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Model for estimating the accumulation of solutes leaching from polymeric containers into parenteral solutions

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Summary

A model allowing for the prediction of the thermodynamically constrained accumulation of leachables migrating from polymeric containers has been developed. The model predicts accumulation based on three accumulation-limiting mechanisms: total available pool, solute solubility and solute partitioning. Equations relating a solute's solvent-water partition coefficients ($P_{\text{o-w}}$ and $P_{\text{h-w}}$) and its aqueous solubility and partitioning properties have been developed. Thus, one can predict leachable accumulations from the physical dimensions of the system being studied (container weight and solution volume) and from the solute's partition coefficients. The maximal accumulation of the leachable in solution will be the lowest value predicted via the three accumulation-limiting mechanisms. The model has been successfully applied to the migration of 2-ethylhexanoic acid out of a styrene-butadiene-styrene block co-polymer and accurately predicts the accumulation behavior of this species as a function of solution pH.

Introduction

A container's usefulness in pharmaceutical applications may be limited by (a) the ability of a chemical component of the container material to migrate out of the material and into the solution it contains (leaching), or (b) the ability of the material to sorb solutes (including active ingredients) from the solution it contains (binding). Of concern in evaluating the practical utility of various solute/solution/container material combinations is that the magnitude of the solute's interaction, regardless of migration direction or the controlling mechanism, be within acceptable limits. For leaching, the maximum permissible amount of migration is determined either by the migrant's toxicology (Autian, 1973; Corley et al., 1977; Petrick et al., 1977; Pollack et al., 1979) or, less commonly, other product use constraints (e.g., solution clarity, color, etc.).

Characterizing a particular solvent/solute/container system with respect to its solute migration properties is a necessary step in container development and compatibility assessments. With respect to leaching, three areas are relevant:

(i) identification of all pertinent leachables (the total leachable profile) and their concentration in the container material (the total available pool);

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(ii) assessment of the accumulation of these leachables in the projected product configuration; and

(iii) determination of the toxicological impact of the leachable's accumulation.

This manuscript will focus on the second of these areas, the assessment of the magnitude to which a leachable substance will accumulate in a contained solution. Although the overall compatibility assessment relies heavily on the accurate generation of the leachable profile, the mechanics of generating a complete profile is beyond the scope of this discussion. In general, however, leachables can be identified via experiments involving a sequential extraction of the container material. This extraction sequence may be as simple as a single extraction with water or it may be aggressive enough to exhaustively and completely remove the solute of interest from the polymer. The resulting extracts can be characterized by several chromatographic and spectroscopic methodologies as proposed in the pharmaceutical literature (Ulsaker and Hoem, 1978; Arbin and Ostelius, 1980; Arbin et al., 1986; Snell, 1989; Kim et al., 1990; Kim-Kang et al., 1990). Total available pools of leachables can be determined by exhaustive extraction of the material followed by rigorous analysis of the extracts. Similarly, techniques for the assessment of toxicological impact will not be considered herein.

Several mechanisms can be envisioned for determining the levels to which leachable substances will accumulate in solution for a particular product configuration. The most direct approach is the measurement of leachable levels in actual product samples subjected to more or less common use conditions (for example, as part of a formal product stability study). While such an approach is attractive from the perspective of providing a reference data base, it can typically suffer from practical constraints. In addition to the logistical problems associated with even a well-designed stability study (analytical method development and validation in a myriad number of matrices, sample preparation and actual sample analysis to name a few), such an approach relegates the investigation to a reactive posture. Potential problems are encountered and can be assessed or addressed only as the study unfolds. Alternatively, a theoretically derived model, relating the interaction properties of solutes with the container material to some fundamental solute property, can be used to estimate the magnitude of the container/solution interaction. This model would be based on a rigorous scientific evaluation of the processes influencing the container/solution interaction and would provide a mathematical expression allowing for the estimation of the levels to which solutes will accumulate in solutions contacted by a source material. Such a model offers flexibility in application (particularly in terms of a forecasting tool) which is not readily obtainable from accumulation (stability) testing. The application of such an approach allows for a proactive assessment of the container/solution interaction and thus represents a more effective means of evaluating the applicability of a new container material.

