, mobile phases, interaction solutions and other analytical reagents were either research or HPLC grade as appropriate. Distilled, deionized water was obtained from a Barnstead NANOpure II water polishing system.

Partition coefficients

Octanol-water partition coefficients ($P_{o\text{-}w}$) were obtained from the literature (Leo et al., 1972; Jenke et al., 1989) and represent direct or indirect (HPLC) experimental measurements. Hexane-water partition coefficients ($P_{h\text{-}w}$) were obtained by the conventional shake flask method. Aliquots of hexane and 4 mM trifluoroacetic acid (used to insure that the solutes were undissociated), spiked to contain known amounts of the test solute, were equilibrated and the equilibrium solute distribution was determined either by direct UV spectrophotometry or HPLC.

TABLE 1

Description of the test solutes

Solute	Abbreviation	log $P_{o\text{-}w}$	log $P_{h\text{-}w}$
Dimethyl phthalate	DMP	2.22	0.82
Diethyl phthalate	DEP	3.22	1.75
Dipropyl phthalate	DPP	4.05	2.67
4-Methylbenzoic acid	MBH	2.27	−0.40
4-Ethylbenzoic acid	EBH	2.97	0.29
4-Butylbenzoic acid	BBH	3.97	1.80
Ethyl paraben[a]	ETPB	2.57	−1.05
Butyl paraben[a]	BUPB	3.59	0.48

[a] 4-Hydroxybenzoic acid, – ester.

Equilibrium interaction coefficients

E_b coefficients were determined by the method of sequential extraction. Specifically, a known amount of test polymer (approx. 1.6 g for the PVC and composites, 0.8 g for the rubbers) was placed in a glass vessel (Pyrex screw-top type containers with total volume of approx. 150 ml) containing approx. 130 ml of a donor solution. For the non-rubber polymers, the polymer samples were thin films cut into approx. 1 cm^2 pieces while the rubbers were cut into more or less cubic pieces of approx. 100 mm^3. The donor solution contained test solutes in concentrations ranging from 10 to 100 ppm. Individual donor solutions contained at most three test solutes; three mixtures (DMP, DEP, DPP; MBH, EBH, BBH; ETPB, BUPB) were used. In this way, competition between interacting solutes was minimized and analytical separation was facilitated. The materials were ‘loaded’ with the solutes by storing the closed reaction system at 55°C for 5 days (with constant gentle agitation). After loading, an aliquot of the donor solution was retrieved for analysis and the loading mass was determined. The donor solution was then discarded, the material was rinsed well with water and then placed in contact with 25 ml of extracting solution. The material was extracted under ambient conditions with constant agitation until equilibrium was obtained (aliquots of the extracting solution were periodically analyzed to monitor extraction progress). After equilibration, the material was again rinsed with water and extracted with a second fresh aliquot of extracting solution. Both the donor and extracting solutions were 4 mM trifluoracetic acid to ensure that the test solutes were completely undissociated. The interaction constants were determined from both the loading and extraction steps; data reported herein represents the mean of these determinations.

Analytical method

The solute concentration in all interaction samples was determined by HPLC. Separation was accomplished on a Supelcosil LC8-DB stationary phase (50 × 4.6 mm column, 5 μm particles) with a binary mobile phase (55:45 methanol/4 mM trifluoracetic acid). Flow rate was 1 ml/min, detection was by UV at 220 nm and sample size was from 10 to 50 μl.

Results and Discussion

Solvent-water partition data for all test solutes used are summarized in Table 1. The test solutes used encompass a fairly wide range of lipophilicity and exhibit varying abilities to interact with the container materials via a secondary (electronic/polarity) mechanism. The direct correlation between E_b and either $P_{o\text{-}w}$ or $P_{h\text{-}w}$ is fairly poor for all the test materials. As shown in Table 2, the direct correlation of these quantities typically exhibits a correlation coefficient (r^2) of less than 0.9. Examination of typical E_b vs solute partition coefficient plots (Figs. 1 and 2 for PVC no. 1) indicates that especially for $P_{o\text{-}w}$ a good correlation between P and E_b can be obtained within a compound class (e.g., phthalates, acids and parabens). However, the correlation breaks down between classes. A similar class distinction is apparent in most of the $P_{h\text{-}w}$-E_b correlations; however, for PVC no. 1 the variation in the correlation between these two solute properties appears to be random as opposed to compound class related. That is the interaction mechanism between the model solutes and PVC no. 1 is sufficiently complex that hexane mimics the interaction only poorly. The distinction in interaction properties relating to the ability of the solutes to act as hydrogen bond donors indicates that this secondary interaction mechanism strongly influences both the polymer-solute interaction as well as the effectiveness of the octanol and hexane as polymer models.

