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Research Article

Determination of Solute–Polymer Interaction Properties and Their Application to Parenteral Product Container Compatibility Evaluations

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Kinetic and thermodynamic interaction properties between dialkyl phthalate test compounds and a polyolefin polymer were examined via a permeation-cell experimental design. Disappearance and appearance rates of solute in the receptor and donor solutions, as well as the equilibrium composition of the test system, are used to determine sorption and diffusion coefficients and the solute/polymer equilibrium binding constant. Sorption rate constants and diffusion coefficients exhibit Arrenhius-type behavior. The binding constants obtained correlate well with the solute's octanol–water partition coefficient. The kinetic and thermodynamic data generated combine with proposed interaction models to identify solute/polymer interactions (binding and leaching) pertinent to evaluating container/solution compatibility for parenteral products.

KEY WORDS: parenteral products; container/solution compatibility; phthalate dialkyl esters; polyolefin/solute interactions.

INTRODUCTION

An important facet of developing container materials for parenteral products involves evaluating container/solution interactions. Two processes in this evaluation are (1) the ability of the container to sorb solutes out of the solution phase (binding) and (2) migration of container components into the solution (leaching). For binding, the major concern is that the product will be adversely impacted by the loss of an important formulation component (e.g., drug) to the container. Numerous instances of solute loss from pharmaceutical solutions by sorption into polymeric containers have been reported (1–16). With respect to leaching, the potential toxicity of trace materials mobilized into a parenteral solution is a matter of concern (17–20).

Four general factors control solute–container interactions (21). They are

(1) the initial or total amount of solute present (the total available pool),
(2) the solute's solubility in the solution phase,
(3) the equilibrium partitioning of the solute between the container and the solution, and
(4) diffusion.

Characterizing a particular solute–solvent–polymer system with respect to these factors is a necessary first step in assessing the nature of the container–solution interaction. Evaluation of container–solution compatibility involves both thermodynamic and kinetic considerations; the former defines essentially the maximum absolute magnitude of the interaction, and the latter the rate at which the interaction occurs. This rate is particularly important since a container–solution interaction impacts product utility only if the interaction occurs during the product's projected shelf life.

Methodologies used to assess polymer–solute interactions involve two steps; the first allows for contact and equilibration between the solution and polymer phases (wherein the solute of interest is typically dispersed initially in one of the phases) and the second involves the analysis of the solute concentration in either or both of the phases. In this study, the former process is accomplished using the "permeation-cell" concept described by Polack *et al.* (20). Specifically, the polymer of interest is formed into a small pouch which is loaded to contain a receptor solution (of known volume and initial chemistry) and completely sealed. The receptor pouch is then immersed in a donor solution (of known volume) containing the solute of interest. The entire test system is sealed and stored (with gentle agitation) at various temperatures. At various points during storage, aliquots of the receptor and donor solutions are chemically characterized.

This research focuses on establishing the thermodynamic and kinetic interactions between a specific polymer (a proprietary composite polyolefin which is a candidate parenteral product container material) and dialkyl phthalate marker solutes. Interaction parameters defined as the result of the experimental work are correlated with fundamental solute properties and are used to model and determine solute distribution in practical container/solution configurations.

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MATERIALS AND METHODS

Materials

The polymer studied is a proprietary polyolefin. Test marker solutes including dimethyl, diethyl, and dipropyl phthalate (abbreviated DMP, DEP, and DPP, respectively) were analytical-grade reagents (98% purity or better). Donor and receptor solutions were research-grade water. Reagents used to prepare the chromatographic mobile phase were HPLC grade.

Sorption Isotherm

Approximately 1.3 g of polymer, cut into 1-cm^2 pieces and supported on inert, small-bore HPLC tubing (PEEK), was placed in a glass reaction vessel containing 50 ml of the donor solution (water) which contained (initially) from 1 to 100 ppm DEP. The polymer pieces, which were completely immersed in the donor solution, were supported by piercing the pieces through the center with the supporting tubing so that the individual pieces did not touch (maximizing polymer/solution interaction). Duplicate closed reaction vessels, along with controls containing no polymer, were equilibrated, with constant gentle agitation, at 45°C for 5 days, at which point the solution phases were characterized for solute content via HPLC. These control samples ensure that the polymer partitioning process can be distinguished from other processes impacting the solute distribution in the test system (i.e., sorption by the reaction vessel, solute degradation).

