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Interactions between polymer containers and parenteral solutions: the correlation of equilibrium constants for polymer-water partitioning with octanol-water partition coefficients

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Summary

Polymer-water equilibrium binding constants (E_B) were determined for twelve organic solutes in contact with a composite polyolefin polymer. The polymer studied is a proprietary candidate parenteral product container material. Excellent correlation between these binding constants and solute octanol-water partition coefficients ($P_{o\text{-}w}$) was observed for all solutes examined that are not effective hydrogen bond donors. For donor solutes, octanol, which has an appreciable hydrogen bonding character, poorly models the essentially non-bonding polyolefin polymer. However, an expression that accounts for both octanol-water type partitioning and the hydrogen bonding ability of the solute (on the basis of experimentally determined hydrogen bond formation constant, K_{HB}):

$$\log E_B = 0.803 \log P_{o\text{-}w} - 0.203 \log K_{HB} - 4.42$$

adequately models the behavior of all solutes studied ($r^2 = 0.983$). The bivariate linear relationship between E_B and $P_{o\text{-}w}$ plus K_{HB} also effectively models polyolefin : solute interactions reported in the literature. This relationship, coupled with typical intravenous container configurations, permits the estimation of the fractional partitioning behavior of solutes in container-solution systems.

Introduction

A polymer's usefulness and lifetime as a container for aqueous parenteral formulations may be limited by either (a) the ability of a minor chemical component of the polymer to migrate out of the container and into the solution it contains, or (b) the ability of the polymer to sorb solutes (including drugs) from the solution it contains. Of particular concern in evaluating the practical utility of various solute/solution/container combinations is that the magnitude of solute migration, regardless of direction or controlling mechanism, be within acceptable limits. For migration of "leachables" out of the polymeric container, the maximum permissible amount of migration is determined by either the migrant's toxicology or, less commonly, optimum use constraints (e.g., clarity, color, and so forth). For the migration of an active

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ingredient into the polymeric container, the maximum permissible amount of migration is determined by the acceptable level of ingredient loss and may be influenced by non-container related loss mechanisms (e.g., drug degradation).

In general, solute migration into or out of a container material is controlled by one or more of the following limiting factors (Sanchez et al., 1980):

(1) the initial amount of migrant present,
(2) the solubility of the migrant in the solution phase,
(3) the equilibrium partitioning of the migrant between the container and solution, and
(4) diffusion.

Focusing on the partitioning aspect of migration, several researchers have demonstrated that polymer-solvent partition coefficients ($P_{p\text{-}w}$) correlate with solvent-solvent partition coefficients (which are readily available in the chemical literature) via a Collander-type expression:

$$\log P_{p\text{-}w} = a \log P_{\text{solvent-water}} + b \qquad (1)$$

where

$$P_{\text{solvent-water}} = C_s/C_w \qquad (2)$$

and C_s and C_w are the equilibrium concentrations of the solute in the solvent and water phases, respectively. For example, octanol-water partition coefficients of various drugs (steroids, narcotic amines and a barbiturate) correlated well with their partitioning from water into 5 "rubbery" polymers (Pitt et al., 1988). Similarly, various authors have established good correlations between polymer-water and hexane-water partition coefficients for various solutes and polyethylene (Jordon and Pollack, 1972; Nasim et al., 1972; Serote et al., 1972).

The equilibrium binding constant (E_B), which describes the polymer/solution/solute interaction, is defined as follows:

$$E_B = (m_p/W_p)/(m_s/V_s) \qquad (3)$$

where: m = mass of solute in a phase at equilibrium, W = weight of polymer, V = solution volume, s = solution phase, and p = polymer phase.

E_B is strictly analogous to P_{p-w} (differing as a gravimetric versus volumetric expression of the concentration of the solute in the polymer) and can replace $P_{p\text{-}w}$ in Eqn. 1. In a practical sense, E_B relates more conveniently to common container/solution design parameters than does the partition coefficient.

In this research, we focus on establishing the nature of the equilibrium partitioning thermodynamic interaction between a specific polymer (a proprietary composite polyolefin) and various test solutes. This polymer material is a candidate for parenteral product containers. Developing a model that relates established polymer-water partition behavior and fundamental solute properties allows for the determination of solute distribution in practical container/solution configurations.

