Kinetics of Release of Particulate Solutes Incorporated in Cellulosic Polymer Matrices as a Function of Solute Solubility and Polymer Swellability. I. Sparingly Soluble Solutes

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ABSTRACT: A comparative study has been made of the kinetics of release into water of simple hydrophilic, but sparingly soluble, solutes (exemplified by $CaSO_4$ or $SrSO_4$) incorporated in varying amounts in cellulosic polymer matrices of low or high water swellability. Hydrophobic cellulose acetate films (cast from an acetone dope containing a dispersion of the appropriate salt particles occupying a fractional volume $\varepsilon_N = 0.1$–0.4 in the loaded hydrated matrix) were found to be particularly useful for this purpose because they could be easily hydrolyzed to cellulose, thus producing hydrophilic polymer matrices containing identical amounts and distributions of solute particles. The kinetic behavior observed exhibited the same main features as previously noted in drug release studies. Thus, a $\sqrt{t}$ kinetic law was obeyed in all cases (apart from a relatively short initial period), while the diffusion coefficient calculated by application of the Higuchi model tended to rise with increasing solute load. This tendency was very strong in the case of the hydrophobic weakly swollen matrix and much weaker in the case of the hydrophilic one. On the reasonable assumption that the diffusion of solute in the salt-depleted matrix (which controls the release rate) occurs via aqueous pathways, the tortuosity τ of these pathways was calculated and found to attain extremely high values in the case of lightly loaded ($\varepsilon_N = 0.1$) matrices. These high τ values were drastically reduced upon either (1) increase of the salt load or (2) hydrolysis to cellulose. This behavior is shown to result from the fact that at $\varepsilon_N = 0.1$, the salt particles were fully coated with cellulose acetate so that water taken up to fill the space vacated by released salt is in the form of globules dispersed in a weakly hydrated polymer matrix and, hence, is ineffective in providing continuous aqueous pathways. In (1), these globules are increasingly bridged by gaps left in the original loaded matrix, as a result of incomplete coating of the solute particles with polymer. In (2), bridging is similarly effected by the formation of aqueous pathways through the polymer when its degree of hydration is sufficiently increased. J Appl Polym Sci **67:** 277–287, 1998

Key words: release kinetics; monolithic controlled release systems; salt permeability of cellulosic polymers; leaching of solidified radioactive wastes

INTRODUCTION

Proper understanding of the effect of various factors on the rate and kinetics of release of solutes embedded in polymeric matrices is needed for (1) intelligent design of monolithic drug (or other chemical) controlled release devices[1] and (2) evaluation of the long-term environmental radioactive pollution hazard arising from accidental contact of "solidified" radioactive wastes with groundwater at the disposal site.[2] In either case, the solute in the monolithic device is in immobilized form;

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and its release is initiated when the said device is contacted by a liquid leachant (the solvent), usually water, which can penetrate and swell the matrix to a greater or lesser extent.

In a previous article,[3] we proposed an improved general theoretical model for this type of release process, taking proper account of the uptake of the solvent by the polymer matrix concurrently with the release of the solute. A simple limiting case arises if (1) the extent of swelling and the rate of solvent penetration in the polymer is not materially affected by the presence of solute and (2) solvent penetration is fast by comparison with solute transport (or the matrix is preswollen with solvent). Then the release is rate-controlled by diffusion of the solute in the fully swollen matrix. These conditions hold for sparingly water-soluble solutes leached out by water. $CaSO_4$ and $SrSO_4$ have been used here as examples of such solutes. Complications arise in the case of highly water-soluble solutes, which will be considered in a forthcoming article.

Any reasonable loading of a polymer matrix (represented by C_{NO} in g/cm^3 of water-swollen polymer) with either of the aforementioned sparingly soluble salts may be expected to exceed greatly the salt solubility in the water-swollen matrix, which is defined as the concentration of solute C^0_{NS} (expressed in the same units as C_{NO}) reversibly absorbed by the swollen polymer from the corresponding aqueous saturated solution of concentration c^0_{NS}. Any amount of solute present in the matrix in excess of C^0_{NS} is commonly in an immobile finely dispersed state and is considered to be at equilibrium with the solute dissolved therein.[4,5] On the reasonable assumption that no significant variation of the degree of swelling of the polymer occurs during the release experiment, the amount of solute M_{Nt} released at time t from a solid matrix, in the form of a thin film (of thickness 2ℓ and cross-sectional area A) with both surfaces exposed to a well-stirred bath of solvent, is given for the case of $C_{NO} \gg C^0_{NS}$ of interest here by[4,5]

$$M_{Nt}/M_{N\infty} = (2D_N C^0_{NS} t/\ell^2 C_{NO})^{1/2} \qquad (1)$$

where $M_{N\infty} = 2A\ell C_{NO}$ is the total amount of the solute initially present in the solid matrix, and D_N is the diffusion coefficient of the solute in the swollen solute-depleted matrix.

