ELSEVIER

International Journal of Pharmaceutics 108 (1994) 1–9

international journal of pharmaceutics

Research Papers

Modeling of the leachables impact on the engineering of parenteral product container systems

Dennis R. Jenke *, Edward K. Chess, George Jakubowski

I.V. Systems Division, Baxter Healthcare Corporation, Round Lake, IL 60073, USA

(Received 16 June 1992; Modified version received 10 May 1993; Accepted 23 November 1993)

Abstract

This study examines the impact, from a leachables perspective, of changing a solution contact component of a polymeric solution container. By changing such a container component, one provides a new source of leachable solutes. The distribution of these leachables within a three phase system (the original container, the new component and the solution) will determine the impact of the container change. Extraction of a material, coupled with chromatographic and/or spectroscopic analysis of the resultant extracts, provides the material's leachable profile. The total organic carbon (TOC) content of the extracts is introduced as a species non-specific measure of the total extractable burden. Leaching models are developed for the container and its changed component by correlating these material's interaction constants with solvent/solvent partition coefficients of model solutes. The solvent-solvent partition coefficients of the members of the leachable profile, as well as the partition coefficients of the composite TOC, are determined. The leaching models are coupled with the leachable's partition coefficients to allow for a prediction of leachable accumulation in a specific product design. These predictions reconcile well with actual experimental observations.

Key words: Leachable; Container compatibility; Polymeric container

1. Introduction

A polymeric container's effectiveness in pharmaceutical applications may be limited by the leaching of polymer components into the contained solution. For a particular container/solution configuration, the amount of solute leached from the container must be within acceptable limits. For pharmaceutical applications, acceptability is essentially defined by the leachable's potential toxicity or, less commonly, other product use constraints (e.g., solution clarity or color).

It is somewhat misleading to think of a polymeric container as a single homogeneous entity. Not only can the container material itself consist of multiple components but the container consists of various parts with varying functional characteristics (e.g., the ports and the injection site). New container development frequently revolves around either the addition of new components or the replacement of existing components with new materials. When such a change is made, the acceptability of the container from a leachables

---

* Corresponding author.

SSDI 0378-5173(93)E0367-Y

perspective is impacted. One readily observes that the new component has its own leachable profile (the set of components which potentially can migrate into the contained solution). However, the impact of this leachable profile on the solution phase is mitigated somewhat by the unchanged portion of the container. While some members of the new component's leachable profile may migrate into the solution, the magnitude of the migration will be lessened somewhat because the unchanged portion of the container can potentially adsorb, or bind, the newly mobilized leachables. Determining the leachable impact of a material change requires that one considers a three phase system; the solution, the new component and the unchanged portion of the container.

This manuscript focuses on developing a procedure for modeling the leachable impact of changing an existing product configuration. The procedure involves several aspects:

(1) The generation of the new component's leachable profile;
(2) The determination of the new component's total ability to contribute organic solutes to the solution;
(3) The development of material/solution interaction models (based on solvent/solvent partition coefficients) for both the new component and the unchanged portion of the container;
(4) The measurement of the partition coefficients for the target leachables and the total leachable burden;
(5) The coupling of the new component's and unchanged material's interaction models to define the system's equilibrium configuration.

2. Materials and methods

2.1. Materials

The container studied consists of DEHP-plasticized polyvinyl chloride (PVC) (Baxter Healthcare Corp., Deerfield, IL). Test samples were obtained from portions of unused production bags. The container change hypothesized in this study allows for solution contact with a synthetic rubber component which is incorporated into the container's design.

Reagents used as model solutes, as analytical standards, as model container contents or in other applications were reagent or analytical grade as was appropriate. Distilled, deionized water from a Barnstead (Boston, MA) NANOpure II water polishing system was used in all preparations.