Permeation Cells

Pouches were made from approximately 3.3 g of polymer (mean film thickness, 0.2 mm) by heat sealing common edges together. The resulting pouches had a typical surface area of 15000 mm^2 and were filled to contain 50 ml receptor and a minimal air headspace. The heat seal seams of the pouches represented less than 0.5% of the total pouch surface area. The sealed pouches were placed in a glass vessel containing 400 ml donor solution. The donor solutions included 50 ppm each of DMP, DEP, and DPP separately and in combination. The pouches were completely immersed in the donor solution with the exception of a small sampling port (from which samples of the receptor solution could be retrieved via syringe). The reaction vessels were closed and equilibrated by storage at temperatures of 25, 35, 45, and 55°C with constant, gentle agitation. Control samples containing the donor solution but no pouch were also stored under the test conditions. During storage, aliquots of the donor, receptor, and control solutions were analyzed via HPLC for solute content. The amount of sample withdrawn was sufficiently small (typically 0.5 and 0.1 ml, respectively, per interval) so that the total solution volume was not significantly changed by the sampling process.

Analytical Method

The solute concentration in the solution phase samples was determined using reversed-phase liquid chromatography. Separation was accomplished with a Supelcosil LC8-DB stationary phase (50 × 4.6-mm column, 5-μm particle size) and a mobile phase consisting of 53/47 (v/v) methanol/water. Mobile phase flow rate was 1 to 1.3 ml/min and sample size was 50 μl. Under these conditions the solutes were baseline resolved and were characterized by a guassian peak shape. Detection was accomplished by monitoring UV absorption at 220 nm, producing a solute quantitation limit of approximately 0.1 ppm. Solute concentration was determined via linear regression analysis of standard response data; peak areas were used throughout.

RESULTS AND DISCUSSION

Sorption Isotherm

The sorption isotherm (Fig. 1) for DEP in the test polymer was linear, with a correlation coefficient (r^2) of 0.99 and an intercept which spanned zero within ±2 standard deviations. The experimental design encompassed solute/polymer interaction conditions used in the pouch experiments and focused on the test solute possessing intermediate hydrophobic character. The isotherm observed is characteristic of type C partitioning (22), wherein its slope (k, equivalent to the partition coefficient of the solute in the polymer) is related to the solubilities (S) of the solute in the polymer (p) and the solution (s) via Eq. (1):

$$K = S_p/S_s \quad (1)$$

Thermodynamics

Disappearance profiles depicting the migration of the test solutes out of the donor solution in the permeation cells are shown in Fig. 2. For all three solutes, the profile is bimodal and consists of a rapid solute uptake from the donor followed by a slower solute loss. The magnitude of the fractional loss resulting from the initial uptake mechanism is clearly related to the solute's hydrophobic character. Examination of the solute distribution profiles (Figs. 3 and 4) for the same experiment reveals that the initial uptake mechanism represents solute sorption by the polymer (presumably a surface effect), while the slower loss mechanism represents solute migration through the polymer and into the receptor solution.

One notes that the distribution profiles represent mea-

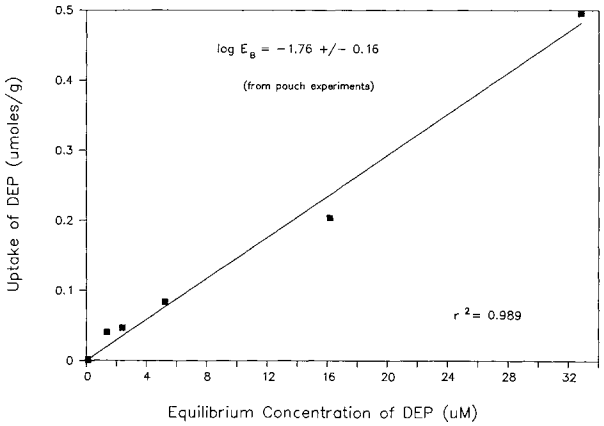

Fig. 1. Sorption isotherm; uptake of DEP from solution by the test polymer. Experiment performed at 45°C.

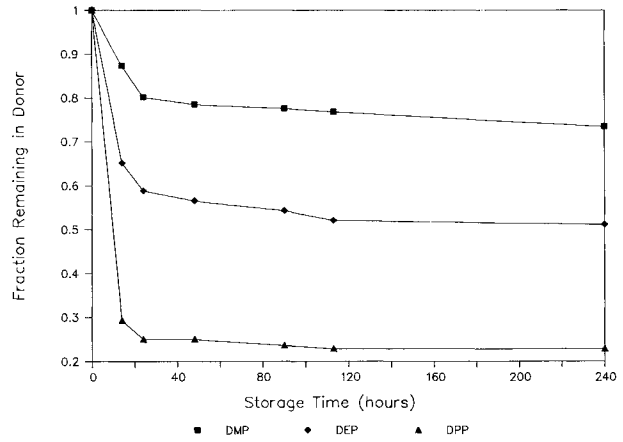

Fig. 2. Disappearance profiles for the test marker compounds; migration out of the donor solution at 55°C.

