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Report

Influence of Solute Degradation on the Accumulation of Solutes Migrating into Solution from Polymeric Parenteral Containers

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Solute stability in solution, in addition to solute–polymer interaction properties and the total solute available pool, impacts the interaction between a polymeric container and a parenteral product, specifically in terms of the migration of trace polymer components into the contained solution. A specific solute/polymer system has been studied with respect to properties impacting the magnitude and rate of solute migration from the polymer into solution. The solute, an alkyl ester, originates in a polyolefin composite packaging material. Solute degradation kinetics were studied as a function of solution temperature and pH. Solute–polymer interaction properties including the equilibrium binding constant and diffusion coefficient were obtained. An accumulation rate model is developed for the determination of the solution phase concentration of the liberated solute as a function of storage time and conditions. Coupling the model with the properties of the polymer–solute system studied provides a tool that accurately predicts solute accumulation behavior in a representative parenteral product configuration.

KEY WORDS: container–solute interaction; container compatibility; solute migration in polymers.

INTRODUCTION

A major concern in evaluating the utility of polymeric containers for packaging of parenteral products is the migration of container components into the contained solution phase (leaching). Specifically, the potential toxicity of trace materials mobilized into a solution is of concern (1–4).

Historically, four general factors controlling solute–container interactions have been identified (5). These are

(i) the initial or total amount of solute present (the total available pool),
(ii) the solute's solubility in either the polymer or the solution phase,
(iii) the equilibrium partitioning of the solute between the container and the solution, and
(iv) diffusion.

For a solute migrating from the container into solution, a fifth factor, the solute's stability in solution (which has received little attention in the literature), can dominate the migration process. Solute stability is important since it impacts the actual solution concentration of the migrating solute and the total amount of leachable material accumulating in solution, and since degradation introduces products whose influence on product utility may be different from that of the parent compound.

This study examines the accumulation properties of a leachable solute which exhibits a variable solution phase stability. The test solute is a carboxylic acid alkyl ester which originates in the polymer of interest and undergoes acid- and base-catalyzed hydrolysis in solution (6). Factors influencing the test solute's accumulation in solution evaluated here included the solute's degradation kinetics and the thermodynamic and kinetic nature of the solute–polymer interaction. An accumulation model based on these data is proposed and the predictive results are compared with accumulation profiles generated in actual product container configurations.

MATERIALS AND METHODS

Materials

The polymer is a proprietary polyolefin composite consisting primarily of polypropylene. The test solute (whose structure has been elucidated) was identified as a polymer leachable in exhaustive extraction studies and authentic samples of the ester were synthesized and purified in-house and used to prepare test articles. All reagents and gases were reagent or chromatography grade, as appropriate. The water was obtained from a Barnstead (Boston, MA) NANOpure II water polishing system.

Hydrolysis Kinetics

The effects of temperature and solution pH on the rate

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of solute hydrolysis were studied as follows. The solute was prepared at the 100-ppm level in a matrix consisting of a phosphate buffer (100 m*M*), an antibacterial agent (sodium azide, 1 g/liter), and sodium chloride (to adjust the solution's ionic strength to approximately 200 m*M*). Test solutions, prepared at a pH of 2, 3, 4, 5, 6, 7, or 8, were placed into glass ampoules and stored at 30, 45, or 75°C for up to 2010 hr. At selected time intervals, individual ampoules were removed from storage and analyzed for solute concentration.

