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Effect of Solution Phase Composition on the Interaction Between Aqueous Model Solutes and Polymeric Container Materials

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The interaction between several marker solutes and a polyolefin laminate polymer was studied in several solutions. Solutions studied included mixtures of sodium chloride and dextrose (at concentrations more less typical of iv administration solutions) and several actual iv products [lactated Ringer's injection, Dianeal, Travasol (amino acid) injection, and alcohol/dextrose injection]. The interaction properties of the candidate container material correlated well with the solute's octanol–water partition coefficient. For nonionic species, the magnitude of the container/solution interaction was independent of solution phase composition. For the ionic test solute, solution pH, which impacts the speciation of the solute, was the only solution composition variable that significantly influenced the interaction. Thus water (or a weak buffer solution) is suggested as an appropriate model solvent for use in container compatibility evaluations involving iv-related products.

KEY WORDS: container/solution interactions; partition coeffient; polymeric container materials; polyolefin laminate polymer.

INTRODUCTION

The utility of a material to serve as a container for an aqueous parenteral product is impacted by the degree to which the material interacts with the contained solution. The main interactions include leaching, wherein a container component is mobilized from the container into solution, and binding, wherein the container takes up solutes from the contained solution. The effect of solute and container properties on the magnitude of a container/solution interaction has been extensively documented (1–7). Systematic evaluation of the effect of solution phase composition on the container/solution interaction is less extensive and is limited primarily to a discussion of the effect of pH on the interaction properties of ionizable solutes (8–10). Little information is available on how the magnitude of the container/solution interaction is affected by the composition of typical iv administration solutions. While PVC shows a differing ability to sorb vitamin A and sodium warfarin from dextrose, saline, or water matrices (11), the differences for warfarin were attributed primarily to a pH effect which is small or negligible for vitamin A.

In this report, the effect of solution composition on the interaction between several marker solutes and a laminate composite polymeric material (typical of the "new" class of container materials being utilized in parenteral applications) is documented. Solutions studied represent typical iv administration solutions including those containing sodium chloride, dextrose, and various inorganic salts and organic constituents.

MATERIALS AND METHODS

Materials

The polymer studied is a proprietary container candidate which consists of laminated coextruded polyolefin layers; the same material lots were used throughout the study. Marker solutes used, their abbreviations, and their octanol–water and hexane–water partition coefficients are listed in Table I and were analytical-grade chemicals (98% purity or better). Specific test solutions used are also summarized in Table I; the sodium chloride- and dextrose-containing formulations were prepared from reagent-grade chemicals and contained 0.01 *M* phosphate buffer. The Dianeal solution was also prepared from reagent-grade chemicals and was adjusted to pH 4.0. Travasol (8.5%; amino acids) injection without electrolytes, alcohol (5%) and dextrose (5%) injection (USP), and Lactated Ringer's injection (USP) were commercially available products (Travenol Laboratories, Deerfield, IL) which were adjusted to pH 4.0 prior to use.

Interaction Study

Polymer/solute interactions were studied by the shake flask method. Test solutions were spiked to contain from 15 to 40 ppm of the marker compounds; one portion of the test solution was spiked to contain DMP, DEP, and DPP, while additional portions were spiked with sets of the others. Fifty milliliters of the spiked solution was mixed with approximately 0.5 g of the polymer and stored in sealed glass containers at 35°C with constant gentle agitation. The polymer was cut into 1-cm^2 pieces to enhance the interaction. Solution vessels containing no polymer were also stored under the same conditions to act as controls. At various times during storage, solution phase composition was determined. The experiment was terminated when solution phase equilibrium had been achieved. Replicate units were prepared and characterized for each solution type and solute mixture.

Analytical Method

The solute concentration in all samples was determined by HPLC. Separation was accomplished on a Supelcosil LC8-DB stationary phase (50 × 4.6-mm column, 5-μm particle size) with binary mobile phases (methanol/water with trifluroacetic acid). The flow rate was 1 ml/min, detection was accomplished by UV at 220 nm, and sample injection size was 10 μl. Under the separation conditions used, all solutes in a given mixture were baseline resolved. Solute concentration was obtained via the use of a three-point calibration spanning the concentration range of 1 to 100 ppm (which encompassed the equilibrium concentration of each test article). In general, the correlation coefficient (r^2) obtained from the linear regression analysis of the calibration data was 0.999 or greater.