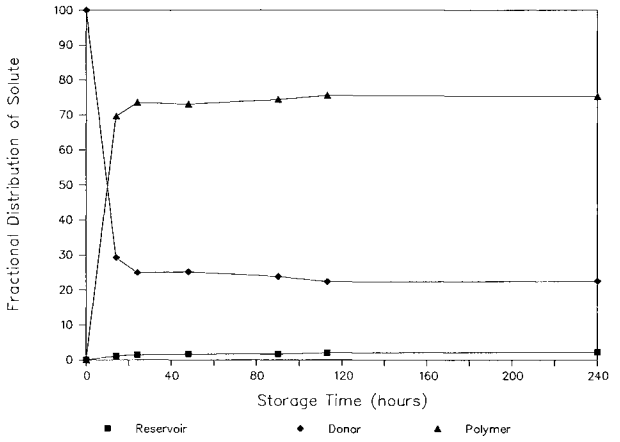

Fig. 4. Solute distribution profile; fractional distribution of the marker solute (DPP) between the donor solution, the receptor (reservoir) solution, and the polymer as a function of interaction time at 55°C.

sured solute concentrations in both the donor and the receptor and calculated (via mass balance) solute concentrations in the polymer. Analysis of control samples confirmed that solute loss via mechanisms other than polymer sorption was minimal. Again, the distribution profiles reinforce the observation that the magnitude of solute binding is related to the solute's hydrophobicity. This behavior is similar to that observed by Roberts *et al.* in their study of solute migration through rigid polyethylene bottles using the permeation-cell approach (23).

Appearance profiles depicting the migration of the test solutes into the donor solution are shown in Fig. 5. As indicated in this figure, the appearance profiles suggest a three-step process which includes (1) an induction period (during which the solute is sorbed from the donor phase by the polymer and the solute migrates through the container), (2) a region characterized by a steady-state accumulation of the solute in the receptor solution (diffusion-controlled migration of the solute through the container which occurs after induction is complete), and (3) a plateau region (which is attained after sufficient solute migration has occurred that the solute concentration in the donor and receptor solution is the same and the thermodynamic driving force for migration has been exhausted).

The concentration (and the time) at which the equilibrium between the donor and the receptor solutions is achieved depends on by how much solute is bound by the polymer. As the amount of solute bound by the film increases, the equilibrium concentration is lowered and (for solutes of similar diffusion coefficients) the plateau concentration is achieved more rapidly. Thus in Fig. 5, the plateau for DPP is achieved within 10 hr, whereas both DEP and DMP concentrations continue to increase after 60 hr. At 25°C, diffusion is sufficiently slow that even after 35 days all solutes still experience steady-state migration into the receptor solution (Fig. 6).

Attainment of equilibrium with respect to both solute sorption by the polymer and solute migration through the polymer was confirmed at each temperature studied via examination of the pertinent appearance and disappearance profiles. At equilibrium, the distribution of the solute between the solution and the polymer phases can be expressed by the equilibrium binding constant E_B,

$$E_B = (m_p/W_p)/(m_s/V_s) \quad (2)$$

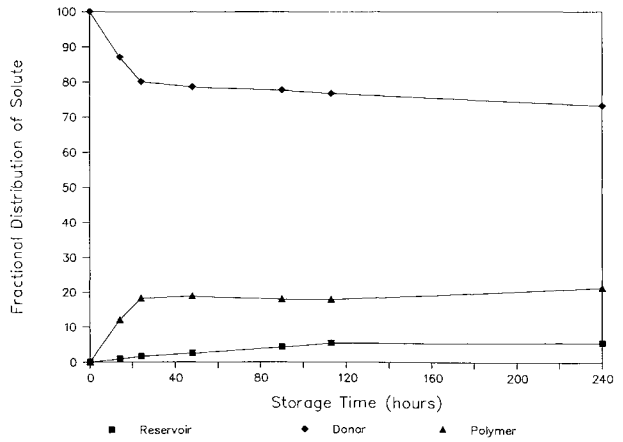

Fig. 3. Solute distribution profile; fractional distribution of the marker solute (DMP) between the donor solution, the receptor (reservoir) solution, and the polymer as a function of interaction time at 55°C.