2.2. Determination of the material's leachable profile

The component was extracted with water under autoclave conditions (121°C, various durations). These aqueous extracts were then back extracted with methylene chloride and concentrated by evaporation under nitrogen to produce working samples. The working samples were subjected to GC/MS analysis under the following conditions. Separation was accomplished with a J & W Scientific (Folsom, CA) DB5 capillary column (30 m × 0.25 μm, 0.25 μm film thickness) using He as the carrier gas (flow rate = 1 cm^3/min). The temperature program was 40°C for 1 min, ramp to 295°C at a rate of 10°C per min, hold at 295°C for an additional 12 min. The column effluent was directed to a Hewlett Packard (Palo Alto, CA) Model HP5970 Mass Selective Detector (MSD).

The aqueous and methylene chloride extracts were also analyzed using LC/MS. Separation was accomplished on a Phase Sep (Queensferry Clwyd, U.K.) Spherisorb S5CN column (250 × 4.6 mm, 10 μm particles) with a mobile phase of 1:1 acetonitrile/0.02 M ammonium acetate (pH 5.4) (flow rate = 1.4 ml/min). The column effluent was directed through a UV detector (wavelength = 250 nm) and a Vestec Corp. (Houston, TX) Model 101 Thermospray interface to the HP 5970 MSD.

Additional LC/MS work was performed using a particle beam MS interface to provide approximate electron impact spectra of the leachables. The particle beam analysis was performed with a similar chromatographic system but reduced mobile phase flow rate. The MS system used was a Hewlett Packard MS Engine and attendant UNIX data system.

The identities of peaks observed in the various chromatograms were confirmed by molecular weight (LC/MS), electron impact spectra library matches (GC/MS) and retention time matches with authentic standards of candidate solutes.

2.3. Determination of the component's total available leachable pool

Approx. 3.8 g of the material were transferred to Pyrex glass bottles containing 80 ml of water. Replicate test articles, as well as appropriate controls, were autoclaved at 121°C for 1 h. After the autoclave cycle was complete and the sample had cooled, the extracting solution was removed, the test article rinsed, and a second fresh aliquot of water was added. The test article was then subjected to another autoclave cycle. This sequential extraction process was repeated to produce four component extracts. These extracts were analyzed for the concentration of individual leachable solutes and for total organic carbon.

2.4. Measurement of the partition coefficients

Octanol-water (o-w) and hexane water (h-w) partition coefficients were obtained from the literature (Leo et al., 1971; Hansch and Leo, 1979), by solvent scouting methods (Garst and Wilson, 1984; Braumann, 1986; Jenke et al., 1990) or by shake flask techniques. In the shake flask methods, the equilibrium distribution of the solute between the two phases was determined by measuring the solute's concentration in the aqueous phase before and after addition of the organic phase. The establishment of equilibrium was verified by multiple analyses at several times during the experiment.

2.5. Measurement of the equilibrium interaction constant (E_b)

E_b, defining the distribution of a solute between contacting material and solution phases, was determined by shake flask methods. Pieces of the PVC and component material were equilibrated with a solution containing a known initial amount of the solute of interest. The weight of material and solute concentration were varied for each analyte to ensure that the amount of solute left in solution after equilibration could be accurately measured and was significantly less than the initial concentration. In general, this required an initial analyte concentration of between 10 and 100 mg/l, a material weight of between 1 and 4 g and a solution volume of 50 ml. The donor solution was water, acidified with 0.05% (v/v) trifluoroacetic acid, when appropriate, to ensure that the acidic solutes were protonated. The binding samples were equilibrated for a period of 14–18 days at ambient temperature with constant shaking. The donor solution's equilibrium concentration of the solute was measured (via HPLC) and used to calculate E_b.

2.6. The impact of solution pH

The component was extracted with solutions of varied pH. Approx. 1.8 g of material was contacted with 65 ml of solution and autoclaved for 60 min. Solutions used were 0.04 M phosphate buffers at pH 3.0, 5.0 and 7.0.

2.7. The test case

To test the accuracy of the predictive model, the behavior of a model system was examined. Specifically, a model system consisting of approx. 0.5 g of the component and 14 g of the plasticized PVC was made by placing pieces of the component and the plasticized PVC into Pyrex bottles containing 50 ml water. Replicate test articles were then subjected to one, two or three successive 60 min autoclave cycles (solution not removed between the cycles) and the resulting extract was characterized for target leachable content.