Materials and Methods

Materials

The polymer used in this research is a proprietary composite consisting primarily of polypropylene with minor amounts of low density polyethylene and other components. Test solutes used are identified in Table 1 and were obtained as reagent grade compounds. All other reagents used to prepare diluents, mobile phases and other analytical solutions were either research or HPLC grade as appropriate. Research grade water was obtained from a Barnstead NANOpure II water polisher.

Octanol-water partition coefficients

Octanol-water partition coefficients ($P_{o\text{-}w}$) were either obtained from the literature (Leo et al., 1971) or via an evaluation of their HPLC retention characteristics. The methodology used for the HPLC determination involved extrapolation of retention data (specifically capacity factor, k') obtained in several binary mobile phases to a 100% aqueous eluent and correlating the resulting k'_w with known log $P_{o\text{-}w}$ values of marker compounds. Marker compounds used in this study and their corresponding literature partition data

TABLE 1

Test solutes and their determined properties

Solute	Abbreviation	Log $P_{o\text{-}w}$	Log K_{HB}	Log E_B
(A) This study				
Dimethyl phthalate	DMP	2.22 [a]	ND [b]	-2.76
Diethyl phthalate	DEP	3.22 [a]	ND	-1.78
Dipropyl phthalate	DPP	4.05	ND	-0.96
Dibutyl phthalate	DBP	4.82	ND	-0.72
Ethyl paraben [c]	ETPB	2.57	6.35	-3.58
Propyl paraben	PRPB	3.04	6.48	-3.36
Butyl paraben	BUPB	3.58	5.98	-2.80
4-Methylbenzoic acid	MBH	2.27 [a]	ND	-2.64
4-Ethylbenzoic acid	EBH	2.97	ND	-2.16
4-Chlorobenzoic acid	ClBH	2.65	ND	-2.15
4-Butylbenzoic acid	BBH	3.97	3.0 [d]	-1.80
(B) From Pitt et al. (1988)				
Meprirdine	ME	2.72	ND	-2.23
Testosterone	TE	3.32	ND	-2.70
Progesterone	PR	3.87	ND	-1.28
L-Methadine	MT	4.18	ND	-0.28
L-a-Acetyl methadol	AM	4.31	ND	-0.68
Androst-4-ene-3,17-dione	AD	2.75	ND	-2.64

[a] From Leo et al., 1971; [b] ND = not determined; [c] 4-hydroxybenzoic acid, ethyl ester; [d] estimated.

are summarized in Table 2. The HPLC approach for the determination of $P_{o\text{-}w}$ has produced excellent correlations between k'_w and $P_{o\text{-}w}$ (for example, El Taylor et al., 1985; Braumann, 1983, 1986; Garst et al., 1984). In this research, the chromatographic separation system consisted of a C8 stationary phase (specifically Supelcosil LC8-DB, 5 μ particles) and methanol/water mobile phases. To ensure that the solutes were in their unionized state during the HPLC analysis, all mobile phases used contained 4 mM trifluoroacetic acid (TFA).

TABLE 2

Solutes used as HPLC log $P_{o\text{-}w}$ markers

Solute	Abbreviation	Log $P_{o\text{-}w}$ *
Benzyl alcohol	BA	1.10
4-Methylbenzyl alcohol	MBA	1.60
Dimethyl phthalate	DMP	2.22
Diethyl phthalate	DEP	3.22
4-Methylbenzoic acid	MBH	3.27
Biphenyl	BP	4.11
Antracene	AN	4.45

* Source: Leo et al., 1971.

Solutes were detected by UV spectrometry at low (210–225 nm) wavelength.