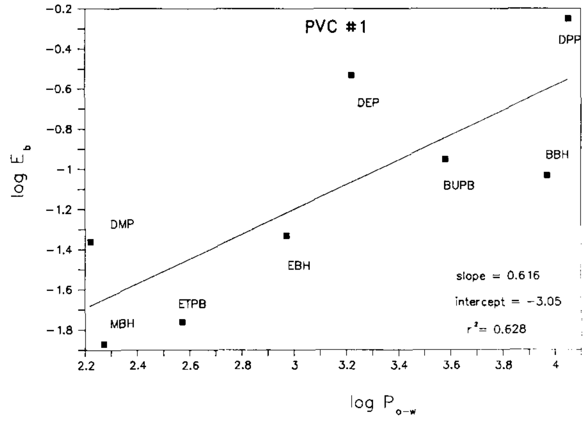

Fig. 1. Univariant interaction model for PVC no. 1; plot of the equilibrium interaction coefficient (E_b) vs the octanol-water partition coefficient ($P_{o\text{-}w}$). The best fit line represents Eqn 1.

TABLE 2

Curve fit parameters for the interaction model relating log E_b and either log $P_{o\text{-}w}$ or log $P_{h\text{-}w}$

Material	Slope	Intercept	r^2
A. Versus log $P_{o\text{-}w}$			
Rubber no. 2	0.546	−3.15	0.76
Polymer no. 2	0.596	−3.40	0.89
PVC no. 1	0.616	−3.05	0.63
Polymer no. 1	0.753	−4.58	0.38
PVC no. 2	0.835	−3.53	0.66
Rubber no. 1	0.898	−4.53	0.61
B. Versus log $P_{h\text{-}w}$			
Polymer no. 2	0.281	−1.78	0.61
Rubber no. 2	0.300	−1.71	0.64
PVC no. 1	0.415	−1.46	0.83
PVC no. 2	0.501	−1.33	0.69
Rubber no. 1	0.640	−2.25	0.90
Polymer no. 1	0.689	−2.79	0.93

The utilization of experimentally determined hydrogen bond formation constants as the secondary interaction correction factor in Eqn 3 has successfully improved correlations between partitioning behavior in different interaction systems.

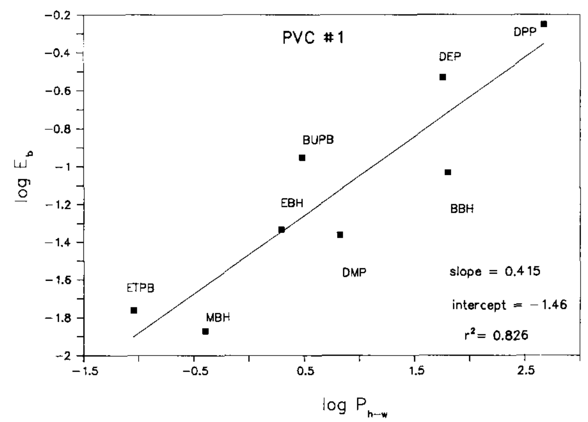

Fig. 2. Univariant interaction model for PVC no. 1; plot of the equilibrium interaction coefficient (E_b) vs the hexane-water partition coefficient ($P_{h\text{-}w}$). The best fit line represents Eqn 1.

