

Interactions Between Polymeric Containers and Their Contained Solution: Modeling of Polymer–Water Solute Partitioning Via Coupled Solvent–Water Partition Coefficients

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SYNOPSIS

The interaction between several polymeric materials, typical of those that have application as parenteral product containers, and 16 marker solutes was evaluated. Polymers used included polypropylene, polyvinyl chloride, ethylenevinyl acetate, an olefin rubber, a polyester ether block copolymer, and various composites of these materials. In addition, the partitioning of solutes between two common PVC plasticizers (dioctyl phthalate and butyryl hexyl citrate) and water was also examined. Correlation between equilibrium interaction constants (E_b) (which describe the equilibrium distribution of a solute between contacting polymer and solution phases) and solute octanol–water (P_{o-w}) or hexane–water (P_{h-w}) partition coefficients were in general poor for all materials studied. However, a bivariate linear interaction model relating E_b to both partition coefficients:

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

effectively mimicked the interaction behavior of all materials evaluated. The utilization of the developed models to facilitate container compatibility assessments is discussed. In addition, the use of a critical ratio of binding constants for a pair of solutes is introduced as a means of qualitatively assessing the effectiveness of a particular solvent as a polymer model.

INTRODUCTION

A polymer's usefulness and lifetime as a container for human use products can be impacted by the interaction between the polymer and contained product. Two processes of concern for aqueous products include (i) the migration of a chemical component of the polymer out of the container and into the contained solution (leaching) and (ii) the sorption of solutes out of the solution phase by the container (binding). For leaching, the toxicity of the mobilized container component is of concern^{1–4} although other product use considerations may also be important. For binding, product efficacy may be adversely im-

acted by the loss of important formulation components to the container. For example, numerous instances of drug loss from pharmaceutical solutions by container sorption have been reported.^{5–20}

Five general factors control container–solute interactions, including^{21,22}:

- the initial or total amount of solute present,
- the solute's solubility in both phases,
- the equilibrium partitioning of the solute between the container and the solution,
- diffusion, and
- the chemical stability of the solute in both phases.

Characterizing a solvent–solute–polymer system with respect to these factors is a necessary step in container compatibility assessments.

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Considering partitioning, several investigators have demonstrated that a solute's polymer-solvent partition coefficient (P_{p-s}) correlates with a solute's solvent-solvent partition coefficient (P_{s-s}), which are frequently available in the literature, via a Colander type expression:

$$\log P_{p-s} = a(\log P_{s-s}) + b, \quad (1)$$

where P_{s-s} represents the equilibrium concentration ratio of the solute in the solvents. The appropriate model solvent system depends on the physicochemical nature of both the polymer and the model solvent; both octanol-water and hexane-water models have been used with varying degrees of success.²³⁻²⁷

The effectiveness of the interaction model rests on the degree to which the model solvent mimics the material studied. Several researchers have noted that polymer-solute interactions occur via several distinct mechanisms and thus that a single solvent is potentially a poor interaction model.^{20,24,28} Specifically, the ability of a solute to interact with a polymer via hydrogen bonding (in addition to the classical lipophilic interaction) represents a commonly cited auxiliary mechanism.²⁹⁻³⁴ Thus, a modified bimodal expression, based on two dissimilar solvent models (say octanol and hexane), has been proposed³⁵:

$$\log P_{p-s} = a(\log P_{o-w}) + b(\log P_{h-w}) + c. \quad (2)$$

As an alternative to P_{p-s} , the equilibrium interaction coefficient (E_b) is defined:

$$E_b = (m_p/W_p)/(m_s/V_s), \quad (3)$$

where

m = mass of solute in a particular phase at equilibrium,
 W = weight of polymer,
 V = volume of solution, and
 s and p refer to the solution and polymer phase, respectively.

E_b is analogous to P_{p-s} differing as a gravimetric, as opposed to a volumetric, expression of the polymer phase solute concentration. In a practical sense, E_b relates more conveniently to common container-solution design parameters than does the partition coefficient and thus can replace P_{p-s} in eq. (2).