2.8. Analytical methods

The concentrations of model solutes in partitioning solutions were determined by various HPLC methods. Similarly, the concentrations of the target leachables were determined in all extracts by an HPLC method. The separation of the target leachables was accomplished on an Alltech

(Deerfield, IL) Adsorbosphere C18 HS column (100×4.6 mm, 3 μm particles) with a mobile phase of 25:75 acetonitrile/0.1 M ammonium acetate. The mobile phase flow rate was 0.7 ml/min and analyte detection was by UV at 225 nm.

Solution TOC was determined using an OI (OI Corp., College Station, TX) Model 700 Total Organic Carbon Analyzer.

3. Results and discussion

3.1. The accumulation model, theoretical

The equilibrium distribution of a solute between a polymer and solution phase can be expressed in terms of an equilibrium interaction constant, E_b:

$$E_b = (m_p/W_p)/(m_s/V_s) \tag{1}$$

where m is the mass of solute in a particular phase at equilibrium, W denotes the dry 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.

In general, a solute's interaction with a polymer can be mimicked by the solute's partitioning behavior in two dissimilar solvent systems (say, octanol-water and hexane-water) (Hayward and Jenke, 1990; Jenke et al., 1991, 1992):

$$\log E_b = a(\log P_{\text{o-w}}) + b(\log P_{\text{h-w}}) + c \tag{2}$$

The magnitude of the a, b and c coefficients in Eq. 2 can be determined by measuring E_b for model solutes whose partition coefficients are known and performing a multiple linear regression analysis of the data.

In the system studied herein (consisting of the solution, the PVC container and the new component), two binding models must be simultaneously satisfied, one for the PVC and one for the component. For a target leachable whose partition coefficients are known, an E_b with both the PVC and the component can be determined. At equilibrium both E_b's must be satisfied. The mass of the target leachable in the polymer phase at equilibrium is, from Eq. 1 (e.g., for the PVC):

$$m_{\text{PVC}} = (E_{\text{b,PVC}} \times m_s \times W_{\text{PVC}}) \tag{3}$$

Additionally, the initial amount of a target leachable in the component (its total available pool, P_T) equals the sum of amount leached into the solution phase (m_s), that sorbed by the PVC (m_{PVC}) and that remaining in the material (m_c):

$$m_s + m_{\text{PVC}} + m_c = P_T \tag{4}$$

Combining Eq. 3 (for both the PVC and the component) and Eq. 4 yields an expression which allows for the calculation of the equilibrium concentration of the target leachable in solution ($C_s = w_s/V_s$):

$$C_s = P_T/[V_s + (E_{\text{b,PVC}} \times W_{\text{PVC}}) + (E_{\text{b,c}} \times W_c)] \tag{5}$$

3.2. The role of total organic carbon

One of the more challenging aspects of a leachable evaluation is actually identifying all the members of a material's leachable profile. The utilization of total organic carbon (TOC) as a measure of the total amount of leachables available in a material impacts the generation of the leachable profile in two respects. Firstly, the TOC allows one to assess the completeness of the leachable profile determination. If all the members of the leachable profile have been identified, then the sum of the TOC contribution from the individual members should equal the measured TOC:

$$\text{TOC (measured)} = \Sigma(C_m \times T_m) \tag{6}$$

where C_m is the concentration of each profile member and T_m represents the member's ratio of carbon content to formula weight. If the sum of the TOC contributions for all identified members of the leachable profile is significantly less than the measured TOC then clearly all the members of the profile have not been identified.

TOC impacts the determination of the leachable profile in a second way. The magnitude of the TOC and its partitioning behavior (i.e., the bulk partitioning behavior of all the components of the leachable profile) may indicate whether the identification of the leachable profile is even necessary. If the total extractable TOC of the new material is small and/or the composite partitioning properties of the leachables are such that they partition favorably into the polymeric materials, then the total amount of leachables which accumulate in the solution phase may be sufficiently small that their concentrations, no matter what their identities, pose no product safety or efficacy concerns. In such an ideal, it would be unnecessary to perform an identification of the components of the leachable profile, unless the presence of a known carcinogen or mutagen was suspected.