In this article, an interaction model for a particular polymer is proposed and developed. The model is used to predict the accumulation of a leachable solute in solutions of varying pH and the results are reconciled with observed accumulation behavior.

Materials and Methods

Materials

The polymer used was Kraton G-1652, a styrene-butadiene-styrene block co-polymer (Shell Chemical Co., Belpre, OH) which is a common component of polymeric containers used in the pharmaceutical and food industries. The leachable solute studied was 2-ethylhexanoic acid (EHA), which is a processing additive for this formulation. Standards of this material were 99 + % pure (Aldrich Chemical Co, St. Louis, MO). Reagents used as model solutes or in solution preparations were reagent grade. All solvents used to prepare the HPLC mobile phases were HPLC grade. Distilled and deionized water was used throughout this study.

Measurement of partition coefficients for the model solutes

Octanol-water ($P_{\text{o-w}}$) and hexane-water ($P_{\text{h-w}}$) partition coefficients were determined for the model solutes and EHA. $P_{\text{o-w}}$ coefficients were determined via HPLC solvent scouting (Garst and Wilson, 1984; Braumann, 1986; Jenke et al., 1990) or were obtained from the chemical literature (Leo et al., 1971). $P_{\text{h-w}}$ coefficients were determined by shake flask experiments wherein the equilibrium distribution of the solute between hexane and water mixtures was determined. In the shake flask experiments, the aqueous phase was acidified to ensure that the solute of interest was in its non-ionized form.

Measurement of the equilibrium interaction constant (E_b)

E_{b} was determined via shake flask methods wherein portions of the test polymer were equilibrated with an acidified aqueous phase containing a known initial amount of the solute of interest. The equilibrium concentration of the solute in the aqueous phase was measured and used to calculate E_{b}.

Identification of EHA in the polymer

5 g of the polymer was contacted with 40 ml of water adjusted to pH 10.7 (with NaOH) for up to 13 days at 70 ° C. 10 ml of these basic leachate solutions were made acidic (pH < 2) by dropwise addition of 0.1 N HCl and then extracted three times with 2-ml aliquots of methylene chloride. Combined organic layers were dried with anhydrous sodium sulfate and the solvent removed with a stream of dry nitrogen. The resulting residues were dissolved in small volumes of methylene chloride for analysis by gas chromatography/mass spectrometry (GC/MS) as described in Table 1. The identification of EHA in the resulting extract was confirmed by the analysis of a standard reference sample of this compound under the same analytical conditions.

TABLE 1

Parameters for GC/MS method

Column
Hewlett Packard HP-1 (cross-linked methylsilicone), 12 m × 0.25 mm i.d. × 0.33 μm (film thickness) fused silica capillary

Detector
Hewlett Packard Model 5970 MSD

Chromatographic conditions
Initial Temperature = 40 ° C
Initial hold time = 1 min
Program rate = 5 ° C/min
Final temperature = 300 ° C
Final hold = 10 min
Injector temperature = 250 ° C
Injection volume = 2 μl (splitless injection used)
Carrier gas = helium
Carrier gas flow rate = 1.5 ml/min

Detector conditions
High mass = 650 amu
Low mass = 35 amu
Electron energy = 70 eV
Interface temperature = 310 ° C
Source temperature = 200 ° C
Emission current = 220 μA
Mass resolution = unit

Determination of the total available pool of EHA in the polymer

1.1-g portions of the polymer were placed into Pyrex bottles and contacted with 15 ml of a 0.1% NaCl, 10 mM phosphate buffer at pH 6.0. The closed test article was autoclaved at 121° C for 45 min and after cooling, the extracting solution was removed and analyzed. The test article was rinsed with water; contacted with a second fresh aliquot of buffer and re-autoclaved. This process was then repeated a third time.

Measurement of leachable EHA accumulation

1.1-g portions of the polymer were placed into Pyrex bottles and contacted with 15 ml of 0.1% NaCl, 10 mM phosphate buffer at pH 2.30, 4.65 and 6.00. The closed test articles were autoclaved at 121° C for 45 min; after the initial autoclave cycle, several test articles were subjected to a second and third autoclave exposure.