In this article, we describe the interaction of several polymers and polymer composites with various test model solutes. Test solutes represent a wide

range in both lipophilicity and hydrogen bond character. The interaction data are used to generate an interaction model based on solvent-water partition coefficients; the models are discussed in terms of the physicochemical nature of the polymers. In addition, the models are used to determine the utility of the studied polymers as container materials.

EXPERIMENTAL

Materials

Polymers studied included polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polypropylene (PP), an olefin rubber (OR), and a polyester ether block copolymer (PEEB). Materials used as solution contact components in parenteral product container-delivery systems were also studied, including two rubbers, two plasticized PVCs, and several polymeric composites. The PVC materials differ in terms of plasticizer: One contained dioctyl phthalate (DOP) and the other contained butyryl trihexyl citrate (BTHC). Composites studied included a linear low-density polyethylene containing a polycaprolactam tie layer (PE), a polypropylene composite with minor amounts of low-density polyethylene and other additives (PP), and a multilayer material consisting of polypropylene and other polyolefins (PO).

Test solutes used are summarized in Table I and were reagent grade chemicals. Other reagents used were either research or HPLC grade as appropriate.

Partition Coefficients

Octanol-water partition coefficients (P_{o-w}) were obtained from the literature^{28,29} and represent direct or indirect (HPLC) experimental measurements. Hexane-water partition coefficients (P_{h-w}) were obtained via conventional equilibrium shake flask methods. Polymer-water interaction constants (E_b) were also determined by shake flask approaches; both solute sorption and desorption was studied and the reported interaction constants represent a mean of the data resulting from individual experiments. Solute concentration in equilibrated shake flask solutions was determined by HPLC.

RESULTS AND DISCUSSION

Solvent-water partition data for the test solutes are summarized in Table I. These solutes encompass a fairly wide range of lipophilicity and exhibit varying

Table I Marker Solutes Used

| Name | Abbreviation | $\log P_{o-w}$ | $\log P_{h-w}$ |
|-----------------------------|--------------|----------------|----------------|
| Aniline | AN | 0.90 | -0.01 |
| 4-Methylbenzyl alcohol | MBOH | 1.60 | 0.1 |
| Dimethyl phthalate | DMP | 2.16 | 0.82 |
| <i>n</i> -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 |
| Ethylbenzoic acid | EBH | 2.97 | 0.29 |
| Diethyl phthalate | DEP | 3.22 | 1.75 |
| Ethylbenzene | EB | 3.31 | 3.00 |
| Butyl-4-aminobenzoate | BUBZ | 3.37 | 1.14 |
| Butyl paraben ^a | BUPB | 3.59 | 0.48 |
| Carbazole | CAR | 3.59 | 2.18 |
| Butylbenzoic acid | BBH | 3.95 | 1.80 |
| Propyl benzene | PB | 3.96 | 3.00 |
| Dipropyl phthalate | DPP | 4.05 | 2.67 |

^a 4-Hydroxybenzoic acid, - ester.

abilities to interact with the polymers studied via a secondary (electronic-polarity) mechanism. Similarly, the polymers studied also exhibit varying degrees of hydrogen bond character. Thus, as shown in Table II, the correlation between the equilibrium interaction constant E_b and either P_{o-w} or P_{h-w} is relatively poor in most cases. As illustrated in Figure 1 for the polyolefin polymer, while a fairly linear correlation between P and E_b can be obtained within a given class of compounds (e.g., phthalates and

parabens) using the single solvent model, the correlation breaks down between classes differentiated by their relative ability to participate in hydrogen bonding. Clearly, a solute's ability to interact with the polymer by several mechanisms (including "classical" lipophilic attraction and hydrogen bonding) influences the magnitude of the polymer-solute interaction, as well as the effectiveness of either octanol or hexane as a polymer model.

