Determination of Solute–Polymer Interaction Properties via Two-Stage Extraction

Dennis R. Jenke[1]

Received October 27, 1993; accepted November 8, 1993

KEY WORDS: solute/polymer interaction; extractables; leaching; material compatibility.

INTRODUCTION

The utility of a solution contact material in pharmaceutical and food applications may be limited by the accumulation of an extractable from the material. The maximal extractable accumulation occurs when equilibrium is established between the material and the solution phases and is controlled by one or more of the following factors (1,2):

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

In a partition-mediated situation, the extractable's solution solubility is not exceeded and its solution concentration at equilibrium (C_p) can be determined from the material's total pool of the extractable (P_T) and the extractable's material equilibrium interaction constant (E_b) via Eq. (1) (3):

$$C_p = (P_T \times W_m)/[(W_m \times E_b) + V_s] \quad (1)$$

where W_m is the material weight, V_s is the solution volume, and E_b is defined via Eq. (2),

$$E_b = (m_m/W_m)/(m_s/V_s) \quad (2)$$

in which M is the mass of the extractable in the solution (s) or material (m) phase at equilibrium. Thus if E_b and P_T are known, an extractable's accumulation can be predicted.

P_T is frequently determined by exhaustive extraction of the material, while E_b is determined via shake flask methods (or approximations thereof). In this manuscript, an alternate approach, which is based on a two-stage extraction of the material and which provides both key pieces of data, is proposed. This methodology is used to predict the accumulation of two extractables from a rubber material and the predictions are reconciled with observed behavior.

MATERIALS AND METHODS

Materials

The material studied is a synthetic polyisoprene rubber. Similar materials have numerous pharmaceutical applications which include direct solution contact. The two extractables examined, 2-phenyl-2-propanol (PP) and acetophenone (AP), were obtained as standard materials from Aldrich Chemical (Milwaukee, WI) and had purities of 95% or greater. Other chemicals used were reagent or chromatographic grade as appropriate. The water was obtained from a Barnstead NANOPure II water polishing system.

Material Extraction

Approximately 5.5 g of material was contacted with 30 mL of phosphate buffer (0.01 *M*, pH 3.0) in Pyrex bottles. These test articles were autoclaved for 1 hr. Autoclaved samples were cooled to ambient temperature, the extracting solution was removed, the material was rinsed with water, and a fresh aliquot of buffer was added. The test articles were then autoclaved again. This sequential autoclave process was repeated to produce five separate extracts.

Extractable Accumulation

Approximately 6.0 g of the material was contacted with 35 mL of the phosphate buffer in Pyrex bottles and stored at ambient temperature for a period of 192 hr. Periodically, an aliquot of the solution was removed and analyzed.

Determination of the Extractable's E_b

Octanol/water and hexane/water partition coefficients for the extractables were determined by shake flask methods. These partition coefficients were used to calculate the extractable's E_b via an existing binding model for the rubber material (e.g., Refs. 3 and 4).

Analytical

The concentrations of PP and AP in the various solutions were determined by HPLC. Separation was accomplished on an Alltech (Deerfield, IL) Adsorbsphere C8 column (150 × 4.6 mm, 5-μm particles) with a mobile phase of 1/3 (v/v) acetonitrile/water. Detection was by UV absorbance at 210 nm.

RESULTS AND DISCUSSION

Theoretical

An extractable's E_b can be expressed as the relationship between the amount of extractable in solution after a single extraction step (C_1) and the extractable's P_T in the material:

$$E_{b,1} = [P_T - (C_1 \times V_s)]/(W_m \times C_1) \quad (3)$$

If the same material is then subjected to a second, equivalent extraction with a fresh aliquot of solution, E_b can again be written in terms of the concentration of extractable in the second extracting solution (C_2) and P_T:

$$E_{b,2} = \{P_T - [V_s \times (C_1 + C_2)]\}/(W_m \times C_2) \quad (4)$$

Now $E_{b,1} = E_{b,2}$ and thus Eqs. (3) and (4) can be combined to produce P_T:

$$P_T = (C_1^2 \times V_s)/(C_1 - C_2) \quad (5)$$

P_T can be substituted back into Eq. (3) or (4) to produce E_b.

---

[1] Baxter Healthcare Corporation, William B. Graham Science Center, Round Lake, Illinois 60073.