Analysis (HPLC)

EHA concentration in all appropriate solutions was determined by HPLC. Separation was accomplished on an Alltech (Deerfield, IL) Adsorbosphere C18 column (150×4.6 mm, 5 μm particles) with a mobile phase of 50:50 acetonitrile/0.04 M phosphoric acid. Mobile phase flow rate was 1 ml/min, the analyte was detected by UV at 220 nm and the sample size was 0.2 ml.

Model solutes were also quantitated by HPLC. Separation was accomplished on a Supelcosil LC8-DB column (50×4.6 mm, 5 μm particles) with various binary methanol/water mobile phases. Analyte detection was by UV at 220 nm and mobile phase flow rate and sample size were modified for each solute mixture to maximize sensitivity and specificity.

Results and Discussion

The interaction and accumulation models

To generate a theoretically sound container/solution interaction model, the mechanisms by which the interaction can occur must be evaluated. 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; Cruz et al., 1990):

(1) The initial amount of migrant present (the total available pool);
(2) the chemical stability of the migrant in either phase;
(3) the diffusion of the migrant through the container;
(4) the solubility of the migrant in either the container or solution phase;
(5) the equilibrium partitioning of the migrant between the container and the solution.

One recognizes that the kinetic aspects of migration (diffusion and degradation) serve to minimize the accumulation of a particular solute in solution and that it is the thermodynamic scenarios which define the maximal, worst-case accumulation. It is obvious that the total available pool (P_T) represents the absolute maximal accumulation, since one cannot mobilize more of a solute than is originally in the polymer. The pool limited accumulation (A_{pool}) of a leachable can be calculated from the solution volume (V_s), container weight (W_c) and P_T as follows:

$$A_{pool} = (P_T \times W_c)/V_s \qquad (1)$$

Similarly, if the solubility of the leachable in the solution phase is less than its total available pool, then its accumulation in solution is solubility limited. The solubility (S) of a solute can be estimated from its octanol-water partition coefficient ($P_{o\text{-}w}$) and melting point (MP) via an empirical relationship (Yalkowsky and Valvani, 1980):

$$\log S = -1.0(\log P_{o\text{-}w}) - 0.01(\mathrm{MP}) + 1.05 \qquad (2)$$

For solutes which exist as a liquid at ambient temperature (such as ethylhexanoic acid), MP is set at 25 ° C (Yalkowsky and Valvani, 1980). The solubility limited accumulation (A_s) of a leachable is the product of its molar solubility (S) and its molecular weight (MW):

$$A_s = S \times \mathrm{MW} \qquad (3)$$

Finally, the relative affinity of the solute for the polymer and solution phases (its partitioning behavior) may limit a solute's accumulation in solution to a level lower than the total available pool. Based on the nature of the polymer and solute, the solute will partition itself between the solution and polymer phases; the equilibrium distribution of the solute between the two phases can be described in terms of an equilibrium interaction constant E_b:

$$E_b = (m_p/W_p)/(m_s/V_s) \qquad (4)$$

where m is the mass of solute in a particular phase at equilibrium, W represents the weight of the polymer (g), V is the solution volume (l), and s and p refer to the solution and polymer phases. E_b is analogous to a partition coefficient, differing in terms of a gravimetric (as opposed to volumetric) expression of the solute's concentration in the polymer.

Several investigators have demonstrated that a solute's partitioning behavior between a polymer and solution can be mimicked by the solute's partitioning between two immiscible phases (say octanol-water) (Nasim et al., 1972; Illum et al., 1983; Pitt et al., 1988);

$$\log E_b = a \log P(_{o\text{-}w}) + b \tag{5}$$

The accuracy of Eqn 5 depends on how well the model solvent mimics the interaction properties of the polymer of interest. For many systems, multi-modal solute interactions are possible (Higuchi et al., 1969; Jordon and Pollack, 1972; Gryllaki et al., 1989; Hayward et al., 1990) and thus a bimodal expression, based on two dissimilar solvents (e.g., octanol and hexane) is more appropriate (Hayward and Jenke, 1990):