Solute–Polymer Interaction Properties

The solute/polymer interaction properties were studied using a permeation-cell approach (4,7). A pouch was made from approximately 3.1 g of polymer (mean film thickness, 0.2 mm) by heat-sealing common edges. The pouches had a typical solution contact surface area of 17,000 mm^2 (less than 0.5% represented the heat-seal seams) and were filled to contain 40 ml of a receptor solution and a minimal air headspace. The sealed pouches were placed in glass vessels containing 400 ml of a donor solution. The donor solution contained approximately 70 ppm of the test solute. Both the donor and the receptor solutions were buffered (0.01 *M* NaH_2PO_4) at pH 5 to prevent solute hydrolysis from occurring during the experiment. The pouches were completely immersed in the donor solution except for a small sampling port through which the receptor solution could be retrieved via a syringe. Four reaction systems were prepared, sealed, and stored at 25°C for up to 35 days (with constant gentle agitation). Controls containing the donor solution but no polymer pouch were stored under the same conditions to confirm that solute lost from the donor because of interaction with the polymer could be distinguished from other solute loss mechanisms (e.g., solute degradation or absorption by the glass vessel). At various times during storage, aliquots of the donor, receptor, and control solutions were retrieved and analyzed for solute concentration. The amount of solution withdrawn from the donor and receptor solution was sufficiently small (typically 0.5 and 0.2 ml, respectively) that the total solution volume was not changed significantly by the sampling process.

Accumulation Study

The test polymer was fabricated into a typical parenteral product configuration and filled to contain 50 ml of a solution adjusted to a pH of 2, 3, or 4 with 1 *N* sulfuric acid. The test containers were stored at either 25 or 65°C for up to 2020 hr. At selected time intervals during storage, triplicate units were removed from storage and the solution phase was characterized for solute concentration.

Analytical Methods

For the hydrolysis rate and polymer interaction studies, solute concentration was determined via a stability-indicating HPLC method. Separation was accomplished with an Alltech (Deerfield, IL) Adsorbosphere C18 column (150 × 4.6 mm, 5-μm particles) and a mobile phase containing 1/1 (v/v) acetonitrile/water. Spectrophotometric detection was at 215 nm.

In the accumulation study, solute concentration was determined by gas chromatography (GC) with flame ionization detection. Separation was accomplished using a J&W Scientific (Folsom, CA) SE-54 capillary GC column (30 m × 0.25 mm) with N_2 as the carrier gas. The temperature program was as follows: 40°C for 1 min, ramp to 290°C at 20°C/min, hold at 290°C for 5 min. Injector temperature was 250°C and the detector temperature was 300°C. Accumulation samples were extracted with methylene chloride prior to analysis.

RESULTS AND DISCUSSION

Hydrolysis Kinetics

Preliminary control experiments confirmed that the buffer and azide did not significantly affect solute hydrolysis rates. The reaction is pseudo-first order with respect to solute concentration (Fig. 1) and the rate expression can be written:

$$C_t = C_0 \exp -(k_{obs}t) \quad (1)$$

where C_t is the solute concentration at time t, C_0 is the initial solute concentration, and k_{obs} is the observed rate constant. k_{obs} is strongly influenced by both solution pH and temperature. Figure 2 shows Arrhenius plots at three representative pH values, while Fig. 3 provides pH–rate profiles at four representative temperatures. At all temperatures, the pH–rate profile has a rate minimum at pH 5 and a rapidly increasing rate under more acidic or alkaline conditions. The hydrolysis is both acid and base catalyzed.

To describe the pH dependence of the hydrolysis reaction, the observed rate constant can be expressed as follows:

$$k_{obs} = k_0 + k_{H^+}[H^+] + k_{OH^-}[OH^-] \quad (2)$$

where k_0 is the pseudo-first-order rate constant for the solute's reaction with water and k_{H^+} and k_{OH^-} are the bimolecular rate constants for the acid- and base-catalyzed hydrolysis respectively (example, Ref. 8). Rate-versus-pH data, coupled with nonlinear least-squares analysis, can be used to compute the rate constants at each temperature studied. Regression of the resulting rate constants versus temperature [and combination with Eq. (2)] produces an expression

