

# Solute Migration through Polypropylene Blend Films

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## SYNOPSIS

The migration of several low molecular weight model solutes through a polypropylene/polyolefin blend was examined via a permeation-cell experimental design. Diffusion coefficients and permeation rates are obtained for the model solutes. The permeation rates exhibit Arrhenius-type behavior. A bimodal permeation model is proposed wherein the permeation rate is correlated with the linear combination of a solute's Permisor constant and solute/polymer equilibrium interaction constant. The model effectively predicts the behavior of the polymer and solutes studied. The implication of the observed behavior to container compatibility assessment is discussed.

## INTRODUCTION

An important facet of developing container materials for parenteral products [that is, those aqueous pharmaceutical products which are introduced to the patient by pathways other than the mouth (such as the muscle or vein)] involves evaluating container/solution interactions. Two processes of interest include the sorption of solutes out of solution by the container (binding) and the migration of container components into the solution (leaching). Both processes are thermodynamically and kinetically constrained, the former defining essentially the maximum absolute magnitude of the interaction and the latter defining the rate at which the interaction occurs. The rate is particularly important because a container/solution interaction impacts product utility only if the interaction occurs during the product's projected shelf life.

This research focuses on an evaluation of the migration properties of several low molecular weight model solutes through a polypropylene/polyolefin rubber blend. The polymer studied was chosen as representative of materials which most recently have shown some promise as parenteral product containers. The effect of temperature and solute identity on the observed migration rates was determined and predictive permeation models are proposed. The

impact of the observed permeation properties on container/solution compatibility is discussed.

## EXPERIMENTAL

### Materials

Polypropylene and polyolefin rubber raw materials were blended ( $\approx$  80/20 weight ratio) by the vendor and provided in pellet form. Pellets were extruded using a standard barrier screw extruder at a temperature of approximately 185°C, producing a uniform and homogenous film. Processing was modified so that two films, differing in terms of relative thickness, were produced. The thick film had an approximate mean thickness of 8 mil while the thin film had an approximate thickness of 0.8–1 mil.

Model solutes used (see Table I) were analytical grade reagents (98% purity or better). Reagents used to prepare the chromatographic mobile phases were HPLC grade. Distilled, deionized water was used for all preparations.

### Polymer–Water Interaction Coefficients

Polymer–water interaction constants for the model solutes and the raw materials comprising the film were determined by a shake flask approach. Raw materials were equilibrated with a solution containing several of the model solutes and the equilibrium concentration of the solutes in solution was determined by HPLC. Interaction constants for the film

**Table I Model Solutes and Their Properties**

Solute	Abbreviation	Interaction Constant (log $E_b$ )	Permicor Constant ( $P_c$ )
Dimethyl phthalate	DMP	-2.58	14.6
Diethyl phthalate	DEP	-1.92	16.6
Dipropyl phthalate	DPP	-0.91	18.6
Ethyl paraben <sup>a</sup>	ETPB	-3.03	20.1
Butyl paraben <sup>a</sup>	BUPB	-2.60	22.1
Butylbenzoic acid	BBH	-2.09	24.4
Aniline	AN	-3.50	16.4
4-Methylbenzyl alcohol	MBOH	-3.01	20.4
Acetic acid	AA	-4.05	15.5

<sup>a</sup> 4-Hydroxybenzoic acid, -ester.

were calculated as the weighted average of the interaction constant obtained for the raw materials.

### Permicor Constants

Permicor constants for the model solutes were calculated based on the additive structure approach of Salame.<sup>1-3</sup>

### Permeation Cells

Solute migration through the film was studied by the permeation cell approach.<sup>4,5</sup> The films were shaped into miniature bags by heat sealing common sides together and filled with a donor solution containing one or more of the model solutes. The sealed bag was placed in a receptor solution (contained within a glass vessel) which originally contained no solute. Test articles were stored at various temperatures and periodically an aliquot of the receptor solution was retrieved and analyzed for model solute concentration.

More specifically, donor solutions used included mixtures of (a) DMP, DEP, and DPP, (b) ETPB, BUPB, and BBH, and (c) AN and MBOH at an initial concentration of approximately 100 ppm in a solution which was 0.1% trifluoroacetic acid (TFA). Additionally, solutions containing 100 ppm acetic acid in phosphate buffers at pH 2.5 or 6 were also used as donors. In the case of the model solutes, the receptor solution was 0.1% TFA; for the acetic acid samples the receptors were the phosphate buffers at pH 2.5 and 6.