To develop a widely applicable, solvent-based partition model, the use of multiple solvent-water partition coefficients is proposed. Specifically, octanol-water and hexane-water are chosen since they

Table II Curve Fit Parameters, Univariate Models

| Material | Slope | Intercept | r^2 |
|--|-------|-----------|-------|
| Model based on P_{o-w} | | | |
| Natural rubber | 0.558 | -3.14 | 0.857 |
| Synthetic rubber | 0.818 | -4.02 | 0.632 |
| DEHP PVC | 0.749 | -3.41 | 0.854 |
| BTHC PVC | 0.817 | -3.46 | 0.893 |
| PO | 0.721 | -3.34 | 0.930 |
| PP composite | 0.624 | -3.94 | 0.691 |
| PE | 0.610 | -3.42 | 0.921 |
| Model based on P_{h-w} | | | |
| Natural rubber | 0.338 | -1.83 | 0.756 |
| Synthetic rubber | 0.641 | -2.23 | 0.933 |
| DEHP PVC | 0.452 | -1.65 | 0.747 |
| BTHC PVC | 0.454 | -1.52 | 0.662 |
| PO | 0.421 | -1.59 | 0.491 |
| PP composite | 0.593 | -2.67 | 0.920 |
| PE | 0.332 | -1.96 | 0.656 |

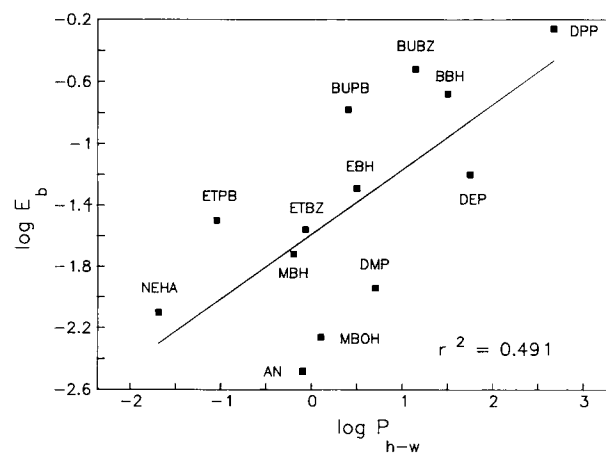


Figure 1 Interaction model, interaction constant (E_b) vs. hexane-water partition coefficient (P_{h-w}) for PO. The solid line represents the linear regression best fit line.

Table III Curve Fit Parameters, Bivariant Model

| Material | Slope (P_{o-w}) | Slope (P_{h-w}) | Intercept | r^2 |
|------------------|------------------------|------------------------|--------------|-------|
| Natural rubber | 0.375 (0.056) | 0.165 (0.036) | -2.76 (0.14) | 0.945 |
| Synthetic rubber | 0.219 (0.086) | 0.540 (0.056) | -2.77 (0.21) | 0.955 |
| DEHP PVC | 0.508 (0.080) | 0.217 (0.051) | -2.91 (0.19) | 0.939 |
| BTHC PVC | 0.643 (0.089) | 0.157 (0.058) | -3.11 (0.22) | 0.932 |
| PO | 0.639 (0.082) | 0.055 (0.050) | -3.20 (0.21) | 0.961 |
| PP | -0.069 (0.106) | 0.624 (0.068) | -2.50 (0.26) | 0.922 |
| PE | 0.495 (0.055) | 0.103 (0.035) | -3.18 (0.14) | 0.953 |

(), standard coefficient of error.

target different interaction mechanisms. While hexane-water targets the classical lipophilic interaction between a solute and a polymer, octanol-water allows for an assessment of hydrogen bonding. Thus, we propose that the polymer-solute interaction can be modeled by the linear combination of P_{o-w} and P_{h-w} via the expression:

$$\log E_b = a(\log P_{o-w}) + b(\log P_{h-w}) + c. \quad (4)$$

Substitution of the measured polymer-solute interaction constants and solute partition coefficients into eq. (4) produces bivariant linear interaction models with linear regression curve fit parameters as shown in Table III. For all multicomponent polymers studied, the resultant correlation between E_b and the linear combination of P_{o-w} and P_{h-w} is excellent and much better than the correlation between E_b and either single partition coefficient. As shown