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Table I. Model Solutes and Solutions Used

A. Solutes used

Solute	Abbreviation	log $P_{o\text{-}w}$	log $P_{h\text{-}w}$
Aniline	AN	0.90	−0.1
4-Methylbenzyl alcohol	MBOH	1.60	0.1
Dimethyl phthalate[a]	DMP	2.16	0.82
n-Ethylbenzyl amine	NEHA	2.17	−1.69
Ethyl-4-aminobenzoate	ETBZ	2.24	−0.07
4-Methylbenzoic acid	MBH	2.27	−0.4
Ethyl paraben[a]	ETPB	2.57	−1.05
Ethylbenxoic acid	EBH	2.97	0.29
Diethyl phthalate[a]	DEP	3.22	1.75
Butyl-4-aminobenzoate	BUBZ	3.37	1.14
Butyl paraben[a]	BUPB	3.59	0.48
4-Butylbenzoic acid[a]	BBH	3.95	1.80
Dipropyl phthalate[a]	DPP	4.05	2.67

B. Solutions used

Solution code	Composition
S1	0.9% NaCl, pH 3[b]
S2	0.9% NaCl, pH 5[b]
S3	0.9% NaCl, pH 7[b]
S4	0.45% NaCl, pH 5[b]
S5	1.8% NaCl, pH 5[b]
W	Water, pH 5[b]
SD	0.9% NaCl, 10% dextrose, pH 5[b]
D1	2.5% dextrose, pH 5[b]
D2	10% dextrose, pH 5[b]
D3	25% dextrose, pH 5[b]
DL	Dianeal PD-1[c]
D/A	5% dextrose, 5% alcohol injection[c]
LR	Lactated Ringer's injection[c]
TR	8.5% Travasol without electrolytes[c]
DX	50% dextrose[c]

[a] Denotes solutes that are used to compare the interaction behavior in the various solutions studied.
[b] In 0.01 *M* phosphate buffer.
[c] Adjusted to pH 4.0.

Partition Coefficients

Octanol–water partition coefficients ($P_{o\text{-}w}$) were obtained from the literature (6,12) and represent experimental measurements. Hexane–water partition coefficients ($P_{h\text{-}w}$) were obtained by conventional shake flask methods. Aliquots of hexane and water, spiked to contain known quantities of the test solutes, were equilibrated and the equilibrium solute distribution was determined by measuring the solute concentration in both phases (by either HPLC or direct UV measurements). For the ionizable model solute determinations, the water phase was spiked to contain 4 m*M* trifluoroacetic acid to ensure that the analyte was protonated.

RESULTS AND DISCUSSION

The equilibrium interaction constant (E_b) describes the equilibrium distribution of a solute between a container and its contained solution and is defined by the expression

$$E_b = (m_c/W_c)/(m_s/V_s) \qquad (1)$$

where m is the mass of solute in a phase at equilibrium, W is the weight of the container (grams), V is the volume of solution (liters), and subscripts s and c refer to the solution and container phases. In essence, E_b is analogous to the solute's container/solution partition coefficient, differing only as a gravimetric (as opposed to volumetric) expression of the container solute concentration. E_b can be related to the solute's solvent–solvent partition coefficient ($P_{s\text{-}s}$) via a Collander-type expression (6,7):

$$\log E_b = a \log P_{s\text{-}s} + b \qquad (2)$$

Such a formalization is consistent with reported log–log correlations between solute–polymer and solute–solvent partition coefficients (1,4,8–10). For the marker solutes used in this study, measured log E_b values can be regressed against the logarithm of the solute's solvent/solvent partition coefficient to generate values for the a and b constants for each solution studied. Thus the variation in these curve-fit parameters, measured as a function of solution phase composition, will serve to characterize the impact that solution composition has on container/solution interactions.