Equilibrium binding constant

The standard shake flask method was employed. Binding chambers were prepared by placing a known amount of polymer (cut into small pieces, typically 1 to 6 g was used) into 50 ml of an aqueous solution containing a known amount of the test solute (typical concentration = 5 ppm). For the ionizable solutes, the solution phase pH was adjusted to 2.5 to insure that binding occurred while all the solute was uncharged; otherwise the equilibrium solution was water. The polymer pieces were cut roughly to the shape of the reaction chamber and were supported with a piece of inert, small-bore HPLC tubing so that the individual pieces did not contact one another and polymer/solution interaction was maximized. The sealed reaction chambers were equilibrated, with gentle agitation, at 30 °C for periods up to 3 weeks, at which point the solution phase was analyzed, via stability indicating HPLC methods, for solute concentration. These HPLC methods

were similar to that used in the $P_{o\text{-}w}$ determinations in that the mobile phase used was a binary mixture of methanol and TFA (exact volume ratio optimized for each solute), the separation was performed on the Supelcosil LC8-DB column and the analyte was detected at low UV wavelength. Experimental controls, including chambers containing the polymer, solution and no solute and chambers containing solvent and solute but no polymer, were also incorporated into the experimental design to insure that partitioning processes could be distinguished from other processes which could influence solute behavior.

Hydrogen bond formation constants

Hydrogen bond formation constants (K_{HB}) were determined via a spectrophotometric titration method wherein the spectral properties of unbound and bound solute were measured as a function of the concentration of titrant (a hydrogen bond acceptor species) added (Higuchi et al., 1969). Specifically, solutes which could reasonably be anticipated to exhibit some hydrogen donating ability were reacted with varying amounts of tributyl phosphate (the hydrogen bond acceptor) in hexane and the absorbance properties of the mixtures were measured. In this treatment, the following relationship holds:

$$p(DA)/\delta B = (D + A)/\delta\epsilon + 1/(K_{HB}\ \delta\epsilon) \qquad (4)$$

where: D = moles of hydrogen bond donor, A = moles of hydrogen bond acceptor (titrant), δB = difference in molar absorptivity between the bound and unbound solute, $\delta\epsilon$ = difference in the molar extinction coefficient for the bound and unbound species, and p = cell path length.

A plot of $p(DA)/\delta B$ versus $(D + A)$ produces a slope of $1/\delta\epsilon$ and an intercept of $1/(K_{HB} + \delta\epsilon)$, the combination of which allows for the determination of K_{HB}.

Results

Partition coefficients

The log $P_{o\text{-}w}$ versus k'_w information generated for the test solutes and marker compounds used in this study is shown in Fig. 1. Squared correlation coefficients (r^2) for the individual capacity factor versus mobile phase composition plots used to generate the k'_w data were 0.998 or greater for all solutes evaluated. Linear regression analysis to produce the least squares fit of the log $P_{o\text{-}w}$ versus k'_w data produces an equation of the form

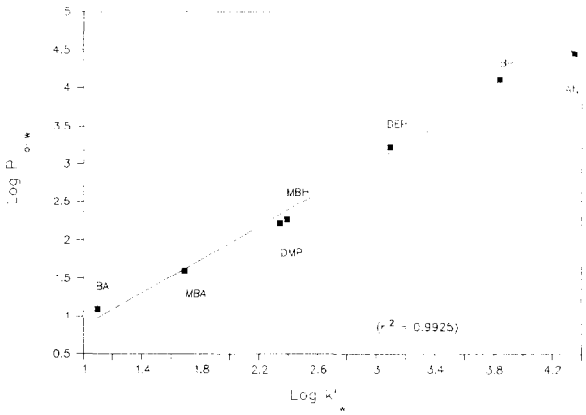

Fig. 1. Calibration plot of log $P_{o\text{-}w}$ versus log k'_w for the marker solutes identified in Table 2.

$$\log P_{o\text{-}w} = 1.087 \log k'_w - 0.2104 \qquad (5)$$

with $n = 7$ and $r^2 = 0.9925$. The near unit slope (95% confidence interval = 0.89 to 1.30) and near zero intercept (95% confidence interval = −0.10 to 0.52) of this best fit line indicates that the HPLC system is essentially equivalent to the octanol/water system in terms of its ability to discriminate between solutes based on the combined interaction mechanisms of hydrogen bonding and hydrophobic character. Partition coefficients obtained from both the literature and this method are summarized in Table 1.