Rather than measuring the formation constants for each solute, an electronic/polarity factor (B) was determined empirically in this research. Since B is a property of the solute (and thus is constant across the polymers used) it can be estimated for each test solute by minimization of the error associated with E_b vs $P_{o\text{-}w}$ (or $P_{h\text{-}w}$) correlations for the entire polymer data set studied. In this research, the B term for the phthalates was assigned a value of 0 (no hydrogen bond ability) while B for the other solutes was determined via an iterative process using the correlation coefficient of each polymer model as the optimization variable.

The results of this empirical strategy to generate B are shown for $P_{o\text{-}w}$ in Table 3 and for $P_{h\text{-}w}$ in Table 4. For each solvent system, an internally consistent set of B values were obtained, which, when used in conjunction with Eqn 3, produced excellent correlations between E_b and the solvent-water partition coefficients. As shown in Figs 3 and 4, the resulting correlation model equations are essentially devoid of any compound class discrimination. Curve fit data provide several insights into the nature of the material-solute interactions. The magnitude of the intercept of the best fit linear models reflects the relative intrinsic lipophilicity of the polymeric material with a more negative intercept indicating a less lipophilic material. Rank ordering of the materials with respect to their intrinsic lipophilicity is constant between solvent model and readily identifies the PVC materials as the most lipophilic and the composites as more hydrophilic. The slope of the partition coefficient term in the model reflects the relative sensitivity of the material in terms of changing solute hydrophobicity with a larger slope indicating a more sensitive material. Rank ordering of the material with respect to sensitivity to solute hydrophobicity is also consistent (within experimental error) across the solvent models employed and indicates that the materials studied exhibit widely

TABLE 3

Curve fit parameters for the interaction model relating log E_b and log $P_{o\text{-}w}$ + log B

Material	Slope (log $P_{h\text{-}w}$)	Slope (log B)	Intercept (c)	r^2
Rubber no. 1	0.929	−0.211	−4.10	0.944
Polymer no. 1	0.790	−0.289	−3.97	0.946
Polymer no. 2	0.609	−0.033	−3.35	0.922
PVC no. 2	0.896	−0.162	−3.32	0.923
Rubber no. 2	0.560	−0.079	−3.00	0.929
PVC no. 1	0.639	−0.139	−2.77	0.955

B factors used (empirical fit)
DMP = DEP = DPP = 0
MBH = 3.0
EBH = 2.5
BBH = 5.0
ETPB = 5.5
BUPB = 4

TABLE 4

Curve fit parameters for the interaction model relating log E_b and log $P_{h\text{-}w}$ + log B

Material	Slope (log $P_{h\text{-}w}$)	Slope (log B)	Intercept (c)	r^2
Polymer no. 1	0.704	0.018	−2.82	0.926
Rubber no. 1	0.857	0.250	−2.68	0.940
Polymer no. 2	0.577	0.320	−2.32	0.944
PVC no. 2	0.960	0.529	−2.24	0.941
Rubber no. 2	0.523	0.232	−2.12	0.911
PVC no. 1	0.647	0.267	−1.92	0.941

B factors used (empirical fit)
DMP = DEP = DPP = 0
MBH = 1.7
EBH = 1.8
BBH = −0.5
ETPB = 2.7
BUPB = 2.5

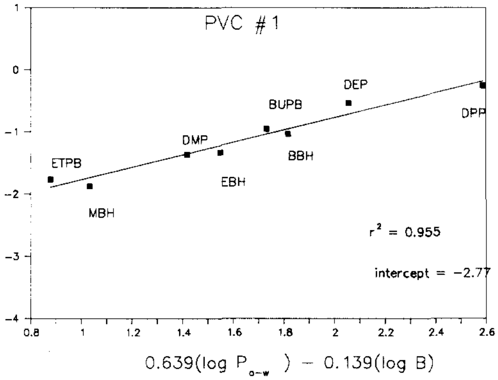

Fig. 3. Empirical bivariant interaction model for PVC no. 1; plot of the equilibrium interaction coefficient (E_b) vs the linear combination of the octanol-water partition coefficient ($P_{o\text{-}w}$) and the empirically determined secondary interaction parameter (B). The best fit line represents Eqn 3.