For the experiments using the thick film, the receptor solution volume ranged from 55 to 65 mL while the donor solution volume ranged from 6.5 to 7 mL. The thick bags weighed approximately 1 g

each and had a typical total surface area of 60 cm<sup>2</sup>. For the thin film experiments, the receptor solution volume was 55 mL and the donor volume was 10 mL. The thin bags weighed approximately 0.2 g and had a typical total surface area of 45 cm<sup>2</sup>.

Duplicate test articles for each solution type were stored at 25, 35, 45, 55, or 65°C and, for acetate in the thick film, 70°C for periods in excess of 100 days. Frequency of sampling and analysis of the receptor solutions was dictated by the observed permeation behavior. Control solutions, representing the donor solutions diluted by a factor of 10, were stored at all temperatures used to insure that migration measurements were not influenced by solute instability. Solute concentration at each interval was determined via HPLC against a standard which was prepared from the donor solution and stored refrigerated over the entire course of the experiment.

### Analysis

Sample analysis involved liquid chromatography. Acetic acid determinations were performed using the ion exclusion method described in Table II. Model solute concentration was determined by reversed phase HPLC; operating conditions were optimized to produce adequate performance for each solute mixture. In general, analytes were separated using a Supelcosil LC8-DB stationary phase and a methanol/water mobile phase containing a small amount of TFA. For the phthalate and paraben containing mixtures, the mobile phase was approximately 1/1 methanol/water and 0.1% TFA. For the aniline and MBOH, the mobile phase was 18/82 methanol/water with (generally) 0.025% TFA. Analytes were detected using UV at a wavelength of 220 nm; other operational variables such as flow rate, sample size,

**Table II Chromatographic Conditions, Ion Exclusion Method**


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Column: Dionex (Sunnyvale, CA) HPICE-AS1, part #035330
Mobile phase: 1 mN HCl
Mobile phase flow rate: 0.8 mL/min
Suppressor: Dionex Anion Micromembrane Suppressor AMMS-ICE, part #037107
Suppressor Regenerant: 5 mN tetrabutylammonium hydroxide
Regenerant flow rate: approximately 2.5 mL/min
Detection: suppressed conductivity (Waters Model 431 conductivity detector used)
Sample size: 20 or 50 $\mu$ L

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and detector sensitivities were modified, as necessary, to insure adequate solute resolution and detectability.

## RESULTS AND DISCUSSION

Properties of the model solutes used are summarized in Table I. The Permisor constant represents an empirically derived estimate of the solute's ability to migrate through the polymeric film. The equilibrium interaction constant ( $E_b$ ) represents the relative affinity of the polymer for the solute and defines the equilibrium distribution of the solute between the polymer and solution phases.  $E_b$  is defined as

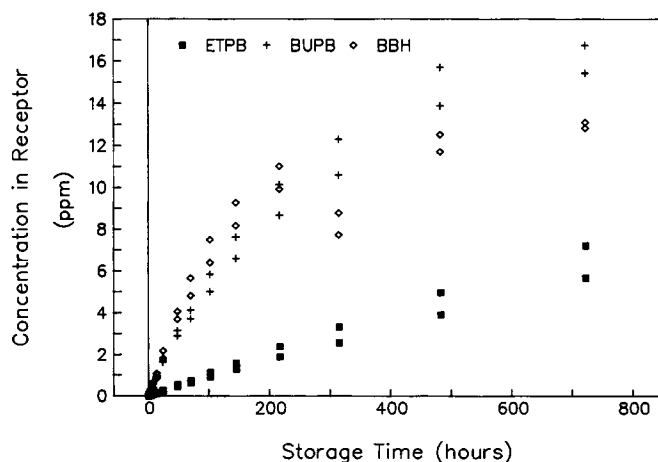
$$E_b = (m_p/W_p)/(m_s/V_s) \quad (1)$$

where  $m$  = mass of solute in either phase at equilibrium,  $W$  = weight of the polymer (g),  $V$  = volume

of solution (L), and  $p$  and  $s$  refer to the polymer and solution phases, respectively. Thus  $E_b$  is very similar to a polymer-solution partition coefficient. One notes from Table I that the model solutes used exhibit a wide range in terms of both permeation and interaction properties.