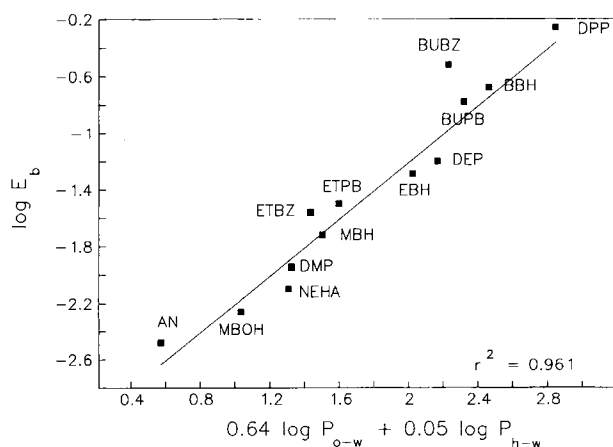


Figure 2 Interaction model, interaction constant (E_b) vs. the linear combination of the octanol-water (P_{o-w}) and hexane-water partition coefficients (P_{h-w}) for PO. The solid line represents the linear regression best fit line.

in Figure 2, little discrimination among compound classes is shown by the combination model.

The magnitude of the respective slopes of the partition coefficient terms in eq. (4) is indicative of the relative ability of a particular solvent to act as a polymer model. Thus, for example, for the polyolefin (PO), whose interaction properties correlate fairly well to P_{o-w} alone, the combination model has a large slope for P_{o-w} compared to that for P_{h-w} . Alternatively, for the polypropylene (PP), whose interaction properties were more effectively modeled by hexane alone, the slope of the P_{h-w} term in the combination model is large and this term dominates the model (Fig. 3). For the other composite test materials, the combination model exhibits important contributions from both solvent systems (e.g., Figure 4).

One can rationalize the interaction properties of the composites on the basis of their structure. Thus,

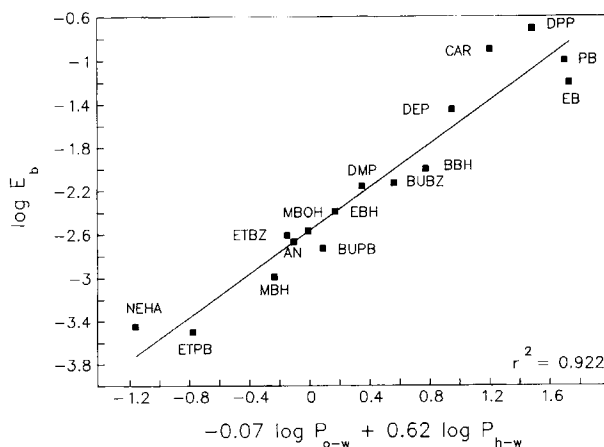


Figure 3 Interaction model, interaction constant (E_b) vs. the linear combination of the octanol-water (P_{o-w}) and hexane-water partition coefficients (P_{h-w}) for PP. The solid line represents the linear regression best fit line.

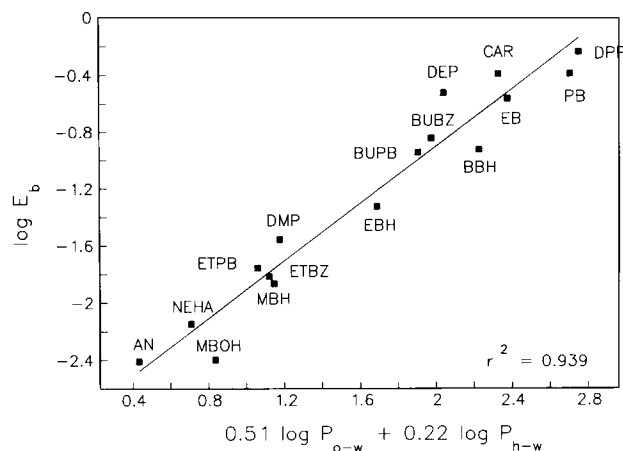


Figure 4 Interaction model, interaction constant (E_b) vs. the linear combination of the octanol-water (P_{o-w}) and hexane-water partition coefficients (P_{h-w}) for DEHP-plasticized PVC. The solid line represents the linear regression best fit line.

for the polypropylene material, which lacks any component that could act as a hydrogen bond acceptor, it is reasonable that hexane would dominate the interaction model. Alternatively, the polyolefin material contains ethylene vinyl acetate with the acetate providing hydrogen bond acceptor sites and thus octanol dominates the interaction model for this material. For the plasticized PVC materials, one anticipates that the plasticizers themselves provide ample H-bond acceptor sites. In addition, since plasticized PVCs typically contain numerous additives, it is not unexpected that their interaction models would possess strong contributions from both P_{o-w} and P_{h-w} .