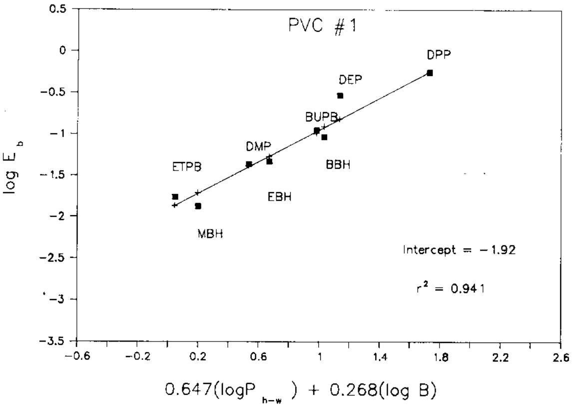

Fig. 4. Empirical bivariant interaction model for PVC no. 1; plot of the equilibrium interaction coefficient (E_b) vs the linear combination of the hexane-water partition coefficient ($P_{h\text{-}w}$) and the empirically determined secondary interaction parameter (B). The best fit line represents Eqn 3.

variable behavior with respect to this interaction property.

The nature of the log B portion of the empirical model provides a qualitative indication of the complexity of the secondary interaction mechanism. While one would expect the absolute magnitude of B to be different in the octanol and hexane solvent models (since these solvents themselves exhibit variable hydrogen bond acceptor ability), one would expect either the rank ordering of B or the slope of the log B term in the interaction models to be consistent in both model systems if the secondary interaction mechanism involved only the ability to interact via a hydrogen bonding mechanism. In point of fact, rank ordering of the B terms in both solvent models is radically different. A plausible explanation of this result is that the secondary solute-material interaction is actually a combination of several mechanisms which are approximated to different extents in the two solvent systems used as models. That is, perhaps octanol and hexane target different secondary solute-material interaction mechanisms.

While the empirically determined B factors provide an internally consistent, solvent model specific interaction equation which presumably could be used to assess the magnitude of the interaction between any potential container material and the test solutes studied herein, such a formalism suffers from several practical drawbacks. In terms of general utility, the empirical nature of the B constants implies that they cannot be readily established for solutes other than those studied herein. Thus in order to develop a solvent based partition model that is applicable to a large number of solutes, a model based on multiple solvent-water partition coefficients is proposed. Both hexane-water and octanol-water solvent systems have shown a consistent ability to model polymer hydrophobicity and sensitivity to solute lipophilicity and apparently target different secondary interaction mechanisms. Thus we propose that the material-solute interaction properties can be effectively modeled by the linear combination of $P_{o\text{-}w}$ and $P_{h\text{-}w}$ via the expression:

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

Substitution of the observed interaction constants and partition coefficients into Eqn 5 produces bivariant linear models with best fit parameters as shown in Table 5. Especially for the rubbers and composite polymers, the resultant correlation between E_b and the linear combination of $P_{o\text{-}w}$ and $P_{h\text{-}w}$ is excellent. As shown in Figs 5 and 6, little discrimination among solute classes is shown by the combination model for these materials. The magnitude of the respective slopes is indicative of the relative ability of each solvent system to model a particular material's interaction properties. Thus, for example, polymer no. 1, whose interaction properties correlated fairly well with $P_{h\text{-}w}$ (Table 2), has a combination

TABLE 5

Curve fit parameters, bivariant interaction model relating log E_b and log $P_{o\text{-}w}$ + log $P_{h\text{-}w}$

Material	Slope (log $P_{o\text{-}w}$)	Slope (log $P_{h\text{-}w}$)	Intercept	r^2
Polymer no. 1	−0.157	0.811	−2.39	0.975
Rubber no. 1	0.262	0.577	−3.01	0.973
Polymer no. 2	0.483	0.094	−3.11	0.929
PVC no. 2	0.497	0.283	−2.69	0.855
Rubber no. 2	0.325	0.206	−2.63	0.967
PVC no. 1	0.249	0.336	−2.16	0.905