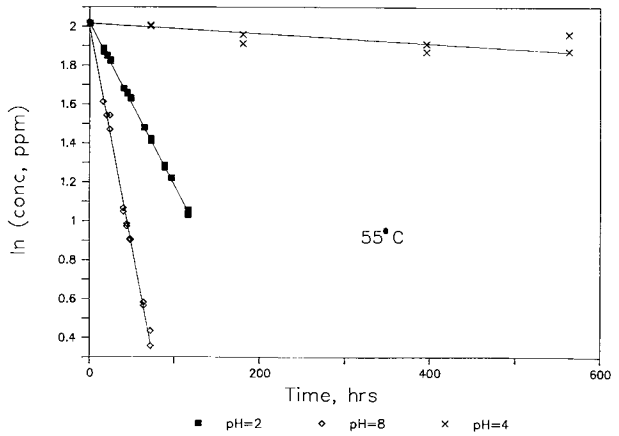

Fig. 1. Rate of solute hydrolysis; concentration versus time plots at 55°C and pH 2, 4, and 8.

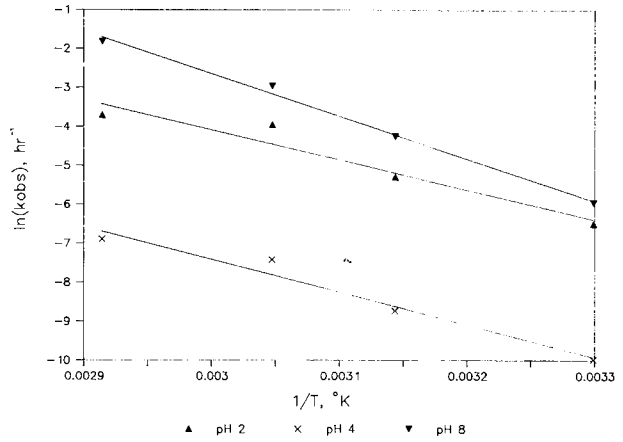

Fig. 2. Effect of temperature on the observed hydrolysis rate constant.

which directly correlates k_{obs} with temperature and pH. Thus, in Eq. (3)

$$k_{obs} = \exp [21.6 - (18710/RT)] + \exp[22.9 - (14902/RT)] \times [H^+] + \exp[44.1 - (21779/RT)] \times [OH^-] \quad (3)$$

where R is the gas constant, T is the absolute temperature, and the activation energies are given as calories per mole.

As shown in Fig. 3, Eq. (3) closely models the observed decomposition behavior of the test solute.

Solute–Polymer Interaction Properties

The solute–polymer interaction can be described thermodynamically by the equilibrium distribution of the solute between the solution and the polymer phases and kinetically by the rate with which the solute migrates out of the polymer. Considering the former, the equilibrium solute distribution can be expressed in terms of an equilibrium binding constant (E_b) which is defined in Eq. (4):

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

where

m = mass of solute in a particular phase at equilibrium
V = volume of solution (liters)
W = weight of the polymer (grams)

and s and p refer to the solution and polymer phases, respectively.

The relationship between E_b and quantities either known or determined in the pouch experiment becomes

$$E_b = [C_i V_D - C_e(V_D + V_R)/W_p]/C_e \quad (5)$$

where

C_i = initial solute concentration in the receptor solution
C_e = equilibrium solute concentration in either solution
V_R = volume of the receptor solution
V_D = volume of the donor solution

For the test solute and polymer studied, log E_b was determined to be -1.4.

Kinetically, solute migration into the contained solution is a bimodal process involving a relatively slow, diffusion-controlled migration of the solute through the polymer and a relatively fast solute desorption step at the polymer–solution interface. The solute's diffusion coefficient in the polymer can be obtained from the solute appearance profile in the receptor solution of the pouch system. The appearance profile is characterized by a well-defined induction period (Fig. 4). Thus the diffusion coefficient D of the test solute can be determined using the time lag method (9):

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

where δ is the polymer thickness and T_L is the time lag (time axis intercept of the steady-state portion of the appearance profile). For the test solute and polymer studied, D was determined to be 2.7×10^{-5} mm²/hr. The effect of temperature on D for substituted phthalates in the test polymer has been studied and the Arrenhius parameters calculated (7). These parameters are used to estimate D for the test solute at the various model temperatures.