It is not unreasonable to hypothesize that the interaction properties of a composite can be represented as a function of the interaction properties of its individual components. Thus, the interaction properties of several single component materials (as well as the plasticizers alone) was studied, producing the interaction model curve fit parameters summarized in Table IV. The differing behavior of the plasticizers is interesting, especially in light of the differing interaction properties of the plasticized PVCs studied. From the intercept of the interaction model for the plasticizers, one notes that while DEHP is somewhat more lipophilic than the citrate-based plasticizer, the citrate plasticizer is more sensitive to changing solute properties (larger slope). The same generalization holds true for the plasticized PVCs; thus, one concludes that the drug-binding properties of plasticized PVC containers would

be dominated by the amount and type of plasticizer used, consistent with observations made by several researchers.^{27,36}

While the model provides a quantitative means of estimating a polymer-solute interaction, there may be applications where knowing whether a particular polymer is octanol- or hexane-like is sufficient to qualitatively assess its solution compatibility. Rather than generating an interaction model in such cases, the relative behavior of the polymer can be assessed by focusing on a smaller suite of model solutes of varying chemical behavior. Consider, for example, BUPB, CAR, and DPP. BUPB and CAR have identical P_{o-w} but greatly different P_{h-w} and thus differ not only in terms of intrinsic lipophilicity but also hydrogen bond activity. On the other hand, CAR and DPP are roughly similar in terms of lipophilicity and hydrogen bond activity. Thus, one expects the ratio of E_b for CAR and DPP to be relatively constant irregardless of polymer properties, while the E_b ratio between BUPB and CAR would differ dramatically depending on the nature of the polymer. For the purpose of discussion, E_b ratios for two model solutes will be termed the critical ratio. One expects the critical ratio for CAR and DPP to be roughly the ratio of the P_{o-w} or P_{h-w} for these solutes (≈ 0.34) corrected by a small amount for the relative sensitivity of the polymer to changing solute lipophilicity. On the other hand, the critical ratio for BUPB and CAR should approach the ratio of P_{o-w} for these solutes (1.0) if the polymer is octanol-like or the ratio of P_{h-w} (0.020) if the polymer is hexane-like.

Critical ratios for the polymer composites studied are summarized in Table V. As expected, the critical ratio for CAR and DPP varies only slightly around a mean value of 0.34, while the critical ratio for

Table IV Curve Fit Parameters, Bivariant Model, Single-Component Materials

| Material | Slope (P_{o-w}) | Slope (P_{h-w}) | Intercept | r^2 |
|---------------|---------------------|---------------------|-----------|-------|
| DEHP | 0.549 | 0.130 | -2.43 | 0.928 |
| BTHC | 0.681 | 0.083 | -2.68 | 0.960 |
| PVC | 0.361 | -0.011 | -3.36 | 0.966 |
| Polypropylene | -0.003 | 0.825 | -3.82 | 0.955 |
| Olefin rubber | 0.709 | 0.079 | -2.64 | 0.989 |
| PCCE | 0.890 | -0.190 | -3.71 | 0.950 |
| EVA | 0.882 | -0.073 | -3.65 | 0.964 |

Note: The standard errors associated with these coefficients are similar in magnitude to those reported in Table III.

Table V Critical Ratio Analysis

| Polymer | Dominant Solvent Model | Critical Ratio | |
|------------------|------------------------|----------------|---------|
| | | BUPB/CAR | CAR/DPP |
| PO | Octanol | 1.02 | 0.30 |
| Natural rubber | Intermediate | 0.22 | 0.66 |
| Synthetic rubber | Intermediate | 0.06 | 0.41 |
| DEHP PVC | Intermediate | 0.28 | 0.22 |
| BTHC PVC | Intermediate | 0.79 | 0.36 |
| PE | Intermediate | 0.52 | 0.55 |
| PP | Hexane | 0.0015 | 0.65 |

BUPB and CAR varies from 1.0–0.015 according to whether the polymer is octanol- or hexane-like. The ability of the BUPB/CAR critical ratio to qualitatively assess the interaction behavior is thus established.