Hydrogen bond formation constants

A typical titration plot for the determination of K_{HB} (in this case for propyl paraben) is shown in Fig. 2. Modest linear behavior is shown for this and the other solutes evaluated (other parabens and butylbenzoic acid). However, the butylbenzoic acid exhibited only a weak hydrogen bond donating ability and the K_{HB} value used herein represents essentially a qualitative estimate. The resulting formation constants are summarized in

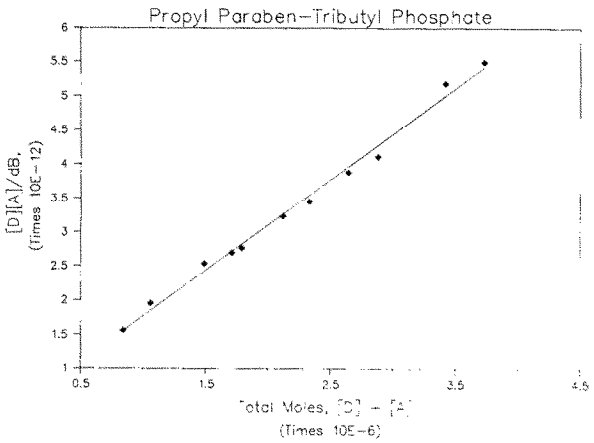

Fig. 2. Typical titration curve for the determination of hydrogen bond formation constants (K_{HB}).

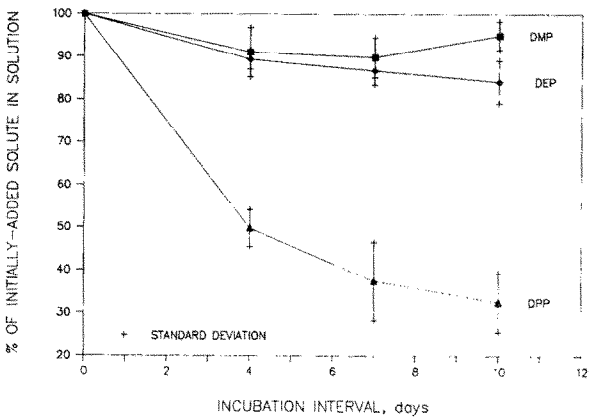

Fig. 3. Binding profile for the test polymer, fraction of solute bound versus incubation time.

Table 1. Functional group considerations for the phthalates and substituted benzoic acids (other than butylbenzoic acid) suggest that these species possess little, if any, hydrogen bond donating capability. Indeed, control experiments verified the absence of a significant change in solute absorption properties when these species were titrated with tributyl phosphate.

Equilibrium binding constants

At the end of the equilibration period, the binding chambers were opened and the solution phase characterized for the amount of solute remaining in this phase. The amount of solute bound by the polymer is then calculated from mass balance considerations. Analysis of the control samples confirmed that solute loss via absorption by the polymer was the only process that significantly influenced the solution phase concentration of the solute in this experimental design. Thus the solute loss calculated by mass balance is an accurate reflection of the amount of solute bound by the polymer and equilibrium binding constants can be calculated from Eqn. 3. Calculated binding constants are summarized in Table 1.

Discussion

Binding profiles

A typical binding profile (fractional solute uptake by the polymer as a function of incubation time) for the phthalates is shown in Fig. 3. This figure documents that the system approaches equilibrium essentially within 10 days of incubation. Thus the binding constants calculated herein truly represent an equilibrium state.

Binding correlations for test polymer

The relationship between the equilibrium binding constant and octanol-water partition coefficients for all solutes studied is shown in Fig. 4. While a good linear relationship can be established between log $P_{o\text{-}w}$ and log E_B for the solutes

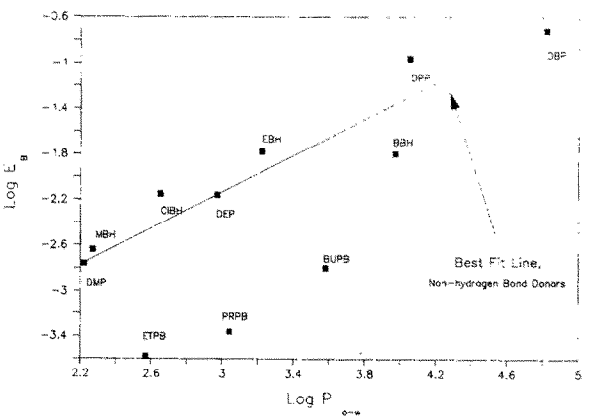

Fig. 4. Plot of equilibrium binding constant (E_B) versus octanol-water partition coefficient ($P_{o\text{-}w}$) for all solutes studied in this research. Solutes are identified by abbreviations given in Table 1.