Accumulation Model

The total available pool of the test solute in the test

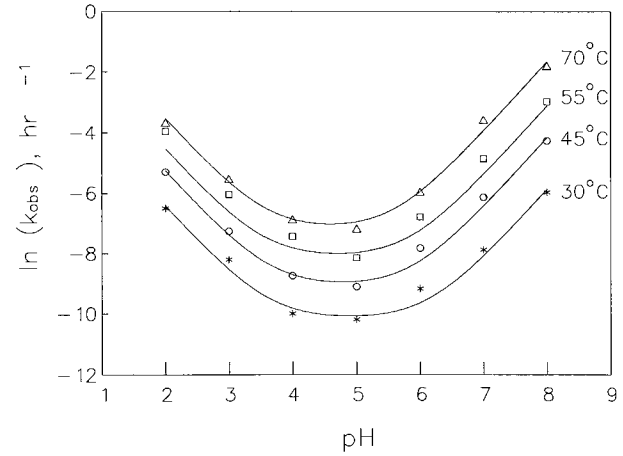

Fig. 3. Effect of solution phase pH on the observed hydrolysis rate constant (k_{obs}) at four temperatures. Symbols represent experimental data; lines represent model fit [from Eq. (3)].

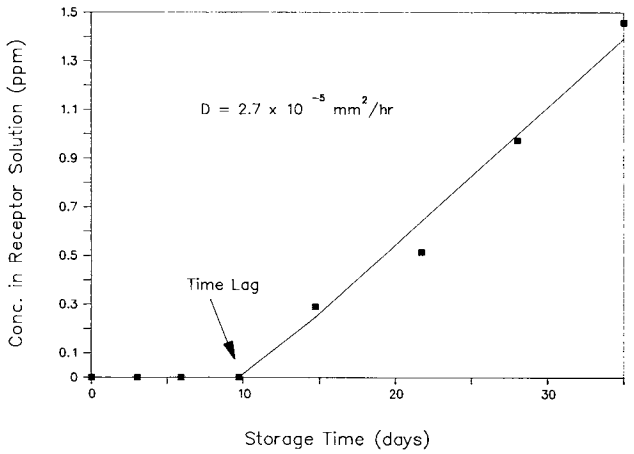

Fig. 4. Concentration of solute migrating into the receptor solution of the pouch experiment versus storage time.

polymer is typically 72 μg solute/g polymer. Coupling the total available pool with E_b allows for the calculation of the partition-mediated maximum (equilibrium) concentration of the solute in solution, which for a 50-ml container configuration is approximately 0.8 ppm. This value agrees favorably with the maximum solute concentration observed in the actual test container samples studied (Table I).

The quantitative assessment of the test solute's accumulation in solution as a function of product storage time requires the mathematical combination of the diffusion and degradation rate equations. Considering each process separately, small-molecule migration from a polymer sheet (i.e., the container) into an essentially infinite bath (the contained solution) can be modeled by the following simplifications of equations derived to relate the amount of solute released from a polymer (M_t) and storage time (t) (7,9,10). For short storage intervals (for which $M_t/M_\infty < 0.6$),

$$M_t/M_\infty = 4\,(Dt/\pi\delta^2)^{1/2} \tag{7}$$

For long periods of storage (for which $M_t/M_\infty > 0.6$),

$$M_t/M_\infty = 1 - (8/\pi^2)\exp(-\pi^2 DT/\delta^2) \tag{8}$$

where M_t is the amount of diffusant lost to solution at time t and M_∞ is the equilibrium desorption attained theoretically at infinite time (and is related to the total available pool and E_b). In this study, we use the short time approximation to model the container/solution interaction.

The test solute degrades in solution via hydrolysis and the hydrolysis is first order with respect to the solute's concentration. The degradation kinetics are summarized in Eq. (1) and the relationship among k_{obs}, temperature, and pH is given in Eq. (3).