0724-8741/94/0500-0774$07.00/0

Table I. Sequential Extraction of the Rubber Material[a]

Extraction no.	Mean extractable concentration (mg/L) PP	AP
1	6.71	0.688
2	2.71	0.374
3	1.26	0.211
4	0.85	0.099
5	0.47	0.063
Total pool		
(a)	12.0	1.435
(b)	11.4	1.380

[a] The data represent the mean of three test articles. (a) The sum of the extractable concentration in extractions 1 through 5. (b) Predicted using the first two extractions and Eq. (5).

These values of P_T and E_b can be substituted into Eq. (1) to calculate the extractable's maximal accumulation in solution.

Material Extraction

The results of the sequential extraction of the rubber are shown in Table I. Clearly, the total pool of both extractables is nearly exhausted after the fifth extraction; thus the extractable's total pool can be determined by either adding up the amount of solute found in all five extracts (the additive pool) or using the results of the first two extractions (the two stage pool). For PP, the additive and the two-stage pools are 0.360 and 0.343 mg, respectively. For AP, the additive pool and two-stage pools are 0.048 and 0.046 mg, respectively. The additive and two-stage data are statistically equivalent; however, the two-stage data were obtained in less than half the time.

Determination of E_b

The logarithms of the octanol/water (o/w) and hexane/water (h/w) partition coefficients determined for PP and AP are shown in Table II and compare favorably with values in the literature. The logarithms of E_b, determined with these coefficients and a binding model generated for this material, were calculated as -2.28 and -1.93 for PP and AP. Values for $\log E_b$ determined with Eq. (3) and the results of the first two extraction steps were -2.43 and -2.08, respectively, for PP and AP. While the results obtained by the proposed approach are somewhat lower than those obtained via the binding model, the magnitude of the difference is within the normal variation associated with the measurement of partition coefficients (5). Thus E_b can be obtained via the proposed two-stage approach without the need to perform additional experiments.

Table II. Partition Coefficients of the Extractables[a]

Solute	$\log P_{o/w}$ This study	$\log P_{o/w}$ Reported	$\log P_{h/w}$ This study	$\log P_{h/w}$ Reported
PP	1.63	1.88	0.32	0.08
AP	1.61	1.58	1.18	—

[a] The reported data are taken from Ref. 6. The data reported for PP are for 3-phenyl-2-propanol. The data represent the mean of four test articles per extractable.

Table III. Accumulation of Extractables at Ambient Temperature[a]

Time (hr)	Mean concentration in solution (mg/L) PP	AP
13	3.7	0.39
24	4.5	0.44
39	5.3	0.47
129	6.5	0.56
192	6.7	0.54
Predicted maximal accumulation	6.3	0.58

[a] The data represent the mean of duplicate test articles.

Extractable Accumulation

The accumulation of the two extractables in solution at ambient temperature is summarized in Table III. After 192 hr of storage, equilibrium has been established and the extractable's accumulation is at its maximum value. These observed accumulations agree well with those generated using Eq. (1) and the P_T and E_b determined by the two-stage method proposed herein.

CONCLUSION

The two-stage extraction process proposed herein for the determination of an extractable's total pool and material interaction constant produces data comparable to those with more standard approaches for the determination of these quantities. The advantage of the two-stage approach is increased rapidity of the determination. Data generated with the two-stage approach predict extractable accumulations which are similar to observed behavior.

REFERENCES

1. I. C. Sanchez, S. S. Chang, and L. E. Smith. Migration models for polymer additives. *Polym. News* 6:249–256 (1980).
2. L. A. Cruz, M. P. Jenke, R. A. Kenley, M. J. Chen, and D. R. Jenke. Influence of solute degradation on the accumulation of solutes migrating into solution from polymeric parenteral containers. *Pharm. Res.* 9:967–972 (1990).
3. D. R. Jenke, E. K. Chess, D. C. Zietlow, and B. E. Rabinow. Model for estimating the accumulation of solutes leaching from polymeric containers into parenteral solutions. *Int. J. Pharm.* 78:115–122 (1992).
4. D. R. Jenke, E. K. Chess, and G. Jakubowski. Modeling of the leachables impact on the engineering of parenteral product container systems. *Int. J. Pharm.* (in press).
5. J. C. Dearden and G. A. Bresnen. The measurement of partition coefficients. *Quant. Struct. Act. Relat.* 7:133–144 (1988).
6. A. Leo, C. Hansch, and D. Elkins. Partition coefficients and their uses. *Chem. Rev.* 71:525–616 (1971).