Typical migration profiles generated with both films are shown in Figures 1 and 2. The profiles exhibit four distinct regions; (1) the time lag, indicative of solute uptake into and migration through the film; (2) the steady rate region wherein the solute concentration in the receptor is linearly related to the storage time via the permeation rate; (3) the deflection region wherein the migration becomes thermodynamically constrained; and (4) the plateau region wherein migration stops as equilibrium is established between the donor and receptor phases.

The migration profiles are strongly influenced by the nature of the polymer and solute being considered. Ideally, the polymer/solute interaction should be minimal and thus the solute should be distributed primarily in the two solution phases. In practice, the fact that various migration curve plateau at different times and different solute concentrations indicates that solute absorption by the film is important and that the system being studied consists of three solute reservoirs: the two solutions and the polymer. The practical ramification of the polymer's binding of the solute is a shortening of the steady state portion of the migration profile which occurs in proportion to the magnitude of the polymer/solute binding. The effect of solute properties on both the permeation rate and the concentration (and time) at which equilibrium is established between the donor and receptor solutions is particularly apparent when the behavior of the phthalates is ex-



**Figure 1** Migration profiles for some model solutes through the thin film at 45°C.

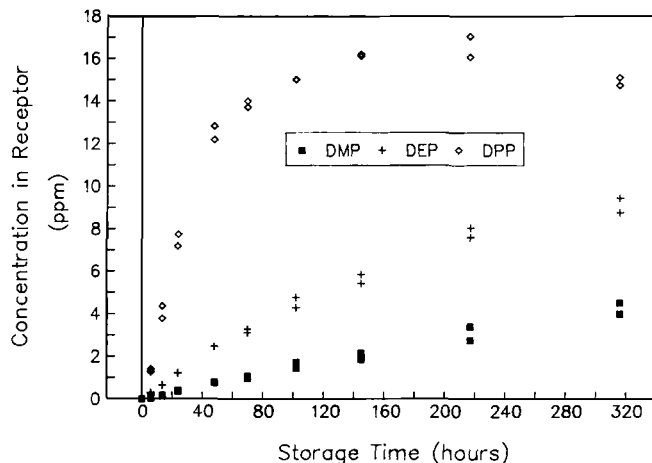


Figure 2 Migration profiles for some model solutes through the thin film at 25°C.

aminated. Considering the equilibrium effect, as the amount of solute bound by the film increases ( $\log E_b$  becomes less negative), the equilibrium concentration is lowered and the plateau concentration is achieved more rapidly. Thus, in Figure 2, the plateau for DPP is achieved within 150 h whereas both DMP and DEP continue to increase after more than 700 h.

Of the four portions of the migration profiles, the first two are most critical in terms of providing rate related information. The time lag  $T_L$  can be related to the solute's diffusion coefficient ( $D$ ) via the expression<sup>6</sup>

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

where  $\delta$  is the film thickness. Alternately, the permeation constant can be obtained as the slope of the steady state portion of the migration profile.

The accurate estimation of the time lag requires that the breakthrough region for the solute be effectively characterized. In most cases, the characterization of the time lag regions in this study is less than adequate since the sample size (and thus the number of testing intervals) was limited. However, for the phthalates, a diffusion coefficient of  $1 \times 10^{-5}$  mm<sup>2</sup>/h at 25°C can be estimated from the thick film data. This value for  $D$  is more or less consistent with diffusion coefficients reported for substituted phthalates in various polymers.<sup>5,7-9</sup>

Permeation rates, defined as the amount of solute going into the receptor solution during the steady state portion of the migration profile per unit time, could be obtained by regression analysis of the linear portion of those profiles. Permeation rates thus obtained were strongly influenced by the nature of the