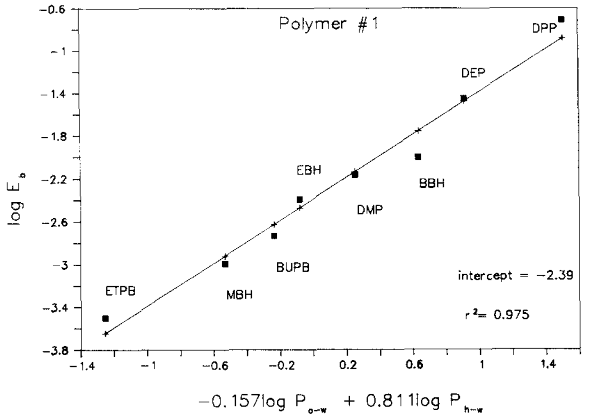

Fig. 5. Bivariant interaction model for polymer no. 1; plot of the equilibrium interaction coefficient (E_b) vs the linear combination of octanol-water ($P_{o\text{-}w}$) and hexane-water ($P_{h\text{-}w}$) partition coefficients. The best fit line represents Eqn 5.

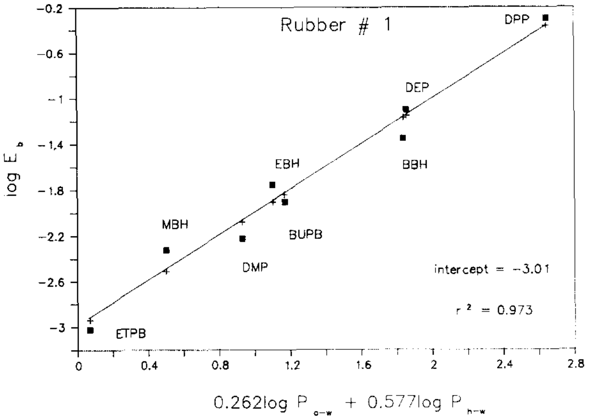

Fig. 6. Bivariant interaction model for rubber no. 1; plot of the equilibrium interaction coefficient (E_b) vs the linear combination of octanol-water ($P_{o\text{-}w}$) and hexane-water ($P_{h\text{-}w}$) partition coefficients. The best fit line represents Eqn 5.

model equation in which the slope of the $P_{h\text{-}w}$ term is large compared to that of the $P_{o\text{-}w}$ term. Alternatively, for polymer no. 2, whose interaction properties were more effectively correlated with $P_{o\text{-}w}$ alone, the slope of the $P_{o\text{-}w}$ term is large and this quantity dominates the model. For the other test materials, the combination model exhibits important contributions from both solvent systems.

While the bivariant combination model provides a useful approximation of the interaction properties of the PVC materials, the fit of the model for these materials is poorer than the fit for the other polymers. Examination of the curve fit diagrams for the PVC materials (Figs 7 and 8) indicates that there is residual compound class discrimination in the combination model. While the model apparently is effective in terms of approximating the behavior of the non-acidic test solutes,

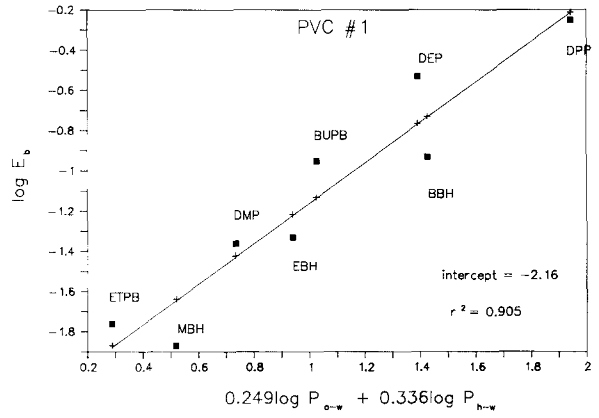

Fig. 7. Bivariant interaction model for PVC no. 1; plot of the equilibrium interaction coefficient (E_b) vs the linear combination of octanol-water ($P_{o\text{-}w}$) and hexane-water ($P_{h\text{-}w}$) partition coefficients. The best fit line represents Eqn 5.