$$\log E_b = a \log P_{o\text{-}w} + b \log P_{h\text{-}w} + c \tag{6}$$

For ionic solutes, the magnitude of E_b is affected by the species distribution of the solute (since generally the ionized form of the solute is hydrophilic and has no affinity for the polymer). Since the species distribution is dictated primarily by pH (at more or less constant ionic strength), the interaction constant of a solute at any pH ($E_{b,i}$) can be related to the interaction constant of the non-ionized form of the solute ($E_{b,u}$) and the solute's dissociation constant (pK_a) via the expression (Illum and Bundgaard, 1982):

$$E_{b,i} = E_{b,u}/(1 + 10^{\mathrm{pH}-\mathrm{p}K_a}) \tag{7}$$

The partition-mediated accumulation of a leachable solute (A_{part}) can be calculated from E_b, the total available pool (P_T) and the amounts of solution and polymer as follows:

$$A_{\mathrm{part}} = (P_T \times W_c)/[(W_c \times E_b) + V_s] \tag{8}$$

Eqns 1, 3 and 8 thus comprise our accumulation model. A leachable will accumulate in solution to the lowest concentration determined by these equations, thus reflecting the mechanism which limits accumulation.

Properties of EHA in the polymer / solution system

The presence of EHA in the polymer studied was confirmed by structural identification (and confirmation against an authentic standard) by GC/MS analysis of polymer extracts. The pK_a of EHA is approx. 4.85. Its log $P_{o\text{-}w}$ and log $P_{h\text{-}w}$ were determined to be 2.90 and 1.16, respectively. From Eqn 2, its calculated molar solubility is 7.9×10^{-3} M. This value compares favorably with a measured molar solubility of 5.0×10^{-3} M. Amounts of EHA found in three sequential extractions of the polymer were 77.8, 1.67 and 0.05 μg/g of material (mean of three test articles). Thus, the extraction of the material is essentially complete after the third cycle and the total available pool of EHA in the polymer can be set at 79.5 μg/g (standard deviation = 1.5 μg/g). The E_b for EHA and the polymer studied, as determined by shake flask methods, was 0.01003 (RSD = 7.7%, $n = 3$).

The partition model

The generation of a partition model, designed to allow for the prediction of E_b for a particular solute and polymer, requires the solution of Eqn 6 for the *a*, *b* and *c* constants. This can be accomplished by determining the polymer-specific E_b for solutes of known $P_{o\text{-}w}$ and $P_{h\text{-}w}$ and fitting the resulting data to the equation using multiple linear regression. Pertinent properties of the solutes studied herein are summarized in Table 2. These solutes were chosen as markers since they:

(i) span 3 orders of magnitude in terms of intrinsic lipophilicity;

TABLE 2

Model solutes and their properties

Solute	Abbreviation	log $P_{o\text{-}w}$	log $P_{h\text{-}w}$	log E_b
4-Methylbenzoic acid	MBH	2.27	−0.40	−2.87
Ethylbenzoic acid	EBH	2.97	0.29	−2.27
Butylbenzoic acid	BBH	3.95	1.80	−1.39
Dimethyl phthalate	DMP	2.16	0.82	−1.94
Diethyl phthalate	DEP	3.22	1.75	−1.27
Dipropyl phthalate	DPP	4.05	2.67	−0.27
Ethylbenzoic acid	EBH	2.97	0.29	−2.27
Ethyl paraben [a]	ETPB	2.57	−1.05	−3.14
Butyl paraben [a]	BUPB	3.59	0.48	−2.09
Butylbenzoic acid	BBH	3.95	1.80	−1.39
2-Ethylhexanoic acid	EHA	2.90	1.16	−2.00

[a] 4-Hydroxybenzoic acid, – ester.

(ii) exhibit a variable ability to interact via hydrogen bonding;
(iii) are, in some cases, ionic (allowing for an assessment of pH effects); and
(iv) are amenable to analysis by HPLC.