TABLE 3

Hansen parameter hydrogen bonding interaction values

Material	δ_H (MPa$^{1/2}$)	
Water	42.3	Strong H bond acceptor
Methanol	22.3	
n-Octanol	11.9	
Acetonitrile	6.1	
Poly(vinyl chloride)	3.1	
n-Hexane	0.0	
n-Octane	0.0	
Poly(ethylene)	0.0	No H bond activity

Source: Barton, 1983.

that do not participate in significant hydrogen bonding, it is clear that the octanol-water system is a poor model for the parabens, which as a class are expected to exhibit fairly significant hydrogen bond donor properties. This inability of the octanol-water system to adequately model solute/polyolefin polymer interactions for strong hydrogen donors has been observed by other researchers (Jordon and Pollack, 1972; Illum and Bundgaard, 1982). Considering the hydrogen bonding ability of various solutes and polymers reveals that octanol (a moderately strong hydrogen bond acceptor) and polyethylene (which exhibits essentially no hydrogen bonding activity) are indeed quite dissimilar in this respect (see Table 3 for a listing of Hansen parameter values for typical solutes and polymers).

In principle, the relationship between partition coefficients and binding constants could be improved for strong hydrogen donor solutes by including a term that corrects for the contribution of hydrogen bonding to the partitioning mechanism in the octanol-water system. For example, Higuchi et al. (1969) have demonstrated a poor correlation ($r = 0.791$) between the partitioning properties of several hydrogen donor solutes in octanol-water versus cyclohexane-water systems (cyclohexane has essentially no hydrogen bond activity). These authors improved the correlation, however, by incorporating a term related to the hydrogen bond formation constant of the solute (K_{HB}) into the relationship via an expression such as:

$$\log P_{o\text{-}w} = 1.00\log P_{c\text{-}w} + 1.20\log K_{HB} + 2.35 \quad (6)$$

This improves the correlation significantly ($r = 0.979$ for $n = 7$ solutes).

Following the reasoning of Higuchi et al., multiple linear regression analysis of the data summarized in Table 1 produces the following least squares relationship for the test polymer:

$$\log E_B = 0.803\log P_{o\text{-}w} - 0.203\log K_{HB} - 4.426 \quad (7)$$

where $r^2 = 0.983$ for $n = 12$ (see Fig. 5). Because the coefficient for the log P term in this equation is less than unity, the polymer used is less sensitive to changes in solute lipophilicity than is octanol.

Binding correlations for various polymers

Eqn. 7 is general in that it should apply to the interaction of most solutes with the polymer studied herein. However, the magnitude of the slopes for the $P_{o\text{-}w}$ and K_{HB} terms and the intercept will depend on the nature of the polymer. The interaction behavior between several drugs (steroids, amines) and various polymers (including

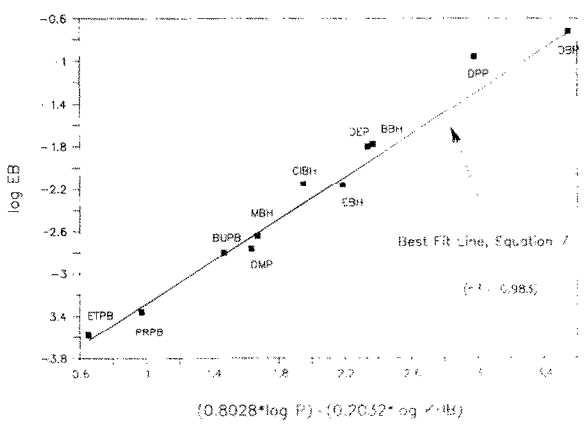

Fig. 5. Plot of the equilibrium binding constant (E_B) versus the linear combination of the octanol-water partition coefficient ($P_{o\text{-}w}$) and the hydrogen bond formation constant (K_{HB}). The best fit line represents equation 7. Solutes are identified by their abbreviations in Table 1.