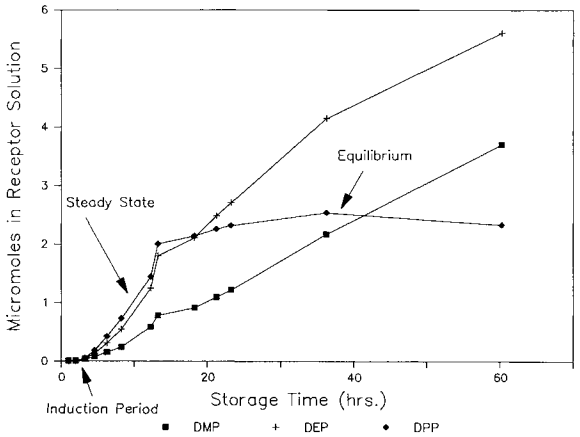

Fig. 5. Appearance profile for the test marker compounds; migration of the solute into the receptor solution at 55°C.

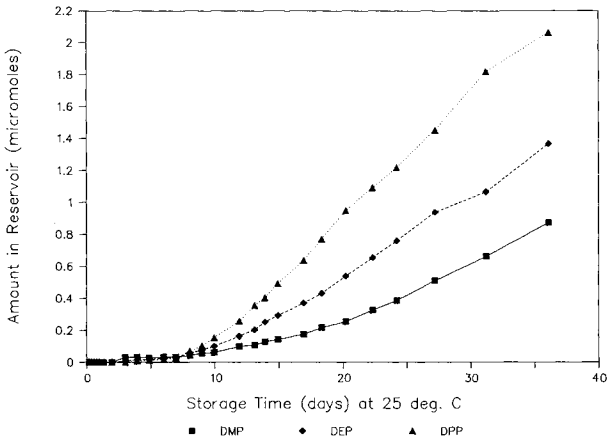

Fig. 6. Appearance profiles for the test marker compounds; migration of the test solutes into the receptor solution at 25°C.

where

m = mass of solute in the particular phase (at equilibrium)
V = volume of solution (in liters)
W = weight of polymer (in grams)
s and p = solution and polymer phases, respectively

For the determination of E_B from quantities pertinent to the pouch experiment, Eq. (2) becomes

$$E_B = [(C_i V_D - C_E(V_D + V_R))/W_p]/C_E \quad (3)$$

where

C_i = initial solute concentration in the receptor solution
C_E = equilibrium solute concentration in either solution
V_R = volume of the receptor solution
V_D = volume of the donor solution

Various authors have correlated solute–polymer partitioning behavior with solute–solvent partition coefficients; octanol–water is commonly used as a reference system (24–26). The equilibrium binding constants (25°C) obtained herein correlate well with published solute octanol–water partition coefficients ($P_{o\text{-}w}$) (27) via a Collander-type expression:

$$\log E_B = 0.818 \times \log P_{o\text{-}w} - 4.05 \quad (4)$$

Additionally, the E_B constants obtained herein agree well with similar constants obtained for these test solutes and similar polyolefin materials (26).

One notes that by definition the slope of the partition sorption isotherm equals the equilibrium binding constant. Experimentally, the slope in Fig. 1 (0.0147) and the calculated E_B for DEP at 45°C obtained from the pouch study (0.0174) are statistically equivalent at the 95% confidence level.

Kinetics

The disappearance of solute from the donor solution can be kinetically described by a biexponential model (23):

$$F_s = Ae^{-\alpha t} + Be^{-\beta t} \quad (5)$$

where F_s is the fraction of solute remaining in the donor at time t, A and B are the fractional intercepts of the disappearance plot, and α and β are the sorption and migration process rate constants. Values for these constants, calculated via least-squares minimization of the difference between observed and predicted disappearance data, are presented in Table I. The A and B coefficients and the α rate constant are affected by the affinity of the polymer for the various solutes. The best-fit β rate constant values for all three solutes are essentially the same. Since the β rate constant reflects migration through the polymer (which is diffusion controlled) and the three test solutes have similar diffusion properties, the approximate equivalence of their β values is reasonable.

Equation (5), coupled with the best-fit constants (for each solute) contained in Table I, represents a disappearance model for solutes migrating out of the donor solution. As shown in Fig. 7, the correlation between the disappearance behavior predicted by the model and that actually observed is excellent for all three solutes.

The effect of temperature on the disappearance kinetics of DPP is shown in Fig. 8. Both the sorption and the migration processes are impacted by temperature. As shown in Fig. 9, the effect of temperature on the sorption kinetics (r_D = rate of solute sorption from the donor solution) is adequately modeled by Arrenhius behavior, indicating that the sorption process is an activated one. Migration kinetics are dominated by diffusion, and since solute diffusion in polymers generally exhibits Arrenhius behavior (28–32), one expects migration to exhibit Arrenhius behavior as well.

