

Utilization of Extraction Profiles to Estimate the Accumulation of Extractables from Polymeric Materials

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ABSTRACT: A method is described whereby an extraction profile is used to determine solute/polymer interaction properties (total pool and partition coefficient) which can be used to estimate the level to which an extractable component of the polymer can accumulate in solution. The extraction profile is obtained by measuring the equilibrium solution concentration of the extractable for varying amounts of polymer extracted. Either the interaction properties obtained from these data or the profiles themselves are used to estimate the maximal equilibrium solution accumulation of the extractable. The method is used to estimate the levels to which several extractables from a rubber material used in the pharmaceutical industry will accumulate in solution. The measured properties produce estimated accumulations which match experimental observations well. © 1997 John Wiley & Sons, Inc. *J Appl Polym Sci* **63**: 843–848, 1997

Key words: polymer extractables; accumulation potential; container/solution interactions

INTRODUCTION

The use of polymeric materials to store and deliver liquid products in the food and pharmaceutical industries may be limited by the migration of an extractable from the polymer into solution. The maximal solution accumulation of an extractable occurs when equilibrium is established between the solution and polymer and is controlled by one or more of the following factors^{1–4}:

1. the total amount of extractable present in the polymer (the total available pool),
2. the solubility of the extractable in either phase, or
3. the equilibrium partitioning of the extractable between the polymer and solution phases.

This paper discusses the utilization of an ex-

traction profile to assess plastic/solution compatibility by establishing which of these processes are operating in a specific application. For partition-mediated applications, the extraction profile is used to generate solute/polymer interaction properties which are employed to estimate solution accumulation levels for a specific polymer's extractables.

MATERIALS AND METHODS

Materials

The material is a synthetic polyisoprene rubber, similar to materials used in several solution-contact pharmaceutical applications (stoppers, device components, etc). Extractables examined included aniline (AN, CAS RN 62-53-3), diphenylguanidine (DPG, CAS RN 102-06-7), dibenzylamine (DBA, CAS RN 103-49-1), and triisopropanolamine (TPA, CAS RN 122-20-3). Standard

materials of these compounds were obtained from commercial sources (Aldrich Chemical, Milwaukee, WI, or Pflatz and Bauer, Waterbury, CT) and had purities of 95% or greater. Other chemicals used were reagent or analytical grade, as appropriate. The water used was from a Barnstead NANOpure II water polishing system.

Generation of the Extraction Profile

Portions of the rubber material (small [≈ 0.12 g] disks) were contacted with 100 mL of water or 0.9% NaCl in closed PyrexTM glass bottles. Material loadings studied varied from approximately 3.7 to 267 g/L, encompassing a range including potential product applications at the low end and exaggerated conditions at the high end. Duplicate test articles were prepared at each material loading and the test articles were extracted by autoclaving ($\approx 121^\circ\text{C}$) for 1 h. Previous experimentation had confirmed that equilibrium was established within this time frame.

In independent experiments, 2 or 20 g of the rubber was extracted in 0.1 L water or 0.9% NaCl. The results of these experiments were compared to estimated accumulations to illustrate the utility of the proposed methods.

Analytical

Solution concentrations of the extractables were determined by reversed-phase high pressure liquid chromatography. For AN, DPG, and DBA, separation was accomplished on an Alltech Adsorbosphere C18 HS column (100×4.6 mm, $3\text{-}\mu\text{m}$ particles) with a mobile phase of 30/70 acetonitrile—0.025M ammonium acetate. For TPA, the separation involved an Alltech Spherisorb CN column (150×4.6 mm, $5\text{-}\mu\text{m}$ particles) and a mobile phase of 30/70 acetonitrile—0.01M ammonium phosphate (pH 5.4). For both procedures, mobile phase flow rate was 1 mL/min and analyte detection was by ultraviolet (UV) absorption at a wavelength of 215 nm.

RESULTS AND DISCUSSION

Theoretical

The basis of this analysis is the extraction profile, the plot of the extractable's equilibrium solution concentration versus the material loading (g of

material extracted per L of extracting solution). This plot differs somewhat from a classical isotherm in that the dependent variable is the material loading as opposed to the concentration of the extractable remaining in the material at equilibrium. This difference is necessary since the initial amount of the extractable in the material (its total available pool, T_p) is not independently known.