Equation (1) may also be written as[6]

$$M_{Nt}/M_{N\infty} = (2P_N c^0_{NS} t/\ell^2 C_{NO})^{1/2} \qquad (1a)$$

where the permeability P_N of the solute in the matrix is given by

$$P_N = D_N K = D_N C^0_{NS}/c^0_{NS} \qquad (2)$$

In eq. (2), K is the partition coefficient defined as $K = C_{NS}/c_{NS}$ (where C_{NS} is the concentration of the solute in the polymer matrix, which would be in equilibrium with an external solution of concentration c_{NS}) and is assumed to be constant. If C^0_{NS} is not known, P_N is the only parameter that can be determined unambiguously from the M_{Nt} data.

Drug release kinetics from both hydrophilic and hydrophobic polymer matrices has been studied experimentally quite extensively, and linearity of the amount released versus $\sqrt{t}$ has generally been observed. In the case of hydrophilic[7–9] or highly porous matrices,[10] eq. (1) describes the release kinetics satisfactorily; but the dependence on C_{NO} is often not predictable on the assumption of a D_N value independent of solute load. In particular, enhanced release rates have been noted for high loads, indicating a clear tendency of D_N to rise with increasing solute content.[7,9] In the case of hydrophobic matrices, the aforementioned tendency tends to be much more marked and release rates much lower than anticipated have been reported for low solute loads.[11–14]

In the present work, the chosen solutes were incorporated in a hydrophobic cellulose acetate matrix, which could be turned into a hydrophilic one by hydrolysis, thus affording the opportunity of comparing kinetic release behavior from hydrophobic and hydrophilic matrices carrying the same solute load and solute particle distribution.

EXPERIMENTAL

Materials

Cellulose acetate of 39.8% (by wt) acetyl content was obtained in powder form from Eastman Chemicals (Switzerland; type CA-398-30) with the following specifications: melting range, 230–250°C; T_g, 189°C; density, 1.31 g/cm^3; and viscosity [measured according to ASTM D-871 (Formula A) and D-1343], 114 poise (30 s).

Powdered $CaSO_4$ of particle size 10–20 μm (obtained from $CaSO_4 \cdot 2H_2O$ by dehydration at 400°C) and $SrSO_4$ of 2 μm approximate particle size were of analytical reagent grade. In both cases, the portion of the powder passing through

a sieve of nominal opening diameter 25 μm was used.

Preparation of Salt-Loaded Polymer Matrices

Salt-loaded cellulose acetate matrices, in the form of films 150–350 μm thick, were prepared by dissolving the polymer (up to 20% by wt) in a stirred dispersion of the appropriate amount of salt in acetone, stirring the viscous mixture for four more hours in a closed vessel (to prevent evaporation of acetone) and casting on a horizontal glass plate by means of a knife blade running parallel to the plate. The acetone solvent was then allowed to evaporate slowly in the atmosphere, and the evaporation was completed *in vacuo*.

The corresponding salt-loaded cellulose matrices were obtained by hydrolyzing pieces of the above-dried cellulose acetate films. The latter (10 cm^2 in size) were immersed in a 0.5% methanolic solution of sodium methoxide for several hours to ensure complete elimination of acetyl groups. The films were then hydrolyzed at 40°C in water saturated with $CaSO_4$ or $SrSO_4$ to prevent any loss of salt from the film. The weight loss suffered by the dry polymer film following this treatment was found to be 39%, confirming complete elimination of acetyl groups.

Release Tests

The salt-containing polymer film (ca. 3×3 cm^2) was mounted on a vertical frame fixed to a stirring rod rotating at a rate of 250–300 rpm in a known volume of distilled water thermostatted at 25°C and renewed at frequent intervals. Cellulose acetate films were preswollen in a $CaSO_4$- or $SrSO_4$-saturated aqueous solution for about 1 h and then blotted with filter paper before commencement of the release test. Cellulose films were used in the as-prepared swollen state. The water content of each film was estimated from the loss in weight of the blotted swollen film when dried to constant weight in an oven at 105°C (Table I). The salt concentration in the desorbing bath was determined by atomic absorption of the relevant cations using a Perkin–Elmer 2380 Atomic Absorption Spectrophotometer and was not allowed to exceed 3 or 10% of the concentration of the saturated solution in the case of $CaSO_4$ ($c^0_{NS} = 2.55$ g/dm^3) or $SrSO_4$ ($c^0_{NS} = 0.114$ g/dm^3), respectively.

The amount of $CaSO_4$ or $SrSO_4$ remaining in the sample at the end ($t = t_f$) of the release test was determined by igniting the film at 600°C. The result of this analysis, together with the total amount eluted, gave a more accurate estimate of the initial salt content of the polymer ($M_{N\infty}$) than that observed from the original weights (in view of the possibility of small losses during sample preparation and/or inaccuracies in measuring the dimensions of the sample cut from the cast film).

Composition of the Salt-Loaded Polymer Matrices Used

To facilitate comparison of results obtained from matrices loaded with $CaSO_4$ and $SrSO_4$, care was taken to prepare films containing very nearly the same fractional volume of salt, $\varepsilon_N = V_N/V$ (where $V_N = M_{N\infty}/\rho_N$ and V are the volumes of the salt load and of the loaded swollen matrix, respectively; and the density of solid salt is $\rho_N = 2.96$ or 3.96 g/cm^3 for $CaSO_4$ or $SrSO_4$, respectively). The corresponding fractional volume of water imbibed by the salt-loaded matrix ε_W was determined gravimetrically, as described above. The composition of the loaded matrices used is shown in Table I.