As indicated in Figs. 5 and 6, the appearance kinetics of solute in the receptor exhibit a pronounced induction period. Thus the diffusion coefficient D of the solute through the polymer can be determined using the time lag method (33):

$$D = \delta^2/(6 \times T_L) \quad (6)$$

where δ is the film thickness and T_L is the time lag (time axis intercept of the steady-state portion of the appearance profile). Calculated diffusion coefficients for DMP, DEP, and DPP at 25°C are 5.6, 4.2, and 3.7×10^{-5} mm²/hr, respectively. These values are similar to diffusion coefficients reported for substituted phthalates in various polymers (primarily PVC) (28,34,35). As shown in Fig. 10, the solute/polymer system studied exhibited Arrenhius-type behavior with respect to the influence of temperature on the diffusion coefficient; essentially all three solutes exhibit a similar temperature dependence. Arrenhius behavior indicates that the migration process is an activated one; activated energies calculated for this test system are approximately 25 kcal/mol, which agrees fairly well with activation

Table I. Kinetic Data for the Disappearance of Solutes from the Donor Solution at 55°C

Solute	A	B	α (hr^{-1})	β (hr^{-1})
DMP	0.19	0.81	0.075	0.00050
DEP	0.41	0.59	0.17	0.00060
DPP	0.75	0.25	0.20	0.00055

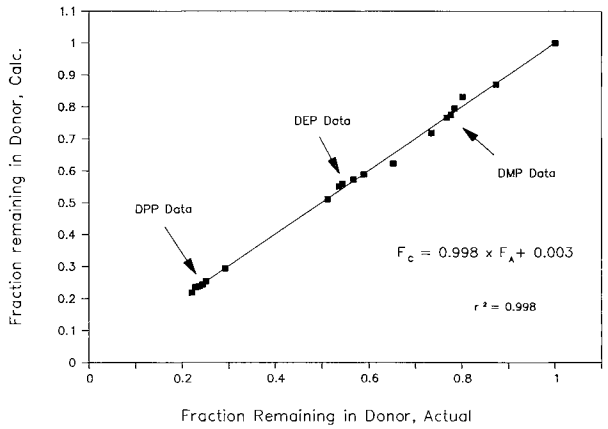

Fig. 7. Comparison of observed disappearance behavior with that predicted by the kinetic disappearance model. Fraction of solute remaining in the donor solution, calculated (F_c) versus experimentally determined (F_A). Temperature = 55°C.

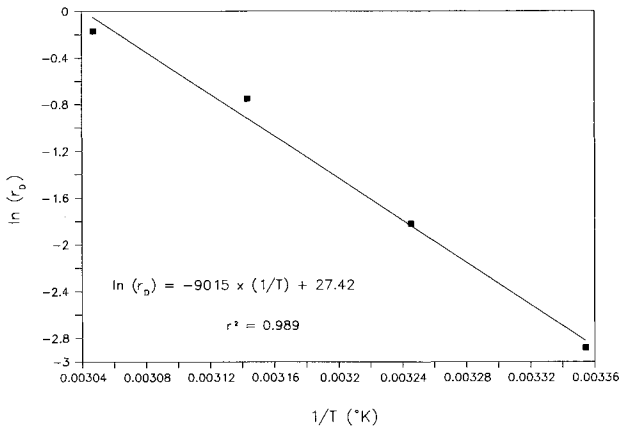

Fig. 9. Arrenhius plot, effect of temperature on the sorption rate (r_D) of DPP from the donor solution by the polymer.

energies calculated for solute migration in PVC and polyethylene systems (see Table II) (30–32,34).

Conceptually, the penetration of solutes into the receptor solution of the pouch system is similar to controlled drug release from a reservoir-type device which is used shortly after its manufacture. Mathematical analysis of reservoir-type drug release systems exhibiting time lag effects has been performed by Peppas (33). For such a system, the amount of solute release at time t (or, for the pouch experiment, the amount of solute which has migrated into the receptor solution), M_t, can be expressed as follows:

$$M_t = (DCt/\delta) - (C\delta/6) - (2C\delta/\pi^2)R \qquad (7)$$

where C is the interfacial solute concentration at the polymer/solution interface and R is the following function:

$$R = \sum_{n=1}^{\infty} [(-1)^n/n^2] \exp(-Dn^2\pi^2 t/\delta^2)$$

At short times ($t < \delta^2/D$), the amount of solute released is 0, while at very long times the amount that migrates into the receptor will reach its equilibrium value M_E. Being characteristic of the equilibrium state, M_E can be calculated from E_B and the physical dimensions of the experimental system via the expression

$$M_E = (C_i V_D)/\{1 + [E_B W_p/(V_R + V_D)]\} \qquad (8)$$

Finally, at intermediate times, Eq. (7) simplifies to the linear relationship:

$$M_t = (DC/\delta)[t - (\delta^2/6D)] \qquad (9)$$

which is the equation of the steady-state portion of the appearance profile. Combination of the short- and long-time approximations and Eq. (9) produces a three-compartment model for solute migration into the receptor solution of the pouch. As shown in Fig. 11, application of such a model to the migration of DPP into the receptor solution at 55°C results in excellent agreement between observed and predicted behavior.