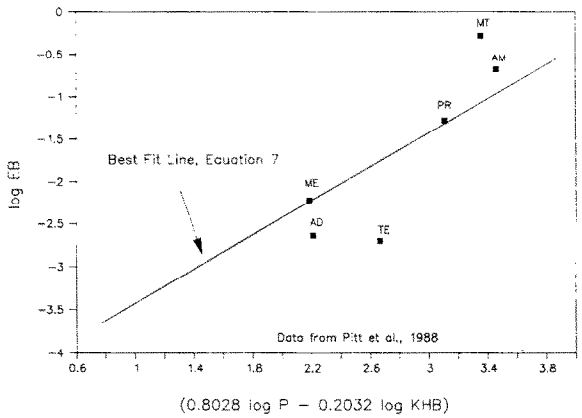

Fig. 6. Plot of E_B versus the linear combination of $P_{o\text{-}w}$ and K_{HB} for solutes studied by Pitt et al. (1988). The best fit line represents Eqn. 7. Solutes are identified by abbreviation in Table 1.

polyethylene) has been studied and partition coefficients ($P_{p\text{-}w}$) were reported (Pitt et al., 1988). The conversion of the reported partition coefficients to binding constants is straightforward (involving the polymer density to convert from volumetric to gravimetric units for the solute concentration in the polymer). As shown in Fig. 6, the resulting data fit fairly well with the model proposed for the polymer studied herein. Lack of hydrogen bond formation constants for some of the drugs studied by Pitt et al. (which one would expect to exhibit some hydrogen bonding activity) contributes significantly to the scatter exhibited by this data.

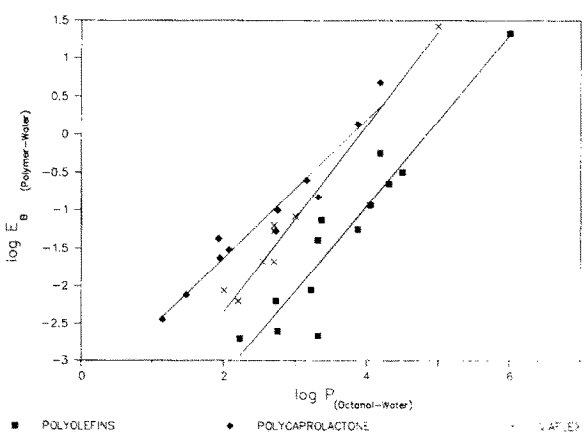

Fig. 7. Binding properties of various polymers; relationship of binding constant to solute octanol-water partition coefficient. Polyolefin data obtained from this study and Pitt et al. (1988), polycaprolactone data from Pitt et al. (1988), and PVC (Viaflex®) data from Illum and Bundgaard (1982).

The binding characteristics of three polymer types can be compared by standardizing the constant used by various researchers in their examination of the binding properties of individual polymers. Thus the data from this study (coupled with the drug data of Pitt et al.) characterize a polyolefin polymer, while the data from Pitt et al. and Illum and Bundgaard can be used to characterize a polycaprolactone and a plasticized PVC polymer (Viaflex®), respectively. This comparison of binding properties is shown in Fig. 7. Qualitatively, it is obvious that the films differ significantly in two respects. Firstly, the magnitude to which they bind solutes is different, with the test polyolefin studied herein exhibiting a significantly reduced binding capability compared to the PVC and polycaprolactone. Additionally, while the polyolefin and Viaflex exhibit similar sensitivity to solute lipophilicity (similar slopes), the polycaprolactone appears to be somewhat less sensitive to this solute property.

Solute migration in parenteral containers

The equilibrium binding constant can be used to predict solute distribution between a polymeric container and the solution it contains. Consider the situation in which a solution of volume V_s, containing m_i moles of a solute is placed in contact with a polymeric container of mass W_f. The solute will partition between the two phases (as defined by the binding constant, Eqn. 3) such that at equilibrium the amount of solute bound by the container is x and the amount remaining in solution is $m_i - x$. Thus Eqn. 3 becomes:

$$E_B = (x/W_f)/(m_i - x/V_s) \tag{8}$$

which, when solved for the fraction of the solute bound by the polymer (F_B), becomes

$$F_B = x/m_i = (W_f E_B)/(V_s + W_f E_B) \tag{9}$$

Using an established relationship between the binding constant and the solvent-water partition