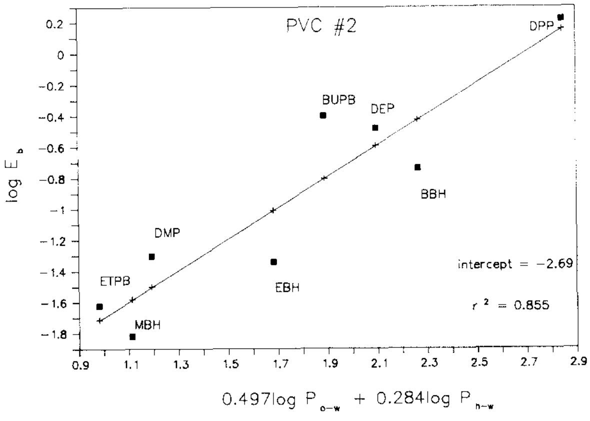

Fig. 8. Bivariant interaction model for PVC no. 2; plot of the equilibrium interaction coefficient (E_b) vs the linear combination of octanol-water ($P_{o\text{-}w}$) and hexane-water ($P_{h\text{-}w}$) partition coefficients. The best fit line represents Eqn 5.

all the acids consistently fall off the calculated best fit line. Actually, the combination model tends to overestimate the binding of these solutes to the PVC materials. This behavior can be interpreted as indicating that the acids interact with the solvent models via a mechanism which is not assessable to the PVC.

The partition coefficient-E_b correlations provide a mechanism by which the relative binding properties of two polymers can be assessed for any solute whose $P_{o\text{-}w}$ and $P_{h\text{-}w}$ are known but whose E_b coefficients have not been experimentally determined. By mathematically equating interaction models for the two polymers of interest (that is, setting the model equations for the two polymers equal to one another and solving for $P_{o\text{-}w}$ and $P_{h\text{-}w}$) a 'line of equivalency' (which contains only the partition coefficients as variables) is generated. Solutes whose partition coefficients fall on this line exhibit the same fractional binding by the two polymers. Generation of a $P_{o\text{-}w}$ and $P_{h\text{-}w}$ grid results in a 'figure of merit' (that is, a pictorial representation of the relative interaction properties of the two materials being compared) which identifies regions in which the magnitude of the solute-material interaction is different for the two materials. Thus, for example, the figure of merit comparing the two rubber materials is shown in Fig. 9. Appropriate $P_{o\text{-}w}/P_{h\text{-}w}$ regions are identified wherein one rubber binds less solute than the other and thus is superior in the context of minimizing the magnitude of the solution-container interaction. Thus we see that rubber no. 1, with a low intrinsic lipophilicity, is superior to rubber no. 2 for the more hydrophilic solutes. However, since rubber no. 1 is more sensitive than the other to changing solute hydrophobicity, rubber no. 2 is superior (in terms of minimizing solute loss due to container sorption) for the more hydrophobic test solutes.

The direct comparison of the measured interaction constants provides an interesting means of evaluating the influence that material composition has on the mechanics of the interaction process. For example, when the measured binding constants of the two rubbers are compared (Fig. 10), an excellent linear correlation is established. Thus, while the two rubbers differ in terms of intrinsic lipophilic nature and relative sensitivity to solute hydrophobicity, the interaction mechanism for the two materials is essentially the same. Similarly, the two plasticized PVC materials are mechanistically similar with respect to their solute interaction properties, even though the identity of the plasticizer (as well as the amount of plasticizer) is different in both materials (Fig. 11). We conclude that while the nature of the plasticizer may influence the magnitude of the solute-polymer interaction, it apparently does not change the mechanism of the interaction. We also observe that the greater fractional binding exhibited by the citrate plasticized PVC studied in this research is consistent

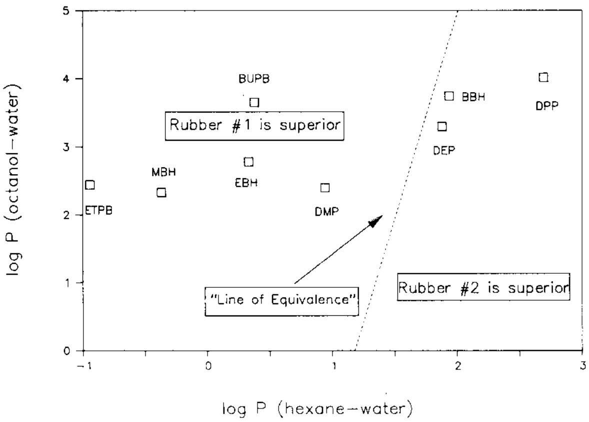

Fig. 9. Figure of merit; comparative binding properties of the two rubber materials.