Thus, the TOC becomes a tool with which one can judge the completeness of a leachable pool identification as well as to determine whether a profile identification is even necessary.

3.3. The accumulation model for the test system

The generation of the partition model for both the plasticized PVC and new component requires the solution of Eq. 2 for the *a*, *b* and *c* constants by measuring the behavior of model solutes. Pertinent properties of the solutes used herein are summarized in Table 1. These solutes were chosen since they: (i) span three orders of magnitude in terms of intrinsic lipophilicity; (ii) exhibit variable hydrogen bonding ability; (iii) are, in some cases, ionic (allowing for a consideration of the pH effect), and (iv) are amenable to rapid and accurate analysis by HPLC.

Multiple linear regression analysis of the partition coefficients (independent variables) vs E_b

Table 1
Properties of the model solutes and target leachables

(A) Model solutes

Compound	Abbreviation	Log $P_{o\text{-}w}$	Log $P_{h\text{-}w}$	Log E_b	
				Component	Container
Dimethyl phthalate	DMP	2.16	0.82	−1.96	−1.56
Diethyl phthalate	DEP	3.22	1.75	−1.17	−0.53
Dipropyl phthalate	DPP	4.05	2.67	−0.14	0.25
Aniline	AN	0.90	−0.10	−2.56	−2.41
4-Methylbenzylalcohol	MBOH	1.60 [a,b]	0.10	−2.36	−2.40
N-Ethylbenzylamine	NEHA	2.17	−1.69	−2.95	−2.15
4-Methylbenzoic acid	MBH	2.27 [a,b]	−0.40	−1.90	−1.87
4-Ethylbenzoic acid	EBH	2.97	0.29	−1.41	−1.33
Butylbenzoic acid	BBH	3.95	1.80	−0.89	−0.93
Ethyl paraben [c]	ETPB	2.57	−1.05	−2.35	−1.76
Butyl paraben [c]	BUPB	3.57 [a,b]	0.48	−1.31	−0.95

(B) Target leachables

Compound	Abbreviation	Log $P_{o\text{-}w}$	Log $P_{h\text{-}w}$	Log E_b, container	
				Measured	Calculated
Aniline	AN	0.90 [a]	−0.10 [b]	−2.21	−2.51
Acetanilide	AD	1.36 [b]	−0.99	−2.62	−2.52
Diphenylguanidine	DPG	−0.05	−0.63	−3.60	−3.15
Leachable composite	TOC	0.94	−0.56	−2.30	−2.61

[a] From Leo et al. (1971).
[b] From Hansch and Leo (1979).
[c] 4-Hydroxybenzoic acid, – ester.

(dependent variable) produces the following interaction models:

For the plasticized PVC:

$$\log E_b = 0.53(\log P_{o\text{-}w}) + 0.27(\log P_{h\text{-}w}) - 2.95 \quad (7)$$

For the material:

$$\log E_b = 0.40(\log P_{o\text{-}w}) + 0.38(\log P_{h\text{-}w}) - 2.97 \quad (8)$$

The standard errors associated with the a, b and c constants are approx. 0.1, 0.1 and 0.28, respectively. The respective correlation coefficients (r^2) for the models are 0.91 for the PVC and 0.95 for the new material. The fit of the binding data to the regression line (which represents the material's binding model) is shown in Figs. 1 and 2. For both the PVC and new component, the distribution of the data is more or less random around the best fit line, indicating that neither material has a solute class related bias. Since the a and b constants in the model equations are larger than the magnitude of their standard errors, both partition coefficients contribute to the accuracy of the model. This implies that both the PVC and the new component have the ability to interact with aqueous solutes via classical lipophilic and hydrogen bonding mechanisms. This behavior is consistent with the composition of these materials in that they are both made up of components of differing chemical functionality.