Mechanistically, solute/container interactions can be multimodal and include (but are not limited to) contributions related to the intrinsic solute and the polymer lipophilicity and to hydrogen bonding between the polymer and the solutes. Thus the marker solutes used include species which exhibit little (phthalates) or variable (parabens and acid) hydrogen bond activity. Additionally, the polymer material studied is dominated by components which typically exhibit some hydrogen bond character. Finally, acidic solutes (substituted benzoic acids) were included so that the effect of pH could be documented.

Considering the pH effect, one notes that only the nonionized form of an ionizable solute actively participates in the container/solution interaction. Thus the relationship among the observed constant at any pH ($E_{b,i}$) for an ionizable solute, the solution pH, and the interaction constant for the nonionized form of the solute ($E_{b,u}$) can be written (9)

$$E_{b,i} = E_{b,u}/(1 + 10^{\mathrm{pH}-\mathrm{p}K_a}) \qquad (3)$$

Observed values of $E_{b,i}$ for BBH in 0.9% NaCL are 0.31, 0.040, and 1.0×10^{-3} at pH 3, 5, and 7, respectively. $E_{b,u}$ for BBH was determined to be 0.36 (measured at a pH of ≈2). Predicted values for $E_{b,i}$ [from Eq. (3)] are 0.33, 0.040, and 5×10^{-4}, respectively, at pH 3, 5, and 7 and agree well with the observed behavior. For the other, nonionizable solutes, no significant pH effect on the container/solution interaction was observed (see Fig. 1).

The relationship between E_b and the solute's octanol–water partition coefficient ($P_{o\text{-}w}$) is shown in Fig. 2. E_b values obtained for replicate sample units agreed to within ±5%. Octanol proved to be a good model for the container material studied, which is not surprising given the inherent hydrogen bond activity of both octanol and the material being studied. The utility of the octanol model is contrasted with the rather poor ability of hexane–water to model polymer behavior (compare Figs. 2 and 3). Specifically, the correlation coefficient (r^2) for the linear correlation of log E_b and

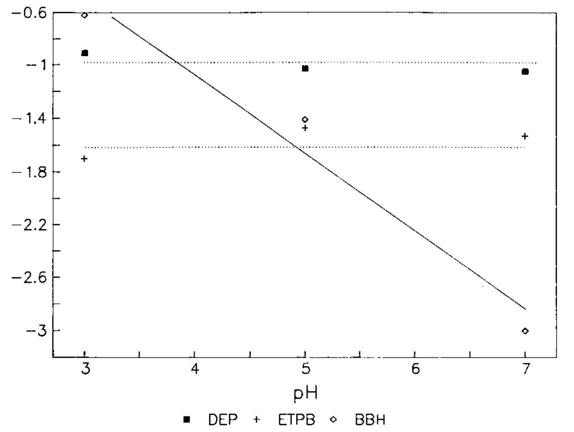

Fig. 1. Effect of solution phase pH on the interaction constant (E_b). Matrix used was 0.9% NaCl. Note: pK_a for BBH is ≈4.2.

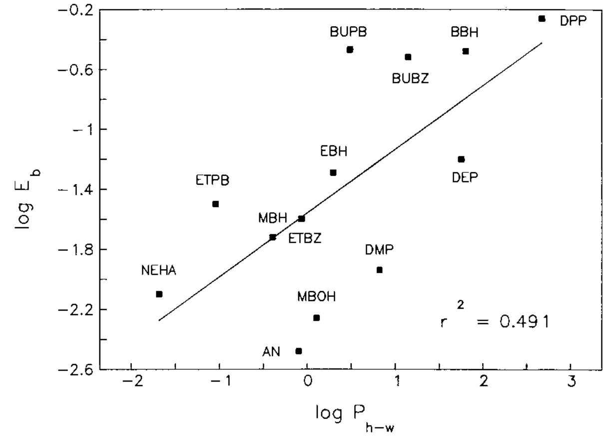

Fig. 3. Interaction model. Solute interaction constant (log E_b) versus hexane–water partition coefficient (P_{h-w}). Interaction data for all test solutes included; the solution phase was water.

log P_{h-w} is poor at 0.49 as compared to the value of 0.93 obtained for the P_{o-w} model.