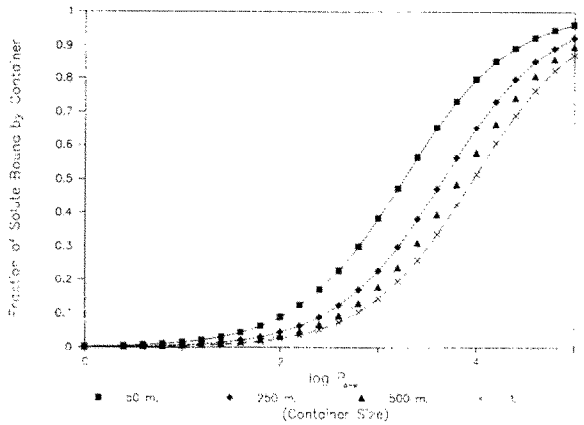

Fig. 8. Binding model for container systems based on the polymer studied in this research. Effect of solute $P_{o\text{-}w}$ and container configuration on fractional solute uptake from solution.

coefficient of a solute (e.g. Eqn. 7) one can calculate the extent of solute binding from the partition coefficient. This scenario applies directly to the uptake of an active ingredient from a parenteral formulation by its container.

For example, Fig. 8 demonstrates the effect of container configuration [typical container size (mass) versus solution volume relationship] and solute $P_{o\text{-}w}$ on the fraction of initially present solute that will be bound by the container. For the sake of simplicity, Fig. 8 assumes that the solute of interest has no hydrogen bonding ability. It is quite clear that both the container configuration and solute partitioning properties strongly influence the potential utility of a particular container/solution combination. Specifically, the more favorable container mass-to-solution volume ratio typical of larger containers minimizes the magnitude of solute loss to the container. For example, a 50 ml container system typically has a mass polymer to solution volume ratio of approximately 64 g/l whereas with the 1 l container the ratio is approximately 17 g/l. Thus when solute migration into the container is a significant solute loss mechanism (potentially impacting product suitability), container configuration can and must be optimized to minimize the impact that migration has on product acceptability. However, Fig. 8 confirms that as the solute log $P_{o\text{-}w}$ increases past 2.5, binding by the container, regardless of container configuration, will represent a significant solute loss mechanism (approaching 10%) which must be considered in product research and development.

The converse of this latter discussion is the migration of a solute out of the container into the solution. In this case, if the total available amount of solute originally in the polymer is P_a (expressed in units of amount of solute per unit weight of polymer), the amount of material which migrates into solution at equilibrium (m_s) is:

$$m_s = (V_s P_a W_f)/(W_f E_B + V_s) \qquad (10)$$

As an example of this scenario, Fig. 9 illustrates the effect of solute log $P_{o\text{-}w}$ and container configuration on the equilibrium concentration of solute in the contained solution resulting from the migration of the solute from a container possessing a solute total available pool of 10 μg/g. Again the favorable container mass to solution volume ratio typical of the larger container sizes tends to alleviate the impact of solute migration from the container; however for solutes with a log $P_{o\text{-}w}$ of 3.5 or less, the solute accumulates in solution at concentrations of 50 ppb or higher. Migration of container leachables to this extent can, depending

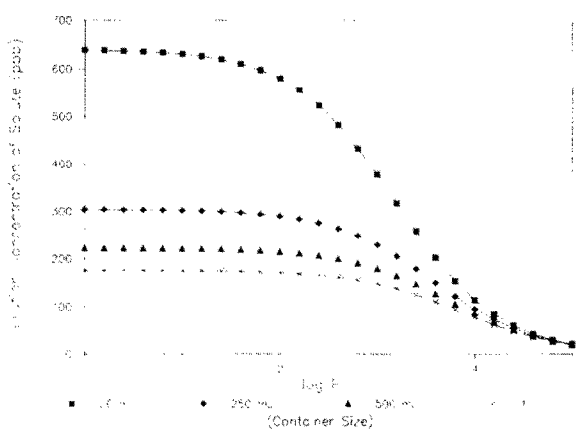

Fig. 9. Binding model for container systems based on the polymer studied in this research. Effect of solute $P_{o\text{-}w}$ and container configuration on the magnitude of solute released into the solution.

on the nature of the solute, represent a significant threat to product utility.

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