The partition coefficient– E_b correlations provide a mechanism for comparing the relative binding properties of two polymers for any solute whose P_{o-w} and P_{h-w} are known but whose E_b coefficients have not been determined. By mathematically equating interaction model expressions for two polymers and solving for P_{o-w} and P_{h-w} , a “line of equivalency” is generated. Solutes whose partition coefficients fall on this line will exhibit the same fractional binding by both polymers being considered. Generation of a P_{o-w}/P_{h-w} grid results in a

“figure of merit” (a pictorial representation of the relative interaction properties of the two polymers) that identifies regions in which the magnitude of the solute–polymer interaction is different for the materials being considered. Thus, for example, the figure of merit comparing the polyolefin composite and the DEHP-plasticized PVC is shown in Figure 5. The application of the figure is straightforward; a solute’s P_{o-w} and P_{h-w} define its position in the grid and allow for a determination of the relative binding of that solute by the two polymers. Thus, DMP binding by the polyolefin is less than that by the PVC and the polyolefin is superior in terms of minimizing solute loss to the container. Since the plasticized PVC is more lipophilic than the polyolefin, it binds the nonhydrogen bonding solutes to a

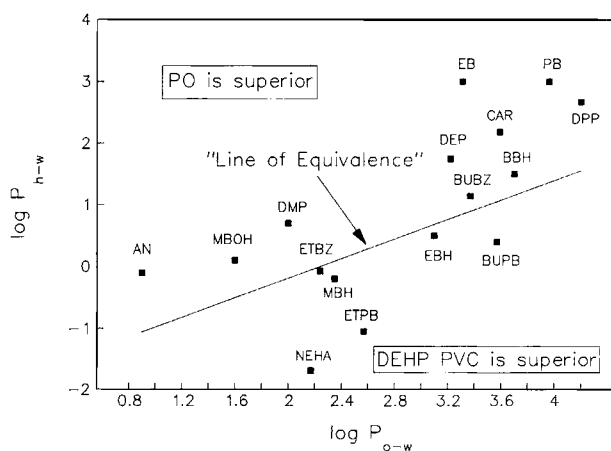


Figure 5 Figure of merit comparing relative binding properties of PO and DEHP-plasticized PVC materials. The “superior” polymer is the one that binds the solute to the lesser extent.

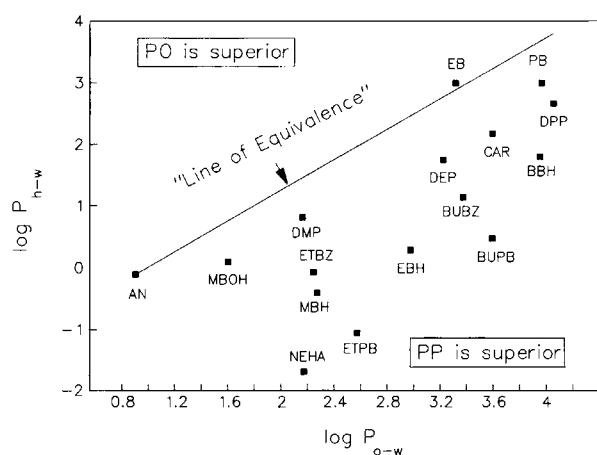


Figure 6 Figure of merit comparing relative binding properties of PO and PP materials. The “superior” polymer is the one that binds the solute to the lesser extent.