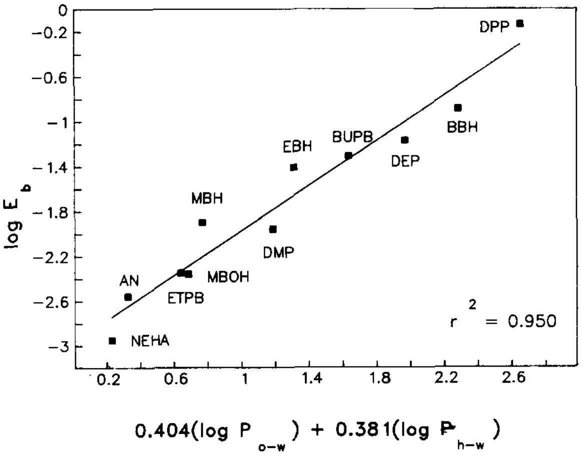

Fig. 1. Partition interaction model, new material. Log interaction constant (E_b) vs the linear combination of the log octanol-water ($P_{o\text{-}w}$) and log hexane-water ($P_{h\text{-}w}$) partition coefficients. The solid line represents the linear regression best-fit line.

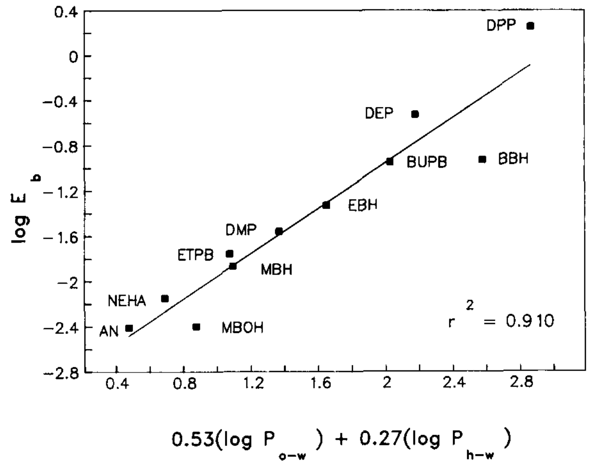

Fig. 2. Partition interaction model, plasticized PVC. Log interaction constant (E_b) vs the linear combination of the log octanol-water ($P_{o\text{-}w}$) and log hexane-water ($P_{h\text{-}w}$) partition coefficients. The solid line represents the linear regression best-fit line.

3.4. Properties of the new component material and its leachables

Aniline (AN), acetanilide (AD) and diphenylguanidine (DPG) were established via the GC/MS and LC/MS experiments as members of the component's leachable profile. They thus become target leachables for further consideration. While additional peaks were observed in the GC and LC chromatograms, the resulting MS information was inadequate for their identification. For the purpose of this study, no further identification work was initiated. In a more rigorous evaluation of a new packaging system, more sophisticated identification methods would be employed to allow for a complete reconciliation of the leachable's individual concentrations and the composite TOC.

The results of the successive extraction of this material are shown in Table 2 and Fig. 3. For the target leachables and the TOC, the material's

Table 2
The total available pool determination: results of the sequential leaching of the new material

Cycle	Concentration in extract (mg/l) [a]			
	AN	AD	DPG	TOC
1	9.83 (0.70)	16.7 (0.3)	23.1 (0.5)	78.0
2	7.70 (0.24)	1.28 (0.22)	7.74 (0.29)	19.6
3	4.32 (0.37)	–	3.51 (0.11)	10.2
4	2.13 (0.22)	–	1.92 (0.07)	8.1
Total pool	24.0 (1.2)	18.0 (0.2)	36.3 (0.90)	115.9

–, not detected; values in parentheses are the standard deviations.
[a] Mean of three test articles.

total available pool is nearly exhausted after four successive extractions. Thus, the sum of the amount of the leachables which was obtained in each cycle represents the total available pool of each leachable.

The reconciliation between the measured TOC and the TOC contributions from the three identified target leachables is incomplete; together these target leachables account for only 50% of the measured TOC. Thus, in this application the TOC reconciliation indicates that profile is not completely identified and additional future identification efforts would be appropriate.