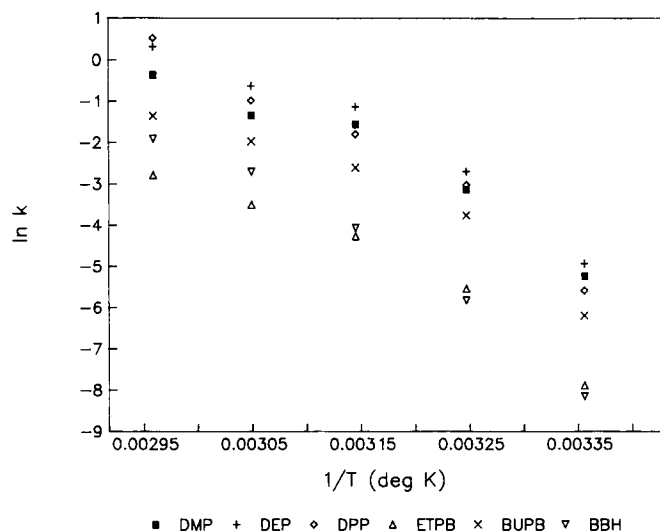
solute and the storage temperature. Permeation rates, corrected for film thickness and differing surface areas, are very similar in both the thick and the thin films (Table III).

As shown in Figures 3 and 4, the permeation rates could be linearly correlated with storage temperature via an Arrhenius model. Curve fit parameters for the Arrhenius models for each film and each solute are summarized in Table IV. For each solute and each film, the fit of the Arrhenius model to the rate  $\times$  temperature data is excellent; thus one can confidently extrapolate the existing database to obtain migration rates at other storage temperatures as long as the polymer does not undergo a significant physical transition at a temperature between the desired storage temperature and the temperature range of the model.

Table III Permeation Rates of Model Solutes through the Polypropylene/Kraton Blends

Solute	Permeation Rate at 65°C <sup>a</sup>	
	Thick Film	Thin Film
DMP	0.094	0.098
DEP	0.18	0.22
DPP	0.23	0.54
ETPB	0.0082	0.012
BUPB	0.035	0.045
BBH	0.020	0.059
AN	0.013	0.013
MBOH	0.22	0.19
AA		0.0042

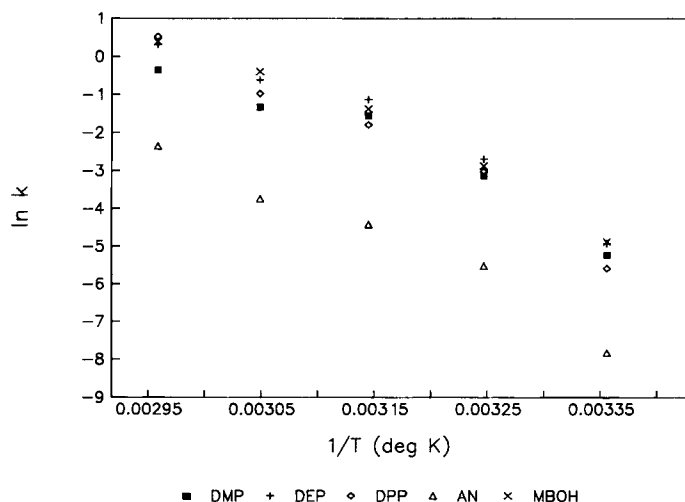
<sup>a</sup>  $\mu\text{mol}\cdot\text{mil}/\text{cm}^2\cdot\text{day}$ .



**Figure 3** Migration through the thick film; Arrhenius plots. Note that the units of  $k$  are  $\mu\text{mol}/\text{day}$ .

A striking feature of Figures 3 and 4 is the consistency of the rank ordering of solutes with respect to their permeation rates. The rank order of permeation rates is consistent across film thickness and storage temperature. This suggests that permeation rates should correlate with some solute property (or set of properties), thus providing the conceptual basis for a permeation rate model specifically applicable for the test films studied but in form applicable for migration of solutes through any film or membrane. In establishing the solute properties to consider, it is useful to examine the migration mechanism. Certainly the migration of a solute

through a polymer layer consists of three processes: solute uptake by the polymer, solute permeation through the polymer, and solute release from the polymer. It is reasonable to hypothesize that solute uptake and release by the polymer is affected by the polymer's affinity for the solute, as measured by a polymer-solution partition coefficient, an equilibrium interaction constant or an appropriate solvent-solution partition coefficient. Several authors have correlated permeation rates with solvent-solution partition coefficients<sup>10-13</sup>; the success of such correlations rests on the ability of the solvent chosen to mimic the polymer in terms of its ability to in-



**Figure 4** Migration through the thick film; additional Arrhenius plots. Note that the units of  $k$  are  $\mu\text{mol}/\text{day}$ .