The actual test solute concentration in solution can be predicted via a linear combination of Eqs. (1) and (7). Such a combination is derived in the following mathematical treatment. Consider that a product's shelf life (T_s) can be divided into numerous small, equally sized time elements (T_p) where $T_s >>> T_p$. Furthermore, assume that T_p is sufficiently small that no significant solute degradation occurs during the first time interval. For the first time interval (ending at t_1), $C_0 = 0$ and C_1, the solute's solution phase concentration at t_1, becomes [from Eq. (7)]

Table I. Experimentally Determined Accumulation of the Test Solute in Solution, 50-ml Container Configuration

	Mean solute concentration (ppm)[a] at a storage time of				
pH	1 week	3 weeks	6 weeks	9 weeks	12 weeks
		(1) Storage at 25°C			
2	0.40	0.33	0.36	0.18	0.07
3	0.40	0.54	0.57	0.62	0.54
4	0.46	0.47	0.53	0.50	0.51
		Storage at 65°			
2	0.03	ND[b]	ND	ND	ND
3	0.50	0.27	0.16	0.09	0.07
4	0.42	0.28	0.35	0.28	0.23

[a] Mean of three units tested per interval.
[b] Not detected.

$$C_1 = M_1/V = (4M_\infty/V)\,[(D/\pi\delta^2)^{1/2}\,](t_1)^{1/2} \tag{9}$$

For the second time interval (beginning at t_1 and ending at t_2) the amount of solute released from the container is still diffusion controlled. Thus,

$$M_2 = 4M_\infty\,(D/\pi\delta^2)^{1/2}(t_2)^{1/2} \tag{10}$$

However, C_2 does not equal M_2/V since some solute has degraded during this time interval. Since the time interval is small (and the concentration change from degradation is small), the magnitude of solute loss ($M_{L,2}$) can be approximated from Eq. (1) as

$$M_{L,2} = (C_1 - C_2)V$$

or

$$M_{L,2} = C_1\{1 - \exp([-k(t_2 - t_1)]\}V \tag{11}$$

Combining Eqs. (9) and (11) produces Eq. (12):

$$M_{L,2} = (4M_\infty/V)\,(D/\pi\delta^2)^{1/2}(t_1)^{1/2}\{1 - \exp[-k(t_2 - t_1)]\} \tag{12}$$

The concentration of the test solute in solution after time t_2 becomes

$$C_2 = M_2/V - M_{L,2}/V$$

or

$$C_2 = [(4M_\infty/V)\,(D/\pi\delta^2)^{1/2}]\,[t_2^{1/2} - t_1^{1/2}\{1 - \exp[-k(t_2 - t_1)]\}] \tag{13}$$

In general, the concentration of solute in solution after the nth interval (where each time interval lasts Δt units), C_n, becomes

$$C_n = A(n\Delta t)^{1/2} - \sum_{i=1}^{n} At_{i-1}^{1/2}\,[1 - \exp(-k\Delta t)] \tag{14}$$

where

$$A = [4M_\infty(D/\pi\delta^2)^{1/2}]/V$$

For the test solute/polymer system, D, δ, V, and k are known, while M_∞ is essentially the product of the partition-mediated maximum solution concentration and V. Thus Eq. (14) can be used to calculate C_n for the 50-ml container configuration and the resulting model can be compared to actual measured accumulation data (Table I). The comparisons of greatest interest will be those wherein both diffusion and degradation contribute significantly to the accumulation process. Such is the case of 25°C, pH 2, and 65°C, pH 3, wherein a rapid initial solute buildup is essentially depleted by solute degradation at longer storage times. Under the other storage conditions studied, either diffusion or degradation dominates the accumulation profile. For example, at 25°C and pH greater than 3, degradation is sufficiently slow that the solution concentration of the test solute builds up to its equilibrium value and essentially stays there as storage time increases (essentially the kinetics are shut down after the equilibrium concentration has been achieved). Alternatively, at 65°C and pH 2, degradation is so rapid that all the test solute degrades immediately upon release from the container. In this case the solution phase concentration of the test solute

is never large and the total pool of the solute is rapidly depleted.