The effect of the solution phase on the interaction properties of the polymer was studied with a subset of the model solutes used in the previous characterization of the polymer. Values for the *a* and *b* constants obtained by least-squares fit of the data to Eq. (1) are summarized, for individual solutions and the composite data set, in Table II. Several properties of the resulting interaction equations are pertinent. The general magnitude of the *a* and *b* constants indicates that the material being studied as a composite is somewhat less lipophilic than octanol and that the material is less sensitive to changing solute lipophilicity than is octanol. More significant to the stated purpose of this study is the observation that, in general, the *a* and *b* constants for all solutions and for the composite data set agree to within the precision of the determination. That is, at the 95% level of confidence there is no difference between the *a* and the *b* coefficients obtained for each solution (see Table II for the typical errors associated with the coefficients). Of secondary importance is that the linear relationship between log E_b and log P_{o-w} is not affected by solution phase composition; that is, correlation coefficients (r^2) of the interaction model for all solutions are greater than 0.91. Additionally, the model generated using all the interaction data from all the solutions studied exhibits excellent linear behavior and is not significantly different from the model generated using any individual solution (Fig. 4). The fit is particularly good for the mixtures containing only dextrose and/or NaCl. As shown in Fig. 5, the variation in E_b with respect to NaCl or dextrose concentration is minimal. Thus for reasonably simple iv diluents, ionic strength and total dissolved solids affect the container/solution interaction (presumably via a "salting-out" type of mechanism) only minimally and water (buffered at an appropriate pH) serves as an effective model solvent for assessing container/solution interactions.

The more complex iv admixtures affected the container/

Table II. Curve-Fit Data, E_b versus P_{o-w} Model

Solution code	Slope (P_{o-w})[a]	Intercept[b]	Correlation coefficient (r^2)
S1	0.850	−3.59	0.977
S2	0.836	−3.59	0.969[c]
S3	0.826	−3.53	0.971[c]
S4	0.835	−3.51	0.970
S5	0.831	−3.55	0.966
SD	0.818	−3.50	0.9857
W	0.831	−3.53	0.975
D1	0.822	−3.54	0.963
D2	0.838	−3.56	0.975
D3	0.828	−3.47	0.979
Composite, simple solutions	0.833	−3.55	0.968
DL	0.786	−3.38	0.918
D/A	0.819	−3.67	0.930
LR	0.780	−3.45	0.919
TR	0.836	−3.60	0.936
DX	0.780	−3.55	0.925
Composite, all solutions	0.825	−3.54	0.950

[a] Typical standard error of coefficient = 0.08.
[b] Typical standard coefficient of error = 0.20.
[c] $E_{b,u}$ used for BBH (due to pH effect).

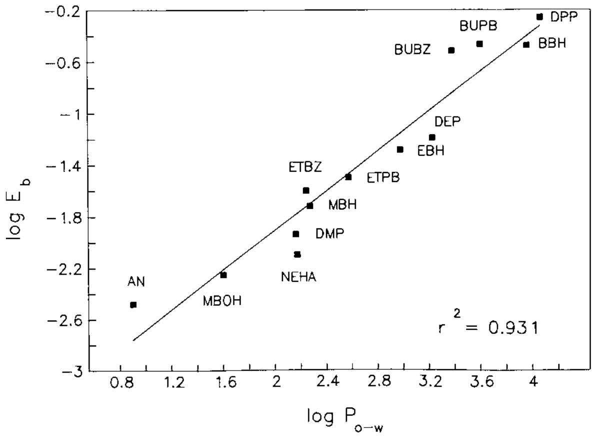

Fig. 2. Interaction model. Solute interaction constant (log E_b) versus octanol–water partition coefficient (P_{o-w}). Interaction data for all test solutes included; the solution phase was water.