In general, the slope of the extraction profile can be divided into three categories, each reflective of which mechanism controls the extractable's accumulation in solution. A slope of 1 indicates a process in which neither the solution nor the material exerts a physicochemical influence on the extractable's solution accumulation. In this case, the T_p of the extractable accumulates in solution at every material loading. A slope of 0 indicates a solubility-constrained situation wherein the material has no practical affinity for the extractable and T_p is larger than the extractable's intrinsic solution solubility. Thus the extractable will accumulate to its solubility limit at all sample loadings.

Slopes intermediate between 0 and 1 indicate partition-mediated interactions wherein the material and solution phases both have an intrinsic affinity for the extractable. The slope of the plot is a reflection of these relative affinities.

As an extractable's solution solubility is approached, the slope of both the total pool-mediated and partition-mediated extraction profiles will change and approach 0.

For a partition-mediated process, the utilization of the extraction profile is straightforward. Once the profile has been generated, the least-squares regression equation can be used to estimate the expected accumulation of the extractable for any material loading within the range examined. Specifically, the equation of the extraction profile takes the form

$$C_s = a(S_L) + b \quad (1)$$

where C_s is the equilibrium concentration of the extractable in solution and S_L is the material loading of the extractable. Once the regression constants a and b are obtained, eq. (1) can be used to estimate C_s for any value of S_L .

Alternatively, one can use the loading data to generate directly the physical parameters of the polymer/solution system, including the extractable's T_p and partition coefficient (P_e). For an equilibrium where the amount of extractable in

solution is X_2 , the amount of extractable originally in the material is X_1 , the solution volume is V , and the material mass is m , P_e becomes:

$$P_e = (X_2/V)/[(X_1 - X_2)/m] \quad (2)$$

Upon rearrangement and the observation that X_2/V equals the extractant's concentration in solution at equilibrium, C_s , this equation becomes

$$P_e = mC_s/(X_1 - X_2) \quad (3)$$

Equation (3) is valid for two different sample loadings; thus

$$P_{e,1} = m_1C_{s,1}/(X_{11} - X_{21}) \quad (4a)$$

$$P_{e,2} = m_2C_{s,2}/(X_{12} - X_{22}) \quad (4b)$$

Now the partition coefficient is a constant and thus $P_{e,1} = P_{e,2}$ and the above expressions are combined to produce

$$m_1C_{s,1}/(X_{11} - X_{21}) = m_2C_{s,2}/(X_{12} - X_{22}) \quad (5)$$

Rearrangement of the above expression produces

$$\begin{aligned} m_1C_{s,1}X_{22} - m_2C_{s,2}X_{21} \\ = m_1C_{s,1}X_{12} - m_2C_{s,2}X_{11} \end{aligned} \quad (6)$$

Now the weight fraction of the extractable in the plastic is constant and thus

$$X_{11}/m_1 = X_{12}/m_2 \quad (7)$$

or:

$$X_{12} = (m_2/m_1)X_{11} \quad (8)$$

Substitution of this expression into eq. (6) plus the observation that $X_{22} = C_{s,2}V_2$, $X_{21} = C_{s,1}V_1$, and V is constant ($V_1 = V_2 = V$), produces

$$\begin{aligned} X_{11} \\ = (C_{s,1})(C_{s,2})V(m_1 - m_2)/[m_2(C_{s,1} - C_{s,2})] \end{aligned} \quad (9)$$

Since all the variables in equation 9 are known from the loading profile, X_{11} , which is equal to the extractable's T_p , can be calculated. Additionally, the partition coefficient P_e can be calculated from the value of X_{11} via eq. (4a).