Predicted versus actual concentration accumulation profiles for the 50-ml container configuration, obtained for the storage conditions for which both diffusion and degradation impact the accumulation, are shown in Figs. 5 and 6. Predicted concentrations are obtained using Eq. (14), decomposition rate constants per Eq. (3), and the total available pool, diffusion coefficient, and binding constant presented previously. In both cases, solutes accumulate in solution (diffusion-controlled rate) until the solution phase concentration is sufficiently high that hydrolysis becomes a kinetically important process. Considering the large relative cumulative error associated with this comparison, the model adequately predicts the experimentally observed behavior. For both storage conditions examined, the model effectively predicts the initial rise and subsequent depletion in solution concentration. In fact, the model does provide a useful approximation of the solute's behavior in the polymer–solution system.

The actual dynamics contributing to the shape of the accumulation profiles shown in Figs. 5 and 6 are delineated in relative release plots for the same storage conditions (Figs. 7 and 8). In these figures, the actual solution phase concentration is presented as a fraction of the partition-mediated maximum (equilibrium) solution concentration, while the total amount of solute released from the container is presented as the fraction of the container's total available pool. At 25°C, the rate of diffusion is such that only approximately 60% of the container's total available pool is released over the 140-day model period. At very short storage times (t less than 10 days) the test solute accumulates in solution as diffusion controls the solution chemistry. However, the solution concentration rapidly becomes sufficiently high that the concentration-dependant degradation rate becomes an important factor controlling solution composition. In fact, the degradation process becomes kinetically important so early in the storage interval (at approximately 10 days) that the solute's concentration never reaches its partition mediated equilibrium value. After 10 days of storage, the concentration of the test solute decreases until the diffusion and degradation rates become nearly equal and a kinetic equilibrium is established (after approximately 100 days of storage). Kinetic equilibrium will persist until the total available pool is exhausted, at which point the solution concentration of solute will decrease at a rate dictated by the degradation kinetics. It may be estimated that the total available pool of the 50-ml container will be exhausted after approximately 240 days of storage and that, at 365 days of storage, the solution concentration of the test solute will be less than 10 ppb.

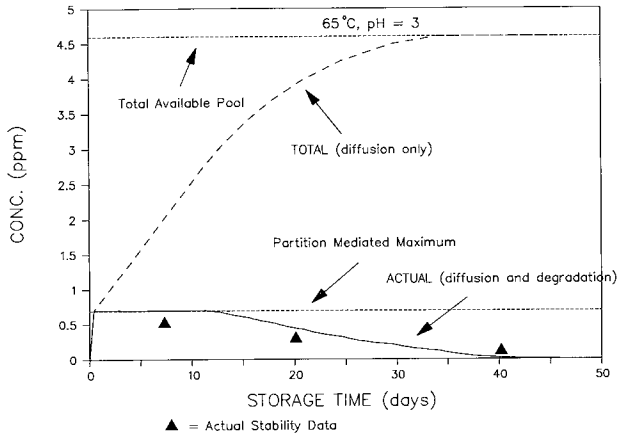

Fig. 6. Observed versus predicted accumulation profile; concentration of the test solute in solution versus storage time. Storage temperature = 65°C, solution pH = 3. See Note, legend to Fig. 5, for explanation of "total" line.

At 65°C and pH 3, the solute's solution phase lifetime is compressed because of faster diffusion and decomposition rates under these conditions. The degradation rate is increased by both the effect of temperature on the rate constant and the fact that since the diffusion rate is faster at this temperature, the solute concentration in solution will be greater than at an equivalent time at a lower temperature. In fact, the increase in temperature from 25 to 65°C produces a much larger change in the diffusion coefficient (approxi-