**Table IV Arrhenius Parameters, Migration through the Test Films<sup>a</sup>**

Solute	Slope	Intercept	$r^2$
A. Thick Film			
DMP	-11,733 (1795)	34.65 (0.56)	0.934
DEP	-12,763 (1695)	38.40 (0.53)	0.950
DPP	-14,444 (1490)	43.34 (0.47)	0.969
ETPB	-12,429 (1694)	34.27 (0.53)	0.947
BUPB	-11,678 (1940)	33.62 (0.61)	0.924
BBH	-15,807 (1363)	45.28 (0.43)	0.978
AN	-12,859 (1381)	35.74 (0.44)	0.967
MBOH	-13,205 (1175)	39.78 (0.37)	0.977
B. Thin Film			
DMP	-9,851 (1118)	30.89 (0.35)	0.963
DEP	-9,390 (1474)	30.31 (0.46)	0.931
DPP	-10,342 (3154)	34.32 (0.99)	0.782
ETPB	-12,733 (783)	37.11 (0.25)	0.989
BUPB	-11,668 (874)	35.22 (0.27)	0.983
BBH	-11,214 (714)	34.20 (0.22)	0.988
AN	-13,572 (512)	39.44 (0.16)	0.996
MBOH	-11,521 (1192)	36.30 (0.38)	0.969
AA	-10,021 (284)	28.45 (0.06)	0.999

Numbers in ( ) are the standard errors.

teract with the solute of interest. Certainly the polymer-specific equilibrium interaction constant is a more direct measure of a solute's attraction for the polymer phase than is the solvent-solution partition coefficient.

The migration of the solute through the polymer is also influenced by the nature of the polymer and the solute. The permeation rates of solutes through polymers have been correlated with empirically determined Permisor constants, which attempt to correlate structural group effects with observed permeation behavior.<sup>1-3</sup>

It thus seems reasonable that the permeation rate of solutes through a polymeric layer which is not itself the source of the solutes should be modeled by a combination of the solute's equilibrium binding ( $E_b$ ) and Permisor ( $P_c$ ) constants. Such a relationship takes the form:

$$\log k = a \log P_c + b \log E_b + c \quad (3)$$

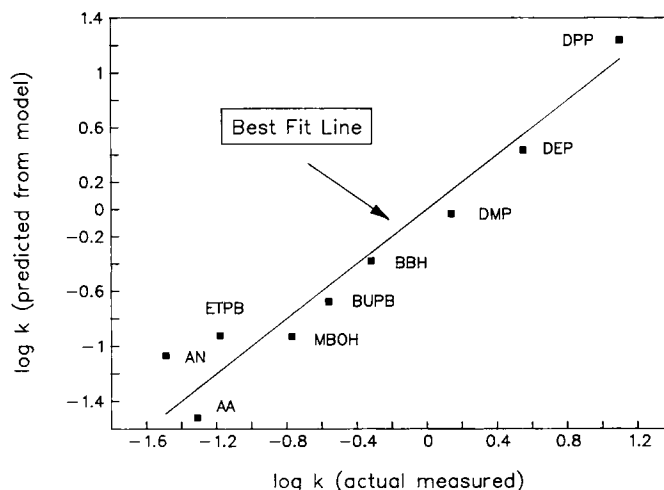
Permisor constants for the model solutes were determined from the solute's chemical structure and additive data provided in Ref. 1.  $E_b$  was obtained from existing data generated for the components of the test polymer. Bimodal linear correlations between the logarithm of the permeation rates and the logarithms of the solute's  $E_b$  and  $P_c$  constants are summarized in Table V. For the thin film, excellent correlations were obtained; for the thick film, the accuracy of the correlations were lessened, especially at the lower storage temperatures, by the relative uncertainty of the individual permeation rates.