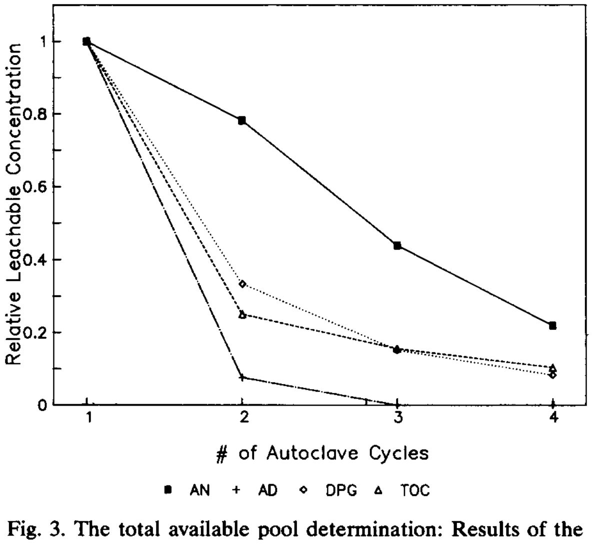

Fig. 3. The total available pool determination: Results of the sequential leaching of the new material. The relative concentration shown for each leachable is taken vs the amount of that specific leachable which was extracted during the first autoclave cycle.

Partition coefficients determined for the target leachables and the leachable composite (TOC) are shown in Table 1. The data represent the mean of at least four independent determinations per compound. The standard deviation associated with the individual coefficients was typically 0.1 log units, well within the normal variation associated with these types of determinations (Dearden and Bresnen, 1988).

E_b constants for interaction between the target leachables (and leachable composite) and the plasticized PVC were determined and calculated by putting the leachable's mean partition coefficients into Eq. 7. The calculated and measured values are contained in Table 1 and agree to within the experimental precision associated with these determinations.

3.5. *The test case*

Sufficient data exist to allow for the calculation of E_b for the target leachables and leachable composite. The total available pool of these species in the new component is known. Thus, one can calculate the equilibrium leachable concentration in solution for a system whose solution volume and weights of the PVC and new component are known. The test case studied herein is an exaggerated approximation of a 50 ml PVC container with the new component. It is exaggerated to the extent that the amount of new component equilibrated in this system is several times greater than the amount which would be found in a practical application. This approach was adopted herein to insure that the leachable accumulation in solution could be accurately measured.

The results of the measured and predicted concentrations of the target leachables are summarized in Table 3. The increase in concentration as a function of autoclave cycle illustrates the combined effect of a slow approach to equilibrium and a small amount of solution loss per autoclave cycle. The predicted and measured accumulation levels agree to within the experimen-

Table 3
Leachable accumulation in the test case

Analyte	Type	Concentration in solution (mg/l)		
		Cycle no. 1	Cycle no. 2	Cycle no. 3
AN	actual	1.4	1.7	2.0
	predicted	1.7	2.4	2.8
AD	actual	2.6	2.5	2.8
	predicted	2.0	2.2	2.3
DPG	actual	4.4	5.1	5.9
	predicted	5.5	5.8	5.9
TOC	actual	–	–	21
	predicted	–	–	16

Note: TOC was measured only after the third cycle and represents the TOC associated with the new material only (contribution from the PVC is subtracted out).

tal error of the determinations for all autoclave cycles. Thus, the accuracy of the model's predictions has been validated in a system which mimics an actual product configuration.

Of course, the equilibrium model can also be used to determine how much of a particular leachable resides in the other system components (PVC and new component) at equilibrium. That is, the equilibrium distribution of the material's leachable can be determined. Table 4 summarizes the predicted distribution of the leachables in the test case after the first autoclave cycle. One appreciates the subtleties of this test case from these distributions. Since the leachables from the new component are very hydrophilic, the new component is essentially depleted of its entire extractable pool. However, except in the case of DPG (the most hydrophilic of the target leachables), the plasticized PVC (which comprises a large fraction of the container on a weight basis) sorbs nearly 45% of the mobilized leachables, thus minimizing the leachable's impact on solution safety and efficacy somewhat.

Table 4
Species distribution after one autoclave cycle in the test case

Species	Percent in this phase at equilibrium		
	Solution	PVC	New material
AN	51.9	46.9	1.2
AD	53.5	45.7	0.9
DPG	83.2	16.4	0.5
TOC	58.4	40.6	0.9

Note: This distribution calculated (predicted) based on the pool of each leachable, their partition coefficients, PVC and component's binding models.