The volume of the swollen matrix V was estimated accurately from the weights of salt, of dry polymer, and of imbibed water. In the case of cellulose, which is highly swollen by water, additivity of the volume of water and of the dry polymer (density 1.6 g/cm^3)[15] could reasonably be assumed. For the weakly swollen cellulose acetate, however, density measurements on the neat (salt-free) water-swollen films showed that 1 cm^3 of dry cellulose acetate absorbs 0.193 cm^3 of water; but the resulting volume dilation amounts to only 0.155 cm^3, in close agreement with the results of Scherer and Bailey.[16]

As shown in Table I, the equilibrium water regain of loaded cellulose acetate films (expressed in g/g of dry polymer) is generally in excess of the amount (=0.148 g/g) required to hydrate the polymer and increases with the salt content (being higher in the case of $SrSO_4$). This excess water uptake, which occupies a fractional volume ε_g, no doubt represents filling of gaps between salt particles not penetrated by polymer in the original dry film. Thus, the volume of swollen cellulose acetate films is the sum of the volumes of embedded salt, of hydrated polymer, and of water filling any gaps between the hydrated polymer matrix and embedded salt particles.

RESULTS

Representative kinetic release curves of $CaSO_4$ or $SrSO_4$ are shown in Figures 1–3. Good reproduc-

Table I Composition of Hydrated Salt-Loaded Polymer Matrices Used

Polymer–Salt System	Weight Fraction of Salt in Dry Matrix	Water Regain (g/g)	ε_N	ε_W	ε_g
Cellulose acetate–$CaSO_4$	0.207	0.148	0.091	0.152	0
	0.436	0.156	0.228	0.135	0.007
	0.610	0.180	0.367	0.125	0.023
Cellulose acetate–$SrSO_4$	0.255	0.155	0.089	0.155	0.007
	0.508	0.173	0.224	0.146	0.024
	0.683	0.199	0.368	0.134	0.036
Cellulose–$CaSO_4$	0.301	0.635	0.103	0.452	—
	0.552	0.627	0.250	0.376	—
	0.721	0.638	0.409	0.299	—
Cellulose–$SrSO_4$	0.628	0.650	0.250	0.382	—

ibility was found between duplicate samples taken from the same film as well as between samples from different films. All plots conform to the $\sqrt{t}$ kinetics predicted by eq. (1) reasonably well, apart from short curved initial portions (not shown in detail in the figures for reasons of clarity), which are most prominent in cellulose acetate films containing low or moderate salt loads. In these cases (see Figs. 1 and 2), the aforementioned deviations from $\sqrt{t}$ kinetics represent an initial stage of enhanced release, attributable to salt located at (or very near) the surface of the film, which is liable to be less well coated with hydrophobic polymer and, hence, more exposed to leachant. This interpretation is supported by the fact that the total excess amount M_{N0} of solute released in this way (determined by the extrapolation of the linear plot to $t = 0$ in Figs. 1 and 2) is independent of the thickness of the film, as shown in Table II. Furthermore, enhanced initial

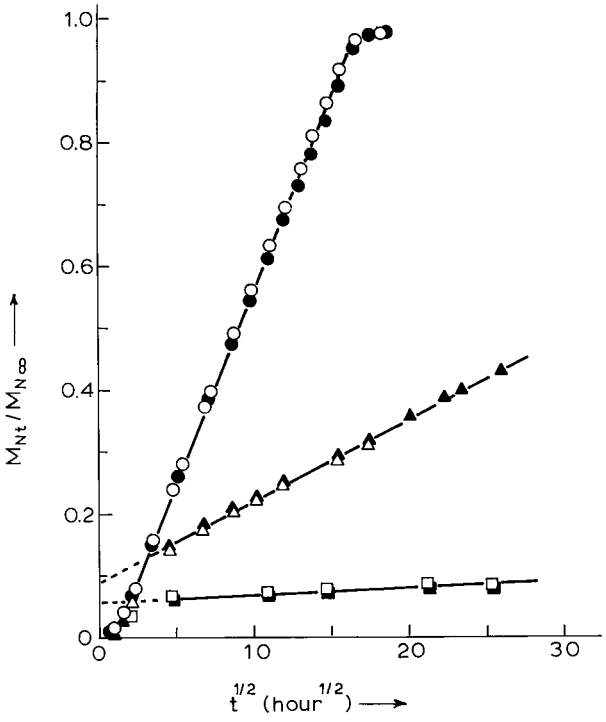

Figure 1 Release kinetics of $CaSO_4$ from duplicate samples of cellulose acetate film containing a fractional volume of salt $\varepsilon_N = 0.091$ (■, □), 0.228 (▲, △), or 0.367 (●, ○). Hydrated film thicknesses are as follows: 325 (■, □), 310 (▲, △), or 341 (●, ○), μm.