Container/Solute Interactions: Binding

Consider a polymer container of mass W_p which contains a solution of volume V_s possessing initially m_i moles of a solute. Furthermore, assume that the solute/container interaction is partition (as opposed to solubility) constrained.

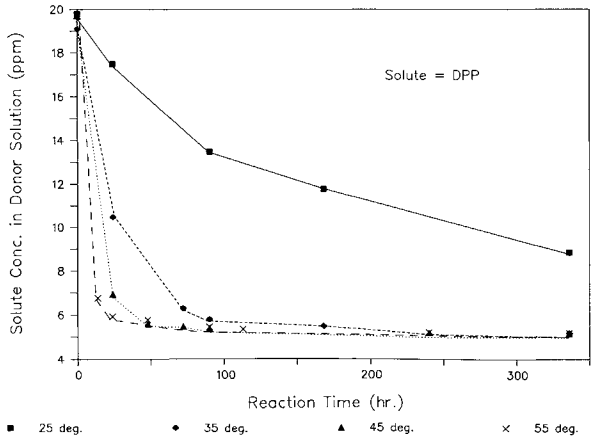

Fig. 8. Effect of temperature on the disappearance kinetics of solutes; migration out of the donor solution.

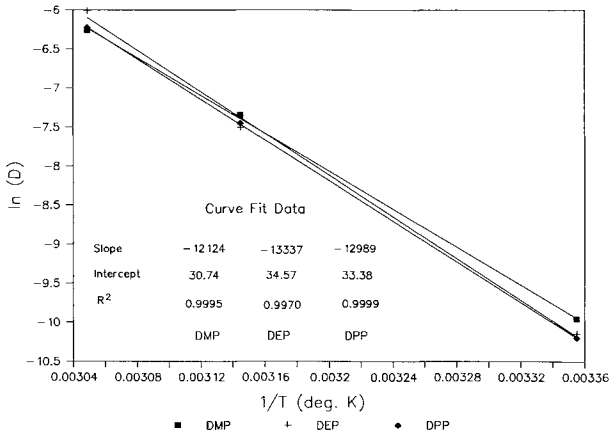

Fig. 10. Arrenhius plot, effect of temperature on the diffusion coefficients of the marker compounds.

Table II. Activation Energies for Solute Migration Through Polymer Films

Film	Solvent	Solute	E_a (kcal/mol)	Reference
Polyethylene	Water	Methyl *p*-aminobenzoate	12.9	32
		Ethyl *p*-hydroxybenzoate	19.5	32
		Methyl *p*-hydroxybenzoate	21.4	32
PVC	—[a]	Di-*n*-alkyl phthalates	11.7–20.3	35
Polyethylene	Water	Acetophenone	18.8	31
		Anisole	13.4	31
		Nitrobenzene	14.4	31
Polyethylene	Water	Acetophenone	17.4	33
Polyolefin	Water	Dimethyl phthalate	24.1	This study
		Diethyl phthalate	26.5	This study
		Dipropyl phthalate	25.8	This study

[a] "Self-diffusion" measured directly in the polymer.

Solute partitioning, defined by E_B, will be such that at equilibrium the amount of solute bound by the container equals x (and the amount remaining in solution is $m_i - x$). Substituting these concentrations into Eq. (2), followed by the solution of the resulting expression for the fraction of solute bound by the container (F_B), produces

$$F_B = W_p E_B/(V_s + W_p E_B) \quad (10)$$

Coupling Eq. (10) with an established relationship between E_B and a fundamental solute property [for example, $P_{o\text{-}w}$ as per Eq. (4)] allows the convenient estimation of the maximum magnitude of solute/container binding interactions. For example, Fig. 12 demonstrates the effect of container size and solute $P_{o\text{-}w}$ on the fractional binding of a solute. Clearly the container configuration and $P_{o\text{-}w}$ both strongly influence the compatibility of the solute and container in terms of their binding interaction. The effect of container configuration is clarified by the differing container mass to solution volume ratios typical of the various container configurations. For example, a typical 50-ml container has a mass polymer-to-solution volume ratio of approximately 64 g/liter, whereas the 1-liter container has a ratio closer to 17 g/liter. Thus in new product development efforts, the container configuration can be modified somewhat so as to minimize the magnitude of the binding interaction. However, as illustrated in Fig. 12, once the solute's log $P_{o\text{-}w}$ increases past 2.5, binding by the container, regardless of the container configuration, will represent a significant solute loss mechanism (approaching 10% loss).