Regression analysis of the partition coefficient vs E_b data produces the following interaction model for the polymer studied:

$$\log E_b = 0.09 \log P_{o\text{-}w} + 0.65\, P_{h\text{-}w} - 2.77 \tag{9}$$

where the standard errors associated with the a, b and c constants are 0.11, 0.07 and 0.15, respectively, and the correlation coefficient (r^2) is 0.974. The fit of the data to the least-squares regression line is shown in Fig. 1. The data's distribution around the best-fit line is more or less random, indicating that the model has no compound class bias. The relative magnitude of the a and b constants indicates that the polymer is dominantly hexane-like and does not interact with the solute via hydrogen bonding to any appreciable extent. This is consistent with the structure of the polymer wherein no moieties are present which one anticipates would participate in hydrogen bonding.

Eqn 9 can now be used to determine the E_b of any leachable substance with known partition coefficients; the resulting E_b can be substituted into Eqn 8 to determine its partition mediated accumulation in solution. Thus, for example, putting the partition coefficient data for EHA into Eqn 9 produces a calculated log E_b of -1.77, which compares favorably with that actually measured (-2.00).

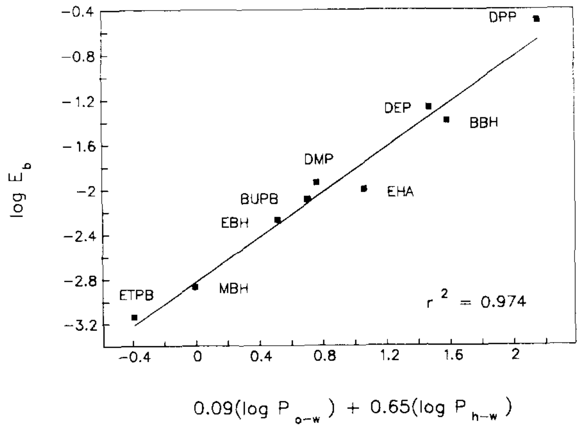

Fig. 1. Partition interaction model. Log interaction constant (E_b) versus the linear combination of the log octanol-water ($P_{o\text{-}w}$) and log hexane-water ($P_{h\text{-}w}$) partition coefficients for the styrene block polymer. The solid line represents the linear regression best-fit line.

TABLE 3

Predicted versus observed EHA accumulations

Solution pH	EHA accumulation in extraction solution (ppm)			
	From total pool	Predicted from solubility	Predicted from partitioning	Observed [a]
2.30	5.89	> 1000	2.62	2.08 (0.02)
4.65	5.89	> 1000	3.34	3.56 (0.14)
6.00	5.89	> 1000	5.44	5.74 (0.10)

[a] $n = 4$ or 6; value in parentheses is the standard deviation.

Observed versus predicted behavior

Eqns 1, 3 and 8 can be used to calculate predicted EHA accumulations from the polymer of interest. In the case of a total pool limited process, solution pH will not influence the predicted accumulation. However, solubility and partitioning behavior are affected by pH (for example, as indicated by Eqn 7) and thus the predicted accumulation will be pH dependent. Predicted and observed accumulations for the experimental system used in this study are summarized in Table 3. Of the three predicted accumulations, the partition limited accumulation level is the lowest. Thus, for this system, EHA accumulation is partition limited and the maximal accumulation is calculated from the partition model. As shown in Table 3, the partition model predictions accurately reflect the observed accumulations at each pH studied.

Conclusions

A model allowing for the prediction of thermodynamically constrained accumulation of leachables migrating from polymeric containers has been developed. The model predicts accumulation based on three accumulation-limiting mechanisms: total available pool, solute solubility and solute partitioning. Equations relating a solute's solvent-water partition coefficients ($P_{\text{o-w}}$ and $P_{\text{h-w}}$) and its aqueous solubility and partitioning properties have been developed. Thus, one can predict leachable accumulations from the physical dimensions of the system being studied (container weight and solution volume) and from the solute's partition coefficients. The maximal accumulation of the leachable in solution will be the lowest value predicted via the three accumulation-limiting mechanisms.

The model has been successfully applied to the migration of 2-ethylhexanoic acid out of a styrene-butadiene-styrene block co-polymer and accurately predicts the accumulation behavior of this species as a function of solution pH.

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