Figures 5 and 6 demonstrate the accuracy of the Permisor-interaction constant models for predicting permeation rates. In these figures, predicted permeation rates are graphically compared to the measured rates for the model solutes. Ideally, an exact

**Table V Permisor-Binding Constant Permeation Rate Models**

Temp (°C)	Slope Permisor, $a$	Slope Binding Constant, $b$	Intercept, $c$	$r^2$
A. Thin Film				
25	-0.0851 (0.0199)	1.135 (0.071)	2.87 (0.18)	0.977
35	-0.0933 (0.0274)	1.016 (0.097)	3.50 (0.24)	0.948
45	-0.0832 (0.0288)	0.961 (0.101)	3.66 (0.26)	0.937
55	-0.0779 (0.0189)	0.810 (0.067)	3.46 (0.17)	0.961
65	-0.0537 (0.0154)	0.649 (0.055)	3.14 (0.14)	0.965
B. Thick Film				
25	-0.0772 (0.029)	0.659 (0.117)	0.37 (0.25)	0.881
35	-0.0786 (0.029)	0.696 (0.117)	1.46 (0.25)	0.890
45	-0.0936 (0.031)	0.731 (0.125)	2.42 (0.27)	0.890
55	-0.0680 (0.026)	0.720 (0.103)	2.19 (0.22)	0.914
65	-0.0810 (0.023)	0.605 (0.091)	2.51 (0.19)	0.914

Numbers in ( ) are the standard errors.



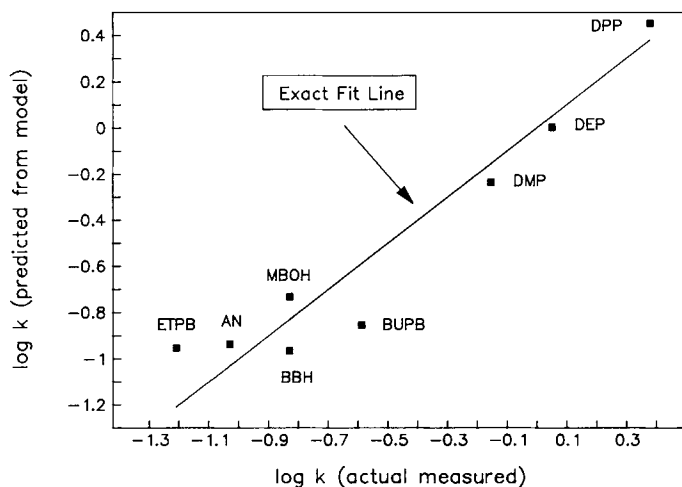
**Figure 5** Predicted versus measured permeation rates; thin film, 45°C.

fit would provide curve fit parameters including a unit slope, a zero intercept, and a unit correlation coefficient. For the thin film model at 45°, the curve fit parameters are (with standard errors in parentheses): slope, 0.94 (0.09), intercept, -0.03 (0.23), and  $r^2$ , 0.937. Similar behavior is exhibited by the models generated for the thin film at the other temperatures studied. For the thick film model at 65°C, the curve fit parameters are: slope, 0.92 (0.11), intercept, -0.04 (0.17), and  $r^2$ , 0.914. Thus, within the precision of the model, the predicted and actual permeation rates are equivalent.

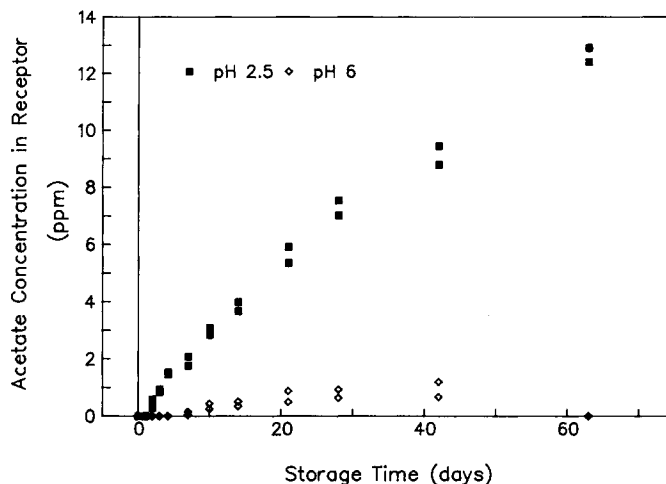
In general, then, the bimodal Permicer/interaction constant model can be used to predict the migration rate of any solute through any polymeric film provided: (a) the coefficients of the model have been determined for the polymer of interest, (b) the

solute's Permicer can be calculated, and (c) the interaction constant can be determined. Step b is a straightforward calculation based on the solute's chemical structure. The interaction constant can be obtained either through direct measurement or indirectly from the solute's solvent/solvent partition coefficients and a solvent-based polymer interaction model (for example, Refs. 14-16). With these data in hand, the permeation rate at a particular temperature can be obtained. The permeation behavior at other temperatures can be extrapolated using the Arrhenius relationships described herein (assuming no significant change in the polymer's physical structure occurs between the temperature of interest and the temperature range used to generate the Arrhenius model).