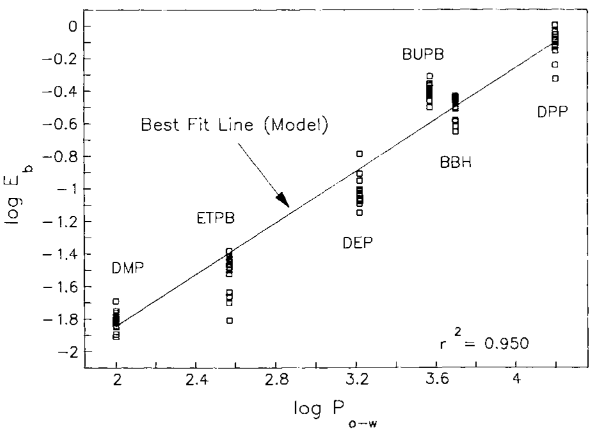

Fig. 4. Interaction constant (E_b) versus solute octanol–water partition coefficient ($P_{o\text{-}w}$). Interaction model for the entire data set. Symbols represent E_b obtained in individual solutions, and the best-fit line represents the composite, all solutions curve fit from Table II.

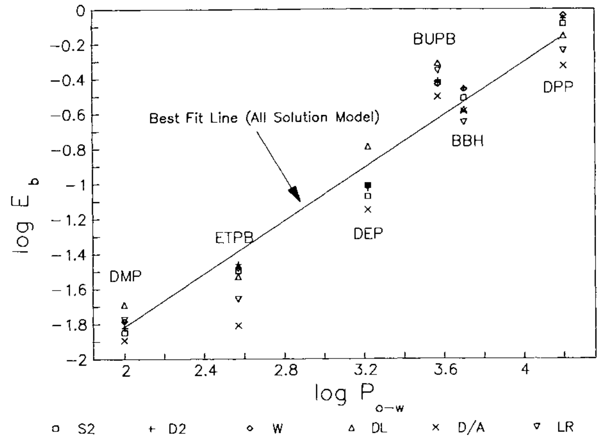

Fig. 6. Typical interaction constants for selected solutions examined. See Table I for a description of the abbreviations.

solution interaction more strongly than did the saline/dextrose solutions; however, the effect in all solvents studied was not significant (<95% level of confidence). Thus, for all the solvents, with the exception of the alcohol/dextrose admixture, the rank ordering of E_b with respect to solute identity is random for a given solute (Fig. 6), i.e., there is no consistent trend across solute identity in the relationship between E_b ordering and solvent type. However, the E_b for the alcohol/dextrose solution is consistently lower than the E_b observed in any other solution; this trend is mirrored in the intercept term (*b*) in the E_b versus $P_{o\text{-}w}$ model for this solution. The low *b* intercept for the model in this solution indicates that the relative lipophilicity of the polymer is lower in this solution than it is in the others studied. The presence of the alcohol serves to increase the solubility of the solute in the solution phase with the result that the apparent lipophilicity of the polymer is decreased. One notes that the somewhat poorer correlation observed in the log E_b/log$P_{o\text{-}w}$ model for the complicated solutions is a reflection of the increased analytical variability in these matrices. For example, assay variability for the phthalates (representing injection to injection variation) increased from 0.3% RSD in the water matrix to 1.2% in the Travasol matrix.

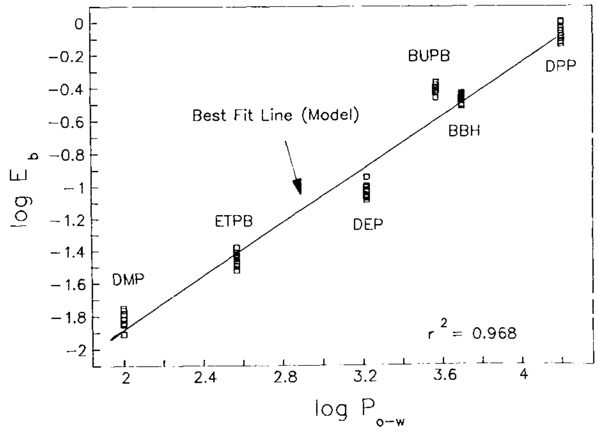

Fig. 5. Interaction constant versus solute $P_{o\text{-}w}$, interaction model for the saline/dextrose solution mixtures. Symbols represent E_b for individual solutions, and the best-fit line represents the composite; simple solutions curve fit from Table II.