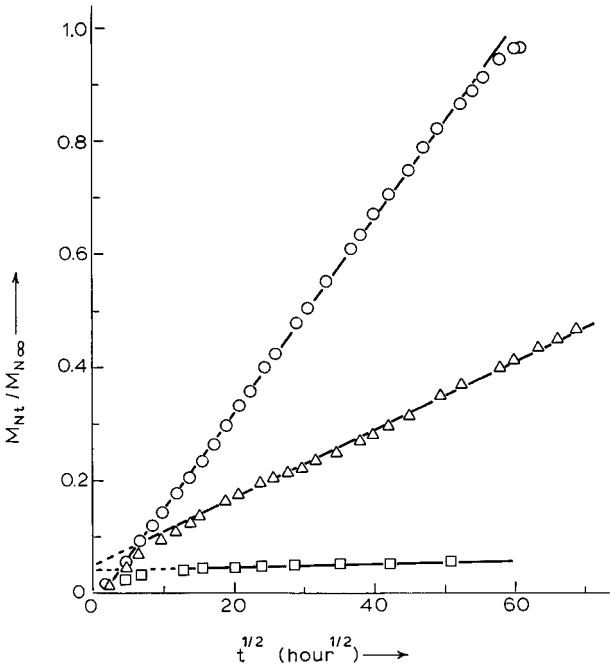

Figure 2 Examples of release kinetics of $SrSO_4$ from cellulose acetate films containing a fractional volume of salt $\varepsilon_N = 0.089$ (□), 0.224 (△), or 0.368 (○). Hydrated film thicknesses are as follows: 335 (□), 342 (△), or 350 (○) μm.

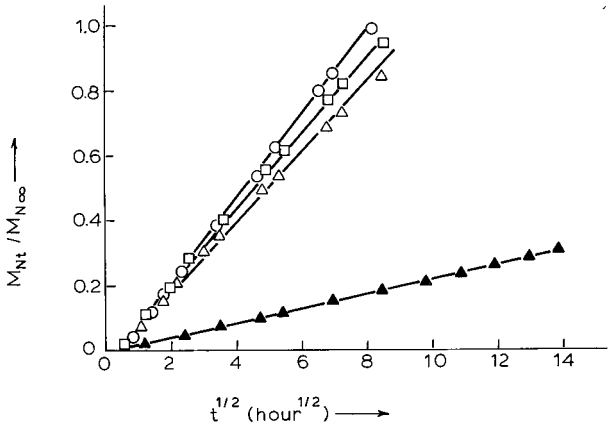

Figure 3 Examples of release kinetics of $CaSO_4$ (□, △, ○) or $SrSO_4$ (▲) from cellulose (fully hydrolyzed cellulose acetate) films containing a fractional volume of salt ε_N = 0.103 (□), 0.250 (△, ▲), or 0.409 (○). Hydrated film thicknesses are as follows: 310 (□, △) or 330 (○, ▲) μm.

salt release is not seen in cellulose acetate films containing large salt loads, where the solute particles may be expected to be incompletely coated with polymer throughout the film (see the following section for a detailed discussion of release kinetic behavior).

Early enhanced release at low loads, which disappears at high loads, was also observed by Siegel et al.[17] in their study of macromolecular drug release from hydrophobic polymer matrices prepared in a manner similar to that used by us. In the present article, we further show that the initial stage of enhanced release also disappears upon hydrolysis of the cellulose acetate matrix to cellulose (see Fig. 3). Here again, the salt particles are brought into good contact with leachant throughout the film because of the large increase in the hydration of the polymer matrix. Note, incidentally, that both the highly loaded cellulose acetate films and the cellulose films at all salt loads exhibit a slight, but definite, initial stage of delayed release. This is consistent with a tendency of the solute particles to be more concentrated in the interior than near the surface of the polymer film (as demonstrated by scanning electron microscopy in the case of the discs used by Siegel et al.[17]).

For cellulose acetate, the slope of the main linear $M_{Nt}/M_{N\infty}$ versus $\sqrt{t}$ plot (Figs. 1 and 2) is strongly dependent on the salt content of the film, in contrast to what is observed in the case of the corresponding cellulose films (Fig. 3). Moreover, in the latter case, release rates are much faster, in line with the much higher water content of these films (see Table I). Figures 1–3 also show that the release rates for a given fractional volume of salt ε_N are considerably higher for the more soluble $CaSO_4$.

In those cases where release of salt was carried to completion, practically the whole elution curve conformed to the $\sqrt{t}$ law. This is consistent with (1) the condition $C_{NO} \gg C^0_{NS}$, which, as previously indicated, undoubtedly applies here for both polymeric matrices (although C^0_{NS} for cellulose is markedly higher than that for cellulose acetate, the condition $C_{NO} \gg C^0_{NS}$ is still valid); and (2) the fact that (in contrast to what is observed in the case of soluble salts) no significant variation in degree of swelling of the polymer was found to occur during the release experiment. As shown in Table III, the fractional volume of water ε_W in the swollen matrix increases during the release experiment; but $\varepsilon_N + \varepsilon_W$ measured at the beginning and at the end of the release experiment remains unchanged within experimental error, indicating that additional water is taken up only to fill the volume vacated by salt particles.