Sorption of the solute by the container is kinetically modeled by an expression similar to Eq. (5) with the exception that instead of the solute migrating into a receptor reservoir (in the pouch experiment) the solute can migrate through the polymer only until the polymer is saturated with the solute (either partition or solubility mediated). Thus for a solute/container binding interaction, at some time t the fraction remaining in solution becomes a constant value (as equilibrium is achieved) whose magnitude is given by Eq. (10). The time it takes to reach this equilibrium state (T_E) can be determined by combining Eqs. (5) and (10) and solving for T_E. For the test solutes and polymer used herein in a 50-ml container configuration, T_E values are approximately 225, 1050, and 2200 hr for DMP, DEP, and DPP, respectively, at 55°C. These somewhat long T_E values reflect both the magnitude of solute binding (which increases for solutes of increasing hydrophobicity) and the fact that at long times the binding is kinetically controlled by a slow diffusion process.

The amount of time it takes the container to sorb 10% of the solute from solution (T_{10}) may be more practically important than T_E since ±10% product limits on active ingredients are common in the pharmaceutical industry. Figure 2 confirms that while attainment of T_E is essentially diffusion

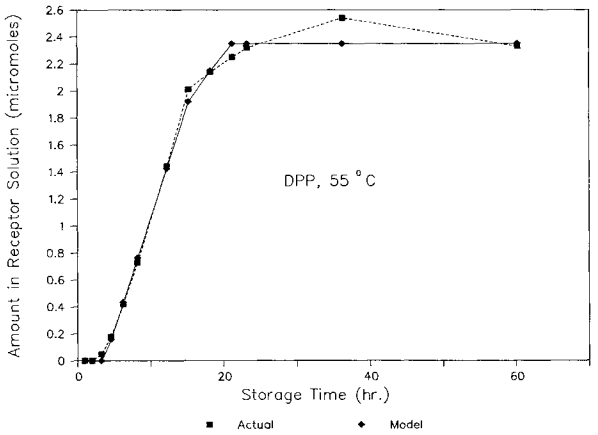

Fig. 11. Migration of DPP into the receptor solution at 55°C; model predicted versus experimentally observed behavior.

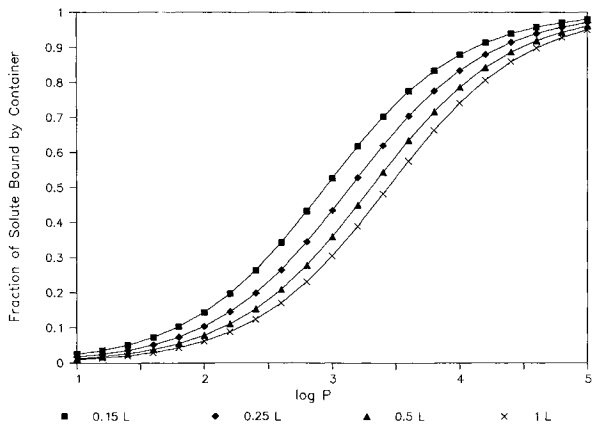

Fig. 12. Effect of solute $P_{o\text{-}w}$ and container configuration on the fractional solute uptake (binding) by the container.

controlled (and thus is fairly slow), attainment of T_{10} is sorption controlled (at least for the phthalate test compounds) and thus is relatively quick. T_{10} values for DMP, DEP, and DPP are approximately 10, 2.5, and 1 hr, respectively, at 55°C. Extrapolation of this behavior to ambient temperature (25°C) via the Arrenhius relationships in Figs. 9 and 10 produces T_{10} estimates of 120, 20, and 10 hr for DMP, DEP, and DPP at this temperature. It is clear that significant solute loss from solution via sorption by a polymeric container can occur quite rapidly, certainly within the typical shelf life of parenteral formulations.

Again, the above argument is valid only if the interaction process is partition, as opposed to solubility, limited. If the ratio of solute concentration in solution to polymer weight falls outside the linear region of the polymer sorption isotherm, it is possible that the polymer would become saturated with respect to the solute before a significant solute loss from the solution occurred.