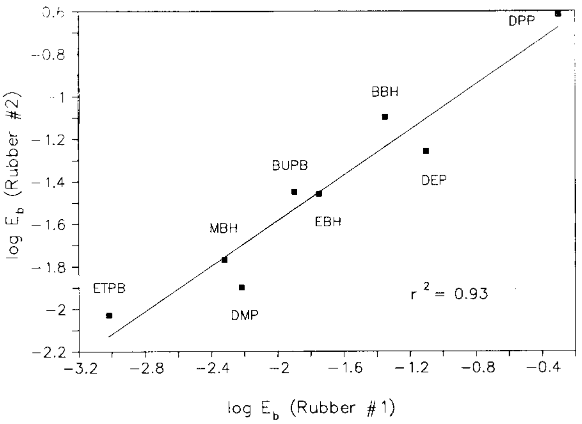

Fig. 10. Comparison of the binding properties of the two rubber materials.

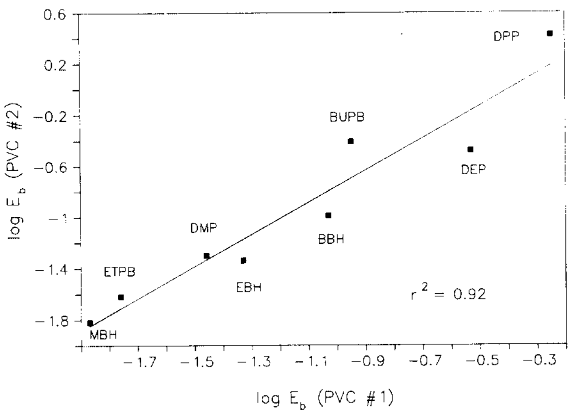

Fig. 11. Comparison of the binding properties of the two PVC materials.

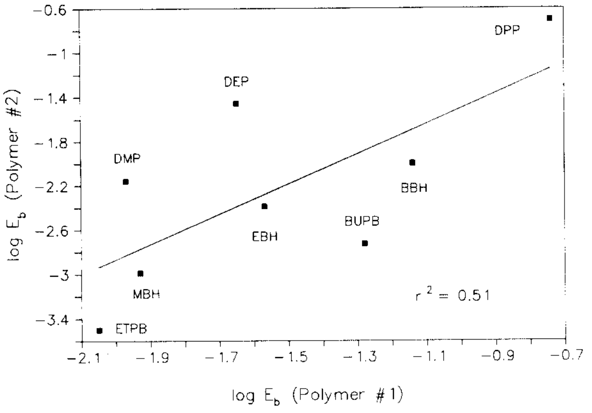

Fig. 12. Comparison of the binding properties of the two composite materials.

with the observation of Bray (1983) that citrate plasticized PVC sorbed larger amounts of benzocaine from solution than did DOP plasticized PVC.

Comparison of the interaction properties of the two composite materials (Fig. 12) indicates that their solute interaction mechanisms are radically different. A clear compound class distinction is apparent in the comparative interaction data; hydrogen bond donor solutes interact quite differently with the two composite materials. While the fact that polymer no. 1 is primarily polypropylene and that polymer no. 2 is primarily polyethylene will influence the relative lipophilicities and hydrophobic sensitivities of the two composites, polypropylene and polyethylene are not radically different in terms of their ability to act as hydrogen bond acceptors (and in point of fact exhibit little (if any) hydrogen bond activity). However, the polycaprolactam tie layer in polymer no. 2 is a very strong hydrogen bond acceptor; thus the greatly different nature of these composite's interaction with hydrogen bond donor solutes can be attributed to the tie layer's contribution to the total composite interaction properties. Thus it is not surprising that the observed interaction behavior does not correlate well across material types.

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