Armed with T_p and P_e , the extractable's equi-

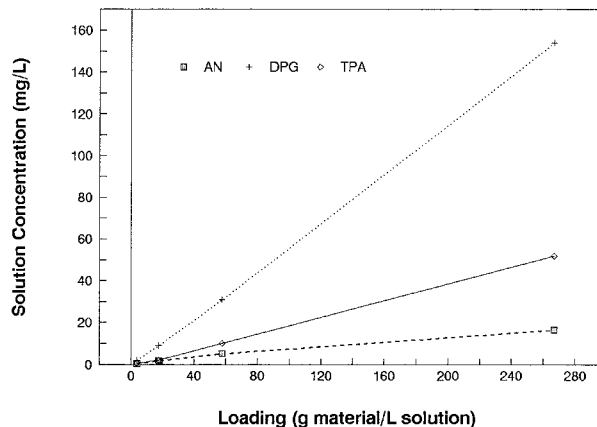


Figure 1 Extraction profile, AN, DPG, and TPA. For these three analytes, the plot of equilibrium solution concentration versus material loading is linear, indicating that the accumulation of these compounds is partition-mediated over the material loading range studied.

librium solution concentration for any solution volume with any material loading can be estimated via the expression

$$C_s = (P_e \times T_p \times m)/[m + (P_e \times V)] \quad (10)$$

It is observed from eq. (10) that the relationship between C_s and the extraction system's mass-to-volume ratio (m/V) is not unilaterally linear. However, when the product of P_e and V is large with respect to m , eq. (10) simplifies to a linear relationship:

$$C_s = T_p \times (m/V)$$

This condition is met when the extraction volume is large, the extracted material's mass is small, and/or the extractable is relatively polar (large P_e). In this study, AN, TPA, and DPG meet the latter criterion.

Alternatively, when the P_e and V product is small with respect to m , C_s is no longer impacted by either m or V and eq. (10) becomes

$$C_s = P_e \times T_p$$

Such a scenario, which essentially reflects a saturated extracting solution, occurs when the extraction volume is small, the mass of extracted material is large, and/or the extractable is highly non-polar (small P_e). In this study, DBA exhibits this latter property.

Experimental Results

Extraction profiles for the four target extractables are shown in Figures 1 and 2. For AN, DPG, and

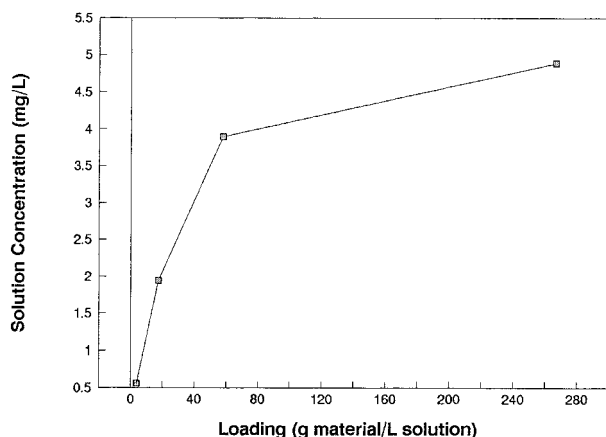


Figure 2 Extraction profile, DBA. At the higher material loadings (greater than 60 g/L) the solution concentration of this extractable becomes solubility-constrained. Thus at higher material loadings, the linearity of the profile diminishes and models developed in this study would tend to overestimate this compound's accumulation.

TPA, the extraction profile is a straight line with a slope between 0 and 1. The accumulation of these extractables is therefore partition-mediated. Alternatively, the extraction profile for DBA is roughly linear at plastic loadings of 50 g/L or lower while above this level the solubility controlled solution level is approached (slope asymptotically approaches 0). Curve-fit parameters from the linear regression least-squares model for each species are given in Table I. Extraction models can be generated by either forcing the regression model through the origin or allowing the

Table II System Properties of the Target Extractables

Compound	T_p ($\mu\text{g/g}$)	P_e	$\log P_{o/w}$ ^a
AN	11.07	2402	0.90
DPG	53.10	6181	-0.05
DBA	16.32	406	2.82
TPA	19.03	5327	-0.82

^a $\log P_{o/w}$ from Hansch and Leo.⁶

model to take on the intercept suggested by the data. The former approach provides a more accurate analysis at lower material loadings whereas both approaches provide similar data at higher material loadings.

Alternatively, the pairs of data points in the extraction profile can be used to calculate each extractable's T_p and P_e . Resultant data are summarized in Table II. The magnitude of T_p obtained in this manner are similar to those data obtained from sequential, exhaustive extraction of the rubber. The trend in the partition coefficients (P_e) roughly match the relative lipophilicity of the extractables, with the least lipophilic (as reflected in the compound's octanol/water partition coefficient, $\log P_{o/w}$) extractable (TPA) exhibiting the smallest P and the more lipophilic extractables (AN and DBA) exhibiting much higher P values.