Evaluation of P_N by eq. (1a) gave the results displayed in Table IV, which show that the changes in the slope of the $M_{Nt}/M_{N\infty}$ versus $\sqrt{t}$ plot resulting from variation of the salt load reflect primarily an accompanying marked change in P_N

Table II Amount of $CaSO_4$ Released During the Initial Stage of Enhanced Release from Cellulose Acetate Films of Different Thickness

ε_N	C_{NO} (g/cm^3)	Hydrated Film Thickness (μm)	$(M_{N0}/2A) \times 10^3$ (g/cm^2)	$M_{N0}/M_{N\infty}$
0.091	0.269	325	0.26	0.060
0.090	0.267	160	0.24	0.117
0.228	0.676	310	0.99	0.083
0.224	0.662	175	0.90	0.143

Table III Fractional Volume of Salt and Water at the Beginning ($t = 0$) and at the End ($t = t_f$) of Various Release Experiments

Polymer–Salt System	ε_N ($t = 0$)	$\varepsilon_N + \varepsilon_W$ ($t = 0$)	t_f (h)	$M_{Nt}/M_{N\infty}$ ($t = t_f$)	ε_N ($t = t_f$)	$\varepsilon_N + \varepsilon_W$ ($t = t_f$)
Cellulose acetate–$CaSO_4$	0.091	0.243	440	0.08	0.084	0.245
	0.228	0.363	320	0.31	0.157	0.351
	0.367	0.492	320	0.97	0.011	0.474
Cellulose acetate–$SrSO_4$	0.089	0.248	2500	0.06	0.084	0.252
	0.224	0.372	4700	0.47	0.119	0.368
	0.368	0.503	3700	0.97	0.011	0.504
Cellulose–$CaSO_4$	0.103	0.555	74	0.94	0.006	0.536
	0.250	0.626	80	0.93	0.018	0.610
	0.409	0.708	74	0.98	0.008	0.690
Cellulose–$SrSO_4$	0.250	0.632	195	0.30	0.175	0.618

(largely due, no doubt, to a corresponding change in D_N) extending over as much as four orders of magnitude in the case of the cellulose acetate matrices. Analogous observations relating to drug release from hydrophobic polymer matrices have been reported previously,[11–14] as indicated in the introductory section.

DISCUSSION

For the interpretation of the above results, it should first be noted that, according to the theoretical approach underlying eq. (1),[3–5] the release process is controlled by diffusion of solute in the dissolved state across a layer of the swollen matrix fully depleted of solid solute. Physically, this diffusion process has been pictured as proceeding through a water-filled pore network, wherein the solute can dissolve to the same extent as in bulk water.[4,5] Assuming that the said pore network comprises the water imbibed by the original dry salt-loaded film, as well as that filling the gaps left behind by the released solid solute, the total porosity of the salt-depleted matrix is given by

$$\varepsilon = \varepsilon_W + \varepsilon_N \tag{3}$$

and

$$C^0_{NS} = Kc^0_{NS} = \varepsilon c^0_{NS} \tag{4}$$

hence

$$D_N = P_N/K = P_N/\varepsilon \tag{5}$$

Since diffusion is deemed to occur in an aqueous

Table IV Release Kinetic Parameters as a Function of Salt Load

Polymer–Salt System	ε_N	Hydrated Film Thickness (μm)	P_N (cm^2/s)	ε	D_{N1} (cm^2/s)	D_{N2} (cm^2/s)	τ_1	τ_2
Cellulose acetate–$CaSO_4$	0.091	325	5.7×10^{-12}	0.243	2.4×10^{-11}	5.8×10^{-11}	370,000	150,000
	0.228	310	1.4×10^{-9}	0.363	3.8×10^{-9}	5.4×10^{-9}	2,400	1,600
	0.367	341	7.2×10^{-8}	0.492	1.5×10^{-7}	1.8×10^{-7}	60	50
Cellulose acetate–$SrSO_4$	0.089	335	1.8×10^{-11}	0.248	7.4×10^{-11}	1.8×10^{-10}	120,000	50,000
	0.224	342	9.6×10^{-9}	0.372	2.6×10^{-8}	3.8×10^{-8}	350	240
	0.368	350	2.1×10^{-7}	0.503	4.2×10^{-7}	5.1×10^{-7}	21	18
Cellulose–$CaSO_4$	0.103	310	5.7×10^{-8}	0.555	1.0×10^{-7}	—	90	—
	0.250	310	1.2×10^{-7}	0.626	1.9×10^{-7}	—	47	—
	0.409	330	3.0×10^{-7}	0.708	4.3×10^{-7}	—	21	—
Cellulose–$SrSO_4$	0.252	330	2.0×10^{-7}	0.632	3.2×10^{-7}	—	28	—

Subscripts 1 and 2 are used to denote values of D_N and τ on the basis of eqs. (4) and (4a), respectively.

environment, D_N has been related to the diffusion coefficient in aqueous solution D_{NS}, modified by a tortuosity factor τ[11–13] (which must be understood to include not only the tortuosity of pores but also other geometrical features, such as pore constrictions or blind porosity, which impede transport through the pore network as compared with diffusion in bulk water),[13,14] namely

$$D_N = D_{NS}/\tau \quad (6)$$

Application of the above treatment [with $D_{NS} \cong 9 \times 10^{-6}$ cm^2/s for both $CaSO_4$ and $SrSO_4$, evaluated from the Nernst equation for dilute electrolyte solutions; see eq. (8-40) in Reid and Sherwood[18]] to our results gave the values D_{N1} and τ_1, shown in Table IV.