If the leachables associated with the new component were more lipophilic than those actually observed, their accumulation in solution would be significantly lower for two reasons. Firstly, less of the new components's pool would leave the component. Secondly, the plasticized PVC would sorb a larger fraction of whatever leachable would leave the component. For example, consider the species distribution if the model compound DMP were present in the new component at the same levels as AN. After one autoclave cycle under the conditions of the test case, the DMP concentration in solution would be only 0.4 ppm, with the species distribution between the solution, PVC and new component being 11.3, 87.5 and 1.3%, respectively. Clearly, the PVC would very effectively limit the solution accumulation of many potential component related leachables.

3.6. The effect of pH on the accumulation of the target leachables

Ionic leachables are of particular interest since their E_b (and therefore their accumulation in solution) is dependent on pH (Illum and Bundgaard, 1982). Aniline itself is a weak base; the weakly basic nature of the leachable composite is indicated by an increase in solution pH which is observed during the extraction of the new component. Thus, one anticipates a potential pH effect on leachable accumulation.

The release of the leachables as a function of solution pH is summarized in Table 5. A pH range of 3–7 was chosen as typical of most i.v.

Table 5
Effect of extractant pH on the release of target leachables

pH	Concentration in solution (mg/l)			
	AN	AD	DPG	TOC
3	5.53	8.74	10.6	41.4
5	5.86	9.02	11.7	36.6
7	7.51	9.50	12.3	46.2

Each data point represents the mean of three test articles.

pre-mixed solutions. While AN accumulation increases somewhat especially at a pH greater than 5 (consistent with its acid/base chemistry), the effect of pH on the accumulation of the other leachables associated with the new component is minimal.

4. Conclusions

An approach for modeling the accumulation of leachables in a contained solution as the configuration or composition of the container is changed has been developed. The model has been successfully applied to a particular container system which resembles commercially available pharmaceutical products. Additionally, the utility of total organic carbon as a surrogate for identifying individual leachables, as well as a test for the completeness of leachable identification, has been discussed.

References

Braumann, T., Determination of hydrophobic parameters by reversed phase liquid chromatography: Theory, experimental technique and application in studies on quantitative structure-activity relationships. *J. Chromatogr.*, 373 (1986) 191–225.

Dearden, J.C. and Bresnen, G.A., The measurement of partition coefficients. *Quant. Struct. Act. Relat.*, 7 (1988) 133–144.

Garst, J.E. and Wilson, W.C., Accurate wide-range, automated high performance liquid chromatographic method for the estimation of octanol-water partition coefficients: I. Effect of chromatographic conditions and procedure variables on accuracy and reproducibility of the method. *J. Pharm. Sci.*, 73 (1984) 1616–1622.

Hansch, C. and Leo, A., *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979.

Hayward, D.S. and Jenke, D.R., Interactions between polymer containers and parenteral solutions: Correlating equilibrium polymer-water interaction constants with solute partition coefficients. *Int. J. Pharm.*, 66 (1990) 87–96.

Illum, I. and Bundgaard, H., Sorption of drugs by plastic infusion bags. *Int. J. Pharm.*, 10 (1982) 339–351.

Jenke, D.R., Chess, E.K., Zietlow, D.C. and Rabinow, B.E., Model for estimating the accumulation of solutes leaching from polymeric containers into parenteral solutions. *Int. J. Pharm.*, 78 (1992) 115–122.

Jenke, D.R., Hayward, D.S. and Kenley, R.A., Liquid chromatographic measurement of solvent/solvent partition coefficients: Application to solute/container interactions. *J. Chromatogr. Sci.*, 28 (1990) 609–612.

Jenke, D.R., Kenley, R.A. and Hayward, D.S., Interactions between polymeric containers and their contained solution: Modeling of polymer-water solute partitioning via coupled solvent-water partition coefficients. *J. Appl. Polym. Sci.*, 43 (1991) 1475–1482.

Leo, A., Hansch, C. and Elkins, D., Partition coefficients and their uses. *Chem. Rev.*, 71 (1971) 525–616.