As was the case with the simple dextrose/NaCl combinations, ionic strength and total dissolved solid load has little effect per se on the container/solution interaction in the more complex iv diluents. While the interaction in the lactate-containing solutions (Dianeal and lactated Ringer's) is such that the apparent polymer sensitivity to solute lipophilicity is decreased somewhat compared to the other solutions studied, the magnitude of the difference is not large and is within the standard error of the determination.

The interaction constant can be coupled with the projected container configuration (material weight and solution volume) to determine the fraction of an aqueous solute which will be bound by the container (F_b) using the relationship

$$F_b = w_c E_b / (V_s + w_c E_b) \tag{4}$$

Table III. Predicted Fractional Binding of Solutes in a 500-ml Container Configuration

Solute	Extreme	Solution	log E_b	F_b (%)
DMP	High	DL	−1.69	28.6
	Low	S2	−1.91	19.4
	Model	Water	−1.78	24.5
ETPB	High	SD	−1.38	45.0
	Low	TR	−1.71	28.7
	Model	Water	−1.48	39.4
DEP	High	DL	−0.85	73.4
	Low	S2	−1.05	63.9
	Model	Water	−1.01	65.7
BUPB	High	DL	−0.31	90.6
	Low	S2	−0.46	87.2
	Model	Water	−0.43	87.9
BBH	High	S3	−0.37	89.4
	Low	LR	−0.65	81.4
	Model	Water	−0.46	87.2
DPP	High	D3	0.00	95.2
	Low	LR	−0.24	91.8
	Model	Water	−0.04	95.1

An appropriate measure of the practical implications of the variable solution phase effect on E_b is the difference in predicted F_b for the solutions exhibiting extreme values of E_b for a particular solute. Table III documents such a comparison for a container size of 500 ml (approximate material weight of 10 g). The difference in predicted F_b is largest for the least strongly bound solutes. Thus for DMP the difference in predicted F_b for the extreme solutions is considerable, while for DPP the difference is similar in magnitude to the experimental error.

The data generated in this study clearly establish water as an effective model solvent for the evaluation of container/solution interactions for nonionized solutes. Since solution pH is a critical evaluation variable for ionized solutes, a weak buffer solution offers the greatest utility in terms of being a "universal" model solvent for all potential solutes. As shown in both Table III and Fig. 7, the water (containing a weak buffer) model provides an effective approximation of all the interaction data generated in this study. This conclusion is significant in terms of streamlining the process of new container compatibility assessment. Utilization of the simple model solvent should simplify the analytical process, but more importantly, the existence of a suitable model obviates the need to study the container/solution compatibility in every matrix which may potentially be packaged in the proposed container material.

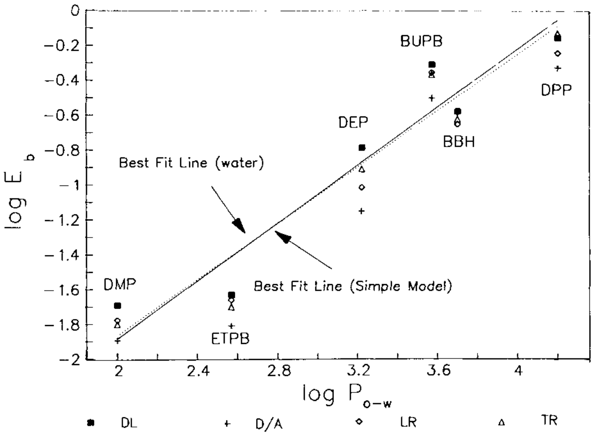

Fig. 7. Utility of water as an interaction model solvent; comparison of the interaction properties observed in actual iv products versus the interaction model generated using the water and simple solution composite data.

The conclusions stated above have the following limitations: (1) they are applicable only if the material/solution interaction is partition mediated (and thus may not be appropriate in terms of evaluating surface phenomena such as protein adsorption), and (2) they assume that the solute's conformation is not greatly affected by changing physical properties of the solvent.

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