However, for the sake of accuracy, it should be borne in mind that eq. (4) may be considered to be appropriate only for highly swollen matrices, like cellulose here.[3,19] In the case of hydrophobic polymer matrices, it is unrealistic to treat the water of hydration of the neat polymer (occupying a fractional volume $\varepsilon_{WP} = \varepsilon_W - \varepsilon_g$ in the swollen loaded matrix) as having the solvent properties of bulk water.[3] On one hand, the low amount of water of hydration present tends, to a very large extent, to be dispersed in the polymer either molecularly or in the form of small clusters of molecules.[20] On the other hand, even if the presence of continuous narrow water-filled pores could be assumed in the neat polymer, a strong "exclusion effect" would still be expected in the case of strongly polar solutes, which are of interest here[21–23] (see below also). For this reason, eq. (4) should be replaced by[3]

$$C^0_{NS} = Kc^0_{NS} = (k_s\varepsilon_{WP} + \varepsilon_g + \varepsilon_N)c^0_{NS} \quad (4a)$$

where k_s is the ratio of salt concentration in the water of hydration of the neat polymer to that in the external salt solution concentration at equilibrium; k_s is close to unity in highly swollen polymers but tends to decrease as the hydration of the polymer is reduced.[3,19]

Measurement of $CaSO_4$ uptake by equilibrating neat cellulose acetate films with saturated $CaSO_4$ solutions gave $k_s = 0.06$, in reasonable agreement with the results for other bibivalent salts reported by Heyde et al.[23] for cellulose acetate of this type. Use of eq. (4a) instead of eq. (4) gave the values D_{N2} and τ_2 shown in Table IV, which are respectively higher and lower than D_{N1} and τ_1. However, the general picture remains the same: the calculated tortuosity increases with diminishing solute load to extremely high values in the case of cellulose acetate, which are drastically reduced upon hydrolysis to cellulose matrices. In our view, only the τ values recorded in the latter case may conceivably be considered consistent with a continuous (albeit still highly constricted or poorly connected) pore network. Values of τ over 1000 have also been recorded in studies of drug release from a variety of hydrophobic polymer matrices[11–13]). So this is a general phenomenon attributable to the fact that, at low solute loads (and assuming that reasonably good dispersion of solute particles in the polymer matrix has been achieved), the said particles are well coated with polymer. Hence, the volume vacated by the eluted solute is in the form of microscopic gaps or holes largely isolated from one another by the intervening weakly hydrated neat polymer matrix ($\varepsilon_W = 0.16$ for neat cellulose acetate), which can hardly be assumed to be traversed by water-filled pores (as noted above). For the particular case of cellulose acetate of interest here, this is clearly demonstrated by the fact that attempts to apply standard flow methods of estimating pore size yield mean effective cylindrical pore diameter values of molecular dimensions ($\sim$ 0.5 nm).[24,25] As the solute load increases, however, neighboring microscopic holes approach one another and occasionally join together (where penetration of viscous polymer solution between the original salt particles could not occur during preparation of the specimen), thus eventually forming a reasonably well-connected continuous pore network only when ε_N becomes sufficiently high.

On the other hand, the results obtained from the aforementioned method of pore size estimation for the highly hydrated ($\varepsilon_W = 0.51$ for the neat polymer) cellulose matrix are consistent with the picture of a continuous water-filled pore system of mean effective pore diameter in the mesopore range ($\sim$ 3 nm),[24,26] which can effectively bridge the isolated holes left behind by an eluted low salt load, thus suppressing the high τ values found in the case of identical lightly loaded cellulose acetate matrices.

Comparison of the results for $CaSO_4$ and $SrSO_4$ in Table IV shows that $P_N(CaSO_4) < P_N(SrSO_4)$ and $\tau(CaSO_4) > \tau(SrSO_4)$. These differences are particularly pronounced for the cellulose acetate matrices and correlate with the higher ε_g values (indicative of more frequent occurrence of gaps between the salt particles), which were shown previously to characterize the $SrSO_4$-loaded matrices (see Table I). This would be consistent with

a more pronounced tendency of the $SrSO_4$ particles to form aggregates that cannot be easily penetrated by the viscous polymer solution. Microscopic examination confirmed that this was indeed the case as a result of the fact that the $SrSO_4$ particles tended to be rough and irregularly shaped, in contrast to the smooth crystalline $CaSO_4$ particles. Furthermore, the fact that sieving of the $SrSO_4$ powder required much longer time than that of the $CaSO_4$ powder, in spite of the fact that the individual particles of the former were markedly smaller than those of the latter (see experimental section), is a clear indication that the $SrSO_4$ aggregates could not be easily broken up mechanically.

It is worth noting that, in spite of the aforementioned differences in P_N, the rates of release of $SrSO_4$ are (as noted in the preceding section) lower than those of $CaSO_4$, due to the fact that the operative rate parameter, according to eq. (1a), is $P_N c^0_{NS}$; thus, the higher water solubility of the latter salt more than compensates for the lower permeability of the $CaSO_4$-loaded matrices.