For an ionic solute, solute speciation, affected by



**Figure 6** Predicted versus measured permeation rates; thick film, 65°C.



**Figure 7** Effect of solution pH on the migration of acetic acid through the thin film, 65°C. Note that the pH of both the donor and receptor solutions was the value indicated in this figure.

solution phase pH, has a marked effect on permeation behavior. In this study, the effect of pH on permeation was assessed by examining the behavior of acetic acid at pH 2.5 and 6.0. With a  $pK_a$  of 4.75, acetic acid is undissociated at pH 2.5 and nearly completely dissociated at pH 6. Although the effect of speciation on the actual migration process is difficult to assess, the effect of speciation on the ability of the polymer to take up the solute (e.g.,  $E_b$ ) is well established via the following relationship<sup>17</sup>:

$$E_{b,i} = E_{b,u} / (1 + 10^{pH-pK_a}) \quad (4)$$

where  $E_{b,i}$  is the interaction constant at the pH of interest and  $E_{b,u}$  is the interaction constant for the completely unionized form of the solute.  $E_b$  values for acetic acid at pH 2.5 and 6 can thus be substituted into eq. (3) to determine what the predicted effect of pH on acetic acid permeation rate would be. For the thin film at 65°C, the resulting calculated rates are 0.48 and 0.071  $\mu\text{mol}/\text{day}$  at pH 2.5 and 6, respectively. Thus one predicts that the permeation rate at pH 2.5 is roughly seven times faster than that at pH 6. The observed behavior of acetate at these pH values is shown in Figure 7; steady state permeation rates at pH 2.5 and 6 are determined to be 0.26 and 0.028, respectively, or permeation occurs roughly nine times faster at the lower pH. The similarity in the predicted versus observed behavior confirms that for acetic acid the pH effect on permeation is mechanistically dominated by the effect that pH has on the uptake of the solute by the polymer.

To illustrate one potential container compatibility implication of the data summarized herein, consider the following situation. In this example, the container of interest consists of two layers: an outer layer of an unspecified material that has a total available pool of a potential leachable of 10  $\mu\text{g}$  (evenly distributed throughout the material) and a solution contact layer of the polypropylene blend studied herein. The surface area of the polypropylene blend layer is 160  $\text{cm}^2$  and the layer is 2 mil thick. To simplify the example somewhat, further assume that the outer layer is such that the leachable preferentially partitions into the solution phase; that is, eventually the entire available pool will distribute itself into the contained solution. The point of interest in this analysis is how long will it take for the leachable to completely accumulate in the solution phase. Of course, such an analysis depends on the thermal stress the container is subjected to and the nature of the solute. In order to illustrate extremes in behavior, the analysis will consider the behavior of the leachables as if it were ETPB or DPP (the slowest and fastest migrating model solutes studied) and reasonable storage temperature extremes including 25°C (ambient storage) and 121°C (autoclave conditions). Using the thin film as the permeation model, one calculates permeation rates for DPP and ETPB to be as follows:

Solute	$k$ ( $\mu\text{mol mil}/\text{day cm}^2$ )	
	25°C	121°C
ETPB	$8.26 \times 10^{-5}$	2.72
DPP	$1.54 \times 10^{-2}$	71.8



For the container configuration as defined, one calculates that the time required for complete migration of the DPP pool into solution would be 8.1 days at 25°C and 2.5 min at 121°C. Similarly, for ETPB, the maximal accumulation time would be 1510 days at 25°C and 1.1 h at 121°C. For a steam sterilized product with a 2-year ambient temperature shelf life, one concludes that both DPP and ETPB model leachables would accumulate to their maximal levels over the useful life of the product. Thus the accumulation in this example is not kinetically constrained and any potential impact of the leachable's presence in solution has to be judged in terms of the accumulation of the total pool in the solution.

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