Utilization of the Methods to Estimate Accumulation Levels

To illustrate these two approaches, the anticipated level to which the extractables will accumu-

Table I Curve Fit Parameters, Least-Squares Regression

Parameter	AN	DPG	DBA ^a	TPA
A. Curves Forced through the Origin, $C_s = a(S_L)$.				
Slope	0.0634 (0.004)	0.575 (0.006)	0.0714 (0.009)	0.192 (0.005)
r^2	0.982	1.00	0.889	0.997
B. Curves with a Calculated Intercept, $C_s = a(S_L) + b$.				
Slope	0.0597 (0.004)	0.581 (0.007)	0.0587 (0.011)	0.197 (0.004)
Intercept	0.82 (0.79)	-1.23 (1.31)	0.59 (0.42)	-0.89 (0.79)
r^2	0.992	1.00	0.968	0.999

Standard error shown in parentheses.

^a DBA data calculated using loadings of 60 g/L or less.

Table III Estimated Versus Observed Extractables Accumulation

Compound	Concentration in Solution (mg/L)			
	Regression, Forced Intercept	Predicted Regression, Calculated Intercept	T_p and P_e	Measured
A) 20 g/L Loading				
AN	1.27	2.01	2.04	1.64
DPG	11.50	10.39	10.29	11.76
DBA	1.43	1.76	2.19	2.12
TPA	3.84	3.05	3.67	3.73
B) 200 g/L Loading				
AN	12.7	12.8	12.1	15.6
DPG	115	115	80.2	122
DBA	14.5	12.3	5.51	7.37
TPA	38.4	38.4	27.2	37.3

late in 0.1 L of solution, given material loadings of 20 and 200 g/L, was determined. To calculate C_s , one either inputs these loadings into the linear regression models for each of the compounds or inputs known values of P_e , X_1 (or T_p), m , and V into eq. (10).

Table III compares the results of the three calculation methods with the measured accumulations of the extractables. For the 20-g/L loading, the measured concentrations agree well with the accumulations estimated from the extraction profile (both regression models) and eq. (10). The minor differences between the levels estimated by the two regression models reflect the influence of the intercept at the lower material loadings.

The results for the 200-g/L loading are also fairly good for all three approaches and AN, DPG, and TPA. The difference between observed and expected behavior for AN may be due to a T_p which varies somewhat between portions of the material evaluated. This variation arises since AN is not a rubber component but is produced from the rubber during the extraction. Thus its T_p will vary somewhat between experiments. The tendency of the linear regression models to overestimate the accumulation of DBA again reflects the nonlinear, solubility-limited accumulation of this species at higher material loadings.

Finally, the difference between the P_e estimated concentration for TPA and its measured value at the 200-g/L loading highlights a practical difficulty of calculating large values of P_e . In

such cases the precision of the analytical method strongly impacts the determination of X_{11} (and eventually P_e) via eq. (9) because small variations in the difference $C_{s,1} - C_{s,2}$ can have a large impact on P_e . The analytical sensitivity for TPA, which has only a weak UV absorbance, is poor ($\pm 5\%$ RSD) and thus the analytical variation-induced uncertainty in P_e is large.

CONCLUSION

Extraction profiles provide an accurate and effective means of estimating the total amount of an extractable that exists in a polymer and the extractable's solution/material partition coefficient. This technique, involving a single preparation-and-analysis sequence of multiple samples, is time-efficient when compared with other methods for obtaining such data, including shake-flask or sequential-extraction procedures.⁵ The method provides the information necessary to estimate the equilibrium level to which extractables will accumulate in solution as a function of the amount of material contacted by the solution. While such information facilitates a preliminary evaluation of the material's impact on product safety and/or efficacy, further evaluation of the product system is necessary in order to establish product/material compatibility unilaterally. This further evaluation could include the chemical analysis of actual or simulated product units to determine the actual accumulation levels of the ex-

tractables, and a consideration of the toxicological potential and chemical reactivity of the extractables at the levels indicated by both the proposed numerical procedure and actual product analysis. Such an evaluation would consider indicated product-use conditions to establish specifically the acute and chronic dose of the extractables which the product's user might experience or to define the conditions under which a specific chemical reaction between an extractable and product component could occur.

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