Another way of interpreting the behavior of P_N (which seems to us more appropriate for relatively lightly loaded matrices) is to regard the hydrated salt-depleted matrix as a binary composite medium, consisting of a hydrated neat polymer continuum of permeability P_{NM} (occupying a volume fraction $\varepsilon_M = 1 - \varepsilon_N - \varepsilon_g$) with interspersed water globules of volume fraction $\varepsilon_d = \varepsilon_N + \varepsilon_g$ and permeability $P_{NS} = D_{NS}$. One then has to choose from a wide variety of formulae describing the variation of P_N/P_{NS} as a function of P_{NS}/P_{NM} and ε_d,[27,28] some of which have been applied in particular ways to drug release data.[11,29] However, the results obtained from different formulae can differ widely, partly because of differences in the approximations used, but mainly because they represent different kinds of composite medium structure.[28] Our objective here is to compare our experimental P_N values with those calculated from three well-known, relatively simple formulae, shown in previous work[28] to be characteristic of such reasonably well-defined structures. These theoretical results can thus serve as a useful backdrop against which the structural implications of the observed behavior of P_N can be usefully assessed. The formulae in question are those of Maxwell, Bruggeman, and Böttcher,[27,28] which, for the high values of $u = P_{NS}/P_{NM}$ of interest here, reduce respectively to

$$P_N/P_{NS} = (1 + 2\varepsilon_d)/(1 - \varepsilon_d)u \qquad (7)$$

$$P_N/P_{NS} = 1/(1 - \varepsilon_d)^3 u \qquad (8)$$

$$P_N/P_{NS} = 1/(1 - 3\epsilon_d)u \quad \text{for } \varepsilon_d < 1/3 \qquad (9a)$$

$$P_N/P_{NS} = (3\varepsilon_d - 1)/2 \quad \text{for } \varepsilon_d > 1/3 \qquad (9b)$$

Note that, according to eqs. (2) and (6),

$$P_N/P_{NS} = K/\tau$$

Equations (7)–(9) converge as $\varepsilon_d \to 0$. As $\varepsilon_d \to 1$, however, divergences become increasingly marked particularly between eqs. (7) or (8) and eq. (9). Equation (7) represents a lower bound for P_N/P_{NS}, corresponding to the maximum possible separation of the dispersed water globules from one another at any given composition.[28] Equation (8) corresponds to a more random distribution (leading to higher P_N/P_{NS} values), but contact between globules is limited to the extent that long chains of globules in contact with one another cannot form, and the structure of the composite medium remains that of a dispersion of water globules in a continuous polymer matrix over the whole composition range. This is in keeping with the observation that eq. (7) applies particularly well to liquid emulsions [the latter undergo phase inversion beyond a certain value of ε_d, but eq. (7) still applies to the new emulsion with the appropriate new values of u and ε_d].[30,31] Finally, eq. (9) applies to two physically equivalent component phases mixed in a perfectly random fashion.[28] Either component phase can be fully continuous or fully disperse if its volume fraction is $> \frac{2}{3}$ or $< \frac{1}{3}$, respectively. In the intermediate composition range, both phases are partly continuous and partly disperse to various degrees. More particularly, for $\varepsilon_d < \frac{1}{3}$, eq. (9) leads to P_N/P_{NS} values only moderately in excess of those given by eq. (8) but predicts a sharp rise in P_N/P_{NS} beyond $\varepsilon_d = \frac{1}{3}$ (percolation threshold). In the present context, the above behavior implies the possibility of progressive complete merging of water globules at higher ε_d, which, of course, is precluded by the fact that solid solute particles have served as templates for the majority of the said globules; hence, eq. (9) can only be considered an upper bound in this region.

The usefulness of the above ideas can be judged best by application to the more detailed $CaSO_4$ data (cf. Table V). The results for the lowest salt load ($\varepsilon_d \approx 0.1$), in which case the salt particles are demonstrably fully coated by polymer ($\varepsilon_g = 0$;

Table V Comparison of Experimental P_N/P_{NS} Values for $CaSO_4$-Loaded Films with Those Predicted from Equations (7)–(9)

Polymer	ε_d	Eq. (7)	Eq. (8)	Eq. (9)	Experimental
Cellulose acetate ($u = 2.2 \times 10^6$)	0.091	6.0×10^{-7}	6.1×10^{-7}	6.3×10^{-7}	6.3×10^{-7}
	0.235	8.9×10^{-7}	1.0×10^{-6}	1.6×10^{-6}	1.5×10^{-4}
	0.390	1.4×10^{-6}	2.1×10^{-6}	8.5×10^{-2}	7.9×10^{-3}
Cellulose ($u = 230$)	0.103	5.9×10^{-3}	6.1×10^{-3}	6.3×10^{-3}	6.3×10^{-3}
	0.250	9.0×10^{-3}	1.0×10^{-2}	1.7×10^{-2}	1.3×10^{-2}
	0.409	1.4×10^{-2}	2.1×10^{-2}	1.1×10^{-1}	3.3×10^{-2}

Using $u = P_{NS}/P_{NM}$ values deduced through eq. (9) from the experimental results for the lowest ε_d.

see Table I), were used to determine u. The choice among eqs. (7)–(9a) for this purpose is immaterial in the present context. Application of eq. (9a) gave $u = 2.2 \times 10^6$ for cellulose acetate. This corresponds to $P_{NM} = 4 \times 10^{-12}$ cm^2/s, (which, in conjunction with the measured value of K, leads to $D_N = 4 \times 10^{-10}$ cm^2/s, a perfectly reasonable value for this type of cellulose acetate).[23] The observed trend of P_N with increasing ε_d conforms most closely to eq. (9), but there are notable quantitative discrepancies.