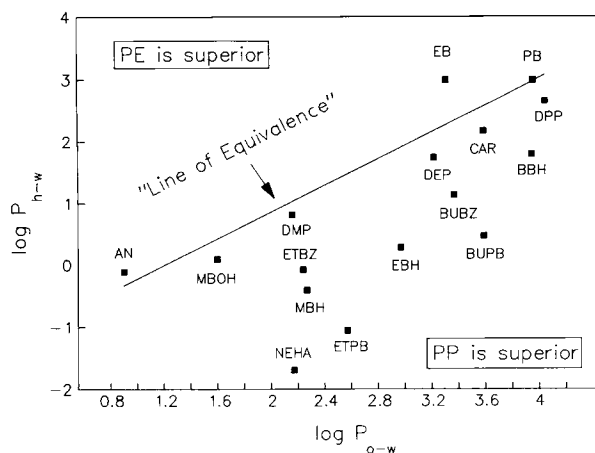


Figure 7 Figure of merit comparing relative binding properties of PE and PP materials. The “superior” polymer is the one that binds the solute to the lesser extent.

greater extent than does the polyolefin and the polyolefin is judged superior from a product perspective in terms of minimizing solute loss by container uptake. However, the polyolefin is more sensitive to a solute’s ability to hydrogen bond than is the plasticized PVC; thus, for the more hydrophilic hydrogen bond donor solutes the plasticized PVC is actually superior in terms of minimizing solute uptake by a container.

Figures of merit comparing the binding properties of the polyolefin, polypropylene, and polyethylene composites are shown in Figures 6 and 7. In general, the polypropylene material is superior to the other composites tested in terms of minimizing solution-

phase solute loss due to solute uptake by the container.

While the figures of merit provide a means of assessing the relative merits of two polymers, they do not directly assess the relative merits of containers made from two polymers if the polymer’s densities are greatly different or if the container configuration using the two polymers is radically different. Table VI contains an assessment of the relative utility of the three composites and the DEHP-plasticized PVC both in terms of the interaction properties of these materials and the physical properties of a 50-mL container made from each material. The significantly greater density of the PVC compared to the composites further strengthens the observation that a container made from one of the composites will bind an aqueous solute to a lesser degree than will the PVC container.

We note that the figure of merit concept can also be used to assess the relative amounts of a leachable substance that would migrate out of a polymeric material. For two polymers that have the same total available pool of a particular leachable solute, the solute’s position on the P_{o-w}/P_{h-w} grid will define which polymer is better in terms of minimizing the amount of leachable that accumulates in a solution in contact with the material. While the leaching figure of merit has the same appearance as those used in the binding assessment, the regions of superiority are reversed from those identified for binding. Thus, in terms of minimizing leaching of chemically similar solutes, the polypropylene composite is in fact the poorest container material of those studied.

Table VI Predicted Fractional Binding for 50-mL Containers

| Solute | Fraction Bound by Container (%) | | | |
|----------------------------------|---------------------------------|----------------------|------|------|
| | DEHP PVC | (Container Material) | | |
| | | PO | PE | PP |
| Aniline | 47.0 | 25.6 | 15.3 | 18.8 |
| ETPB | 79.8 | 76.7 | 47.6 | 3.3 |
| DMP | 86.2 | 54.4 | 52.2 | 42.7 |
| BUPB | 96.2 | 94.5 | 84.2 | 16.7 |
| DEP | 98.5 | 86.8 | 69.5 | 79.3 |
| BBH* | 96.4 | 95.6 | 88.1 | 51.9 |
| DPP | 99.8 | 98.2 | 94.8 | 95.4 |
| Approximate container weight (g) | 11.2 | 5.2 | 5.1 | 5.4 |

* In the un-ionized form.