Container/Solute Interactions: Leaching

For a polymeric container whose total solute available pool is P_a (expressed as units of mass of solute per unit weight of container), the amount of solute which will migrate into the solution phase at equilibrium (m_s) is (assuming that the interaction is partition mediated):

$$m_s = [V_s P_a W_f/(W_f E_B + V_s)] \quad (11)$$

Using Eq. (11), Fig. 13 documents the effect of container configuration and solute $P_{o\text{-}w}$ on m_s for a container with a P_a of 10 μg/g. Again, favorable container mass-to-solution volume ratios typical of the larger containers tend to alleviate the impact of solute migration out of the container. However, for solutes whose log $P_{o\text{-}w}$ is 3 or less, potentially significant quantities of solute (100 ppb or greater) accumulate in the solution phase at equilibrium. Migration of container leachables to this extent can, depending on the nature (e.g., toxicity) of the solute, significantly impact product utility.

Fick's law describes small-molecule migration from a polymer sheet (e.g., the container) into essentially an infinite bath (the contained solution). Assuming that

(1) diffusion occurs in only one direction (out of the container),
(2) D is concentration independent,
(3) the diffusing solute is evenly distributed in the polymer, and
(4) the polymer surface concentration of solute is instantaneously brought to zero (good mixing),

equations have been derived which relate the amount of solute released to the storage time (33,36). Useful approximations of these somewhat complicated expressions are as follows.

For short times ($M_t/M_\infty < 0.6$),

$$M_t/M_\infty = (4Dt/\pi\delta^2)^{1/2} \quad (12)$$

For long times ($M_t/M_\infty > 0.6$),

$$M_t/M_\infty = 1 - [(8/\pi^2)\exp(-\pi^2 Dt/\delta^2)] \quad (13)$$

where M_t is the amount of diffusant lost to solution at time t and M_∞ is the equilibrium desorption of solute obtained theoretically at infinite time. Additionally, immediately after product manufacture (that is, when the container is filled with solution), there may be an induction period associated with the mobilization of the leachable solute resulting from either (1) the migration of the solute to the surface of the container (uneven distribution), (2) poor desorption kinetics (poor mixing), or (3) solvent migration into the polymer. During any induction period $M_t/M_\infty = 0$. Combination of this relationship with Eqs. (12) and (13) produces a three-compartment kinetic leaching model, as shown in Fig. 14, which represents a release rate profile for a leachable substance. M_∞ is affected by the solute's binding constant via

$$M_\infty = [P_a W_p/(W_p E_B + V_s)] \quad (14)$$

As an example of the implications of this kinetic model, consider (1) a solute with a $P_{o\text{-}w}$ of 1000 and a diffusion coefficient similar to that of the phthalates and (2) a 250-ml container made of the test polymer possessing a P_a of 10 μg/g solute. Under this set of conditions, one calculates that the solution phase will reach a partition-mediated equilibrium solute concentration of approximately 160 ppb (representing approximately 53% of the containers total solute available pool) approximately 10 days after unit production.

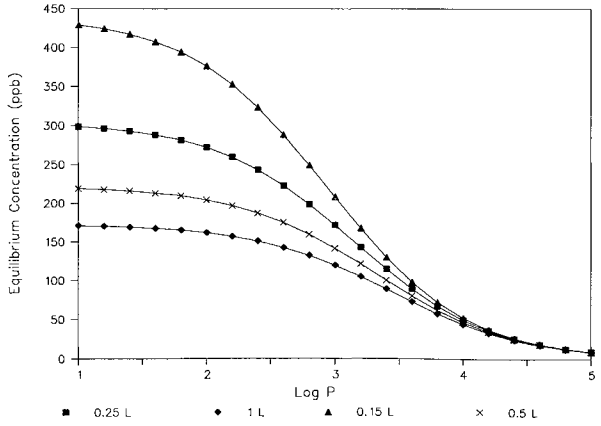

Fig. 13. Effect of solute $P_{o\text{-}w}$ and container configuration on the amount of solute released (leached) into solution from the container. Solute total available pool in the container is 10 μg/g.

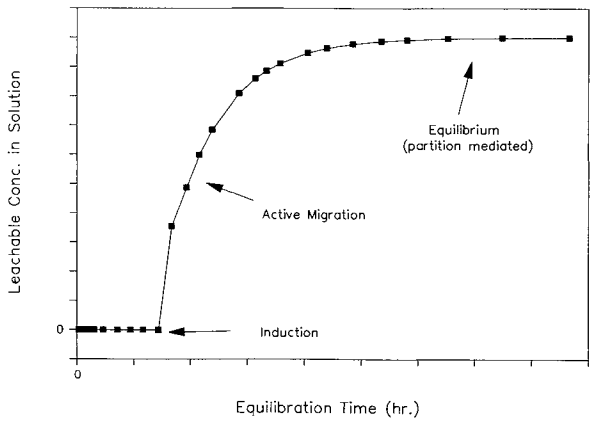

Fig. 14. Three compartment migration model for the liberation of a leachable substance from a polymer container to its contained solution.

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