The fact that the experimental P_N value at $\varepsilon_d = 0.235$ is markedly higher than predicted is attributable to less effective coating of the original salt particles with polymer, corresponding to more extensive interglobule contact or merging (cf. $\varepsilon_g > 0$ in Table I) than would correspond to the random mixing process envisaged in eq. (9). For $\varepsilon_d > \frac{1}{3}$, however, the reverse situation arises because the extensive merging of water globules implied in the theory [which is responsible for the sharp rise in P_N predicted by eq. (9b) in this region] cannot occur in reality, as explained above.

Application of the same procedure to the cellulose–$CaSO_4$ data yielded $u = 230$, corresponding to $P_{NM} = 4 \times 10^{-8}$ cm^2/s. It is interesting that the negative deviation of the observed P_N noted above at $\varepsilon_d > \frac{1}{3}$ from the theoretical value of eq. (9) persists here too, as expected; whereas the marked positive deviation seen above at $\varepsilon_d = 0.235$ is absent here. This might appear strange at first sight, in view of the fact that the distribution of water globules in the polymer matrix has not been changed, but it offers a reasonable explanation, on the basis of the difference in the magnitude of P_N in the two cases. Thus, referring to Table V, the presence of a few continuous water-filled pores in a cellulose acetate matrix, which can raise its normalized permeability from the (theoretical) value of $P_N/P_{NS} \sim 10^{-6}$ to the observed value of $P_N/P_{NS} \sim 10^{-4}$, can have very little effect on a cellulose matrix of $P_N/P_{NS} \sim 10^{-2}$.

SUMMARY AND CONCLUSION

The present work affords a good illustration of the fact that study of model monolithic controlled release devices of the type considered here has several advantages. From the point of view of kinetics, it is easy to fulfill the conditions ensuring validity of a simple limiting kinetic law, thus facilitating the interpretation of any observed deviations therefrom. From the mechanistic point of view, the use of simple strongly hydrophilic solutes ensures that the mechanism of release will be, as nearly as possible, one of dissolution and subsequent diffusion of the solute in aqueous regions of the matrix. Finally, the possibility of converting the polymer from a hydrophobic to a hydrophilic one offers a unique opportunity of comparing release kinetic behavior in these two important cases, under conditions as closely similar as possible.

The kinetic behavior observed here exhibits the salient features previously seen in drug release studies. The most prominent of these features is the tendency of D_N to rise (or the corresponding tendency of the tortuosity $\tau = D_{NS}/D_N$ to fall) with increasing solute load, which is very strong in the case of the hydrophobic polymer matrix and much weaker in the case of the hydrophilic one. In quantitative terms, the former effect here is more pronounced than any so far recorded in the literature; with τ attaining a value as high as 150,000 in $CaSO_4$-loaded cellulose acetate matrices at the lowest load used ($\varepsilon_N \approx 0.1$), which drops approximately 3000-fold (as compared with only four-fold in the corresponding cellulose matrices) following an increase of the said load to $\varepsilon_N \approx 0.4$.

This dramatic change in τ can be explained in terms of structural changes, which accompany the aforesaid increase in ε_N. Thus, it was found that, at $\varepsilon_N \approx 0.1$, the solute particles are fully enveloped with polymer. This means that the additional water taken up by the salt-depleted matrix (through which the solute has to diffuse) by filling the volume vacated by salt is in the form of separate globules dispersed in the weakly hydrated polymer matrix. The resulting enhancement of the permeability of the latter, under these conditions, is shown theoretically to be very limited (cf. Table V). At higher ε_N, microscopic gaps appear increasingly in the salt-loaded matrix, as a result of the inability of the viscous polymer solution to penetrate the narrow interstices between solute particles in close proximity. This results in merging of the aforementioned water globules in the salt-depleted matrix, with eventual formation of continuous aqueous pathways or pores, which can greatly enhance the diffusion of solute through the said matrix. (For the same reason, a tendency of solute particles to form aggregates not easily penetrable by the viscous polymer solution can lead to significantly lower τ values, as demonstrated here in the case of $SrSO_4$). Our use here of strongly hydrophilic solutes provides a very sensitive means of detecting the formation of such pathways. Thus, the experimental P_N value at $\varepsilon_N \approx 0.25$ exceeds the theoretically predicted values for a completely disperse globule phase of approximately 100-fold (see Table V); this result can reasonably be attributed only to the formation of some continuous aqueous pathways. These structural effects are much less prominent in cellulose matrices, where continuous aqueous pathways already exist through the polymer, thanks to the high degree of swelling of the latter. Thus, it is noteworthy that hydrolysis of the aforementioned cellulose acetate matrices containing salt particles fully coated with polymer causes an approximately 1700-fold drop in τ.

The above findings have some significant practical implications. Thus, in the field of radioactive waste disposal, where maximum confinement of the solute(s) is required, one should obviously guard against increasing the solute load beyond the limit where complete coating of the solute particles with the embedding medium can be achieved. In the design of monolithic controlled release devices, a very wide range of release rates can be achieved by using a hydrophobic polymer matrix and adjusting the solute load or by adjusting the hydrophilicity of the polymer. The latter method would generally seem to be easier to use in a controlled manner in practice.

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