REFERENCES

1. J. Autian, *Environ. Health Perspect.*, **4**, 3 (1973).
2. R. J. Petrick, S. P. Loucas, J. K. Cohl, and B. Mehl, *Am. J. Hosp. Pharm.*, **34**, 357 (1977).
3. J. H. Corley, T. E. Needham, E. D. Sumner, and R. Mikeal, *Am. J. Hosp. Pharm.*, **34**, 259 (1977).
4. A. E. Pollack, L. J. Nunez, and J. Autian, *Int. J. Pharm.*, **3**, 151 (1979).
5. N. E. Richardson, D. J. G. Davies, B. J. Meakin, and D. A. Norton, *J. Pharm. Pharmacol.*, **29**, 717 (1977).
6. H. D. Blackburn, A. E. Polack, and M. S. Roberts, *J. Pharm. Pharmacol.*, **30**, 666 (1978).
7. J. K. Stark, T. D. Sokoloski, W. T. Winsley, and P. E. Stach, *Am. J. Hosp. Pharm.*, **35**, 537 (1978).
8. W. G. Crouthamel, B. Dorsch, and R. Shangraw, *N. Engl. J. Med.*, **299**, 262 (1978).
9. J. I. Hirsch, M. J. Frakin, J. H. Wood, and R. B. Thomas, *Am. J. Hosp. Pharm.*, **34**, 583 (1977).
10. D. M. Baaske, A. H. Amann, D. M. Wagenknecht, M. Mooers, J. E. Carter, H. J. Hoyt, and R. G. Still, *Am. J. Hosp. Pharm.*, **37**, 201 (1980).
11. H. Christiansen, T. J. Skobba, R. Anderson, and J. N. Saugen, *J. Clin. Hosp. Pharm.*, **5**, 209 (1980).
12. J. MacKichan, P. K. Duffner, and M. E. Cohen, *N. Engl. J. Med.*, **301**, 332 (1979).
13. W. A. Parker and M. E. Maclara, *Am. J. Hosp. Pharm.*, **37**, 505 (1980).
14. J. C. Cloyd, C. Vezeau, and K. W. Miller, *Am. J. Hosp. Pharm.*, **37**, 492 (1980).
15. C. Petty and N. L. Cunningham, *Anesthesiology*, **40**, 400 (1974).
16. S. S. Weber, W. A. Wood, and E. A. Jackson, *Am. J. Hosp. Pharm.*, **34**, 353 (1980).
17. S. E. Tsuei, R. L. Nation, and J. Thomas, *Eur. J. Clin. Pharmacol.*, **18**, 333 (1980).
18. L. D. Butler, J. M. Munson, and P. P. DeLuca, *Am. J. Hosp. Pharm.*, **37**, 935 (1980).
19. P. Moorhatch and W. L. Chiou, *Am. J. Hosp. Pharm.*, **31**, 72 (1977).
20. L. Illum and H. Bundgaard, *Int. J. Pharm.*, **10**, 339 (1982).
21. I. C. Sanchez, S. S. Chang, and L. E. Smith, *Polym. News*, **6**, 249 (1980).
22. L. A. Cruz, M. P. Jenke, R. A. Kenley, M. J. Chen, and D. R. Jenke, *Pharm. Res.*, **9**, 967 (1990).
23. C. G. Pitt, Y. T. Bao, A. L. Andrady, and P. N. K. Samuel, *Int. J. Pharm.*, **45**, 1 (1988).
24. D. O. Jordon and A. E. Pollack, *Aust. J. Pharm. Sci.*, **N51**, 82 (1972).
25. K. Nasim, M. C. Meyer, and J. Autian, *J. Pharm. Sci.*, **6**, 1775 (1972).
26. D. G. Serota, M. C. Meyer, and J. Autian, *J. Pharm. Sci.*, **6**, 416 (1972).
27. I. Illum, H. Bundgaard, and S. S. Davis, *Int. J. Pharm.*, **17**, 183 (1983).
28. D. S. Hayward, R. A. Kenley, and D. R. Jenke, *Int. J. Pharm.*, **59**, 245 (1990).
29. A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).
30. T. Higuchi, J. H. Richards, S. S. Davis, A. Kamada, J. P. Hou, M. Kakano, N. I. Nanano, and I. H. Pitman, *J. Pharm. Sci.*, **58**, 667 (1969).
31. P. Seiler, *Eur. J. Med. Chem.*, **9**, 473 (1974).
32. R. F. Rekker, *The Hydrophobic Fragment Constant. Its Derivation and Application*, Elsevier, Amsterdam 1977.
33. H. Van de Waterbeemd and B. Testa, in *Advances in Drug Research*, vol. 16, B. Testa, Ed., Academic Press, London, 1987, pp. 85-225.
34. M. Gryllaki, H. Van de Waterbeemd, B. Testa, N. El Taylor, J. M. Mayer, and P. Carrupt, *Int. J. Pharm.*, **15**, 95 (1989).
35. D. S. Hayward and D. R. Jenke, *Int. J. Pharm.*, **66**, 87 (1990).
36. C. S. Bray, *Acta Pharm. Suec.*, **Suppl 3**, 76 (1983).

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