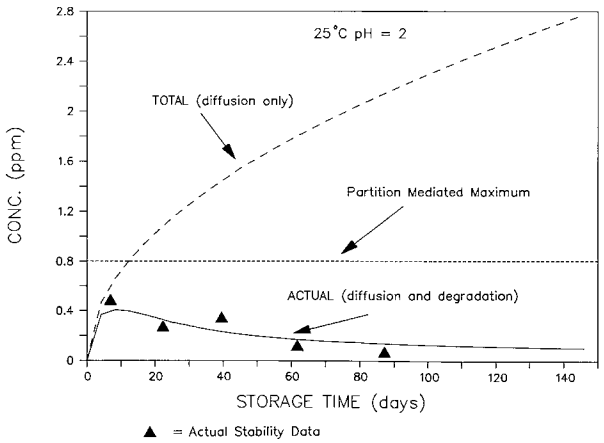

Fig. 5. Observed versus predicted accumulation profile; concentration of the test solute in solution versus storage time. Storage temperature = 25°C, solution pH = 2. Note: "total" line represents accumulation which is diffusion-controlled and not limited by partitioning (total release of available pool).

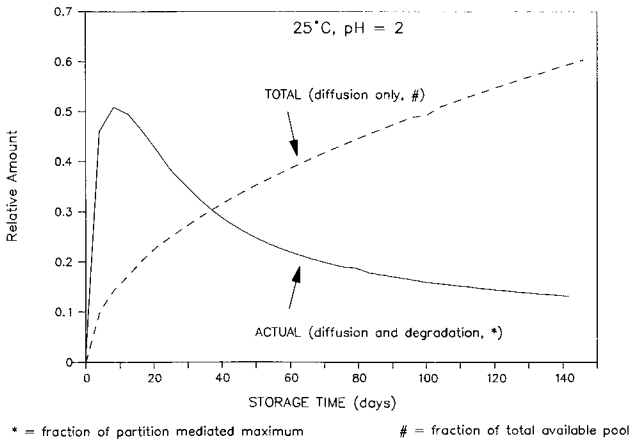

Fig. 7. Predicted accumulation profiles, relative solution concentration, and total amount of solute released as a function of storage time. Storage temperature = 25°C, solution pH = 2.

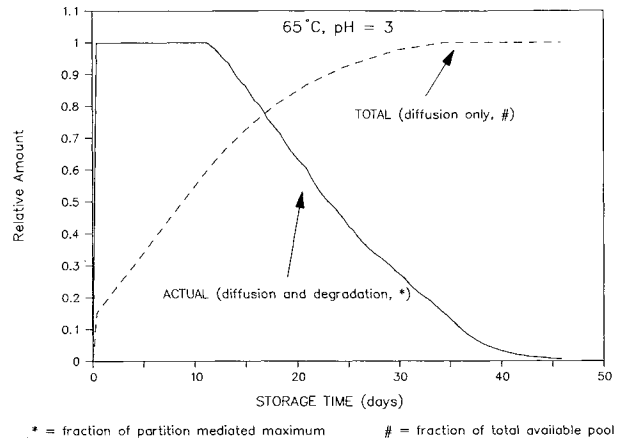

Fig. 8. Predicted accumulation profiles, relative solution phase concentration, and relative total amount of solute released as a function of storage time. Storage temperature = 65°C, solution pH = 3.

mately a factor of 200) than the combined effect of temperature and pH produces on the hydrolysis rate constant (approximately a factor of 4). The net result is that the diffusion-controlled release of solute from the container rapidly outpaces its solution phase degradation. Thus for short periods of storage time (T less than 15 days), the solute's concentration "equilibrates" at the partition-mediated maximum and a large fraction of the container's total available pool is depleted. After 15 days, the diffusion-controlled release of the solute from the container decreases (since at $M_t/M_\infty > 0.6$ the rate expression changes) and the continued rapid degradation of the solute results in a rapid decrease in the solute concentration. At approximately 30 days of storage, the total available pool is exhausted and the solution concentration of solute continues to decrease at a rate dictated by the degradation kinetics. After approximately 50 days of storage, the solution concentration of the solute is